Volume 36 Number 10
PHARMACEUTICAL TECHNOLOGY
OCTOBER 2012
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OCTOBER 2012 Volume 36 Number 10

Advancing Development & Manufacturing

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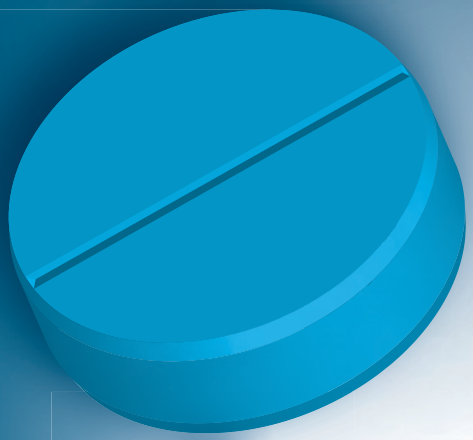
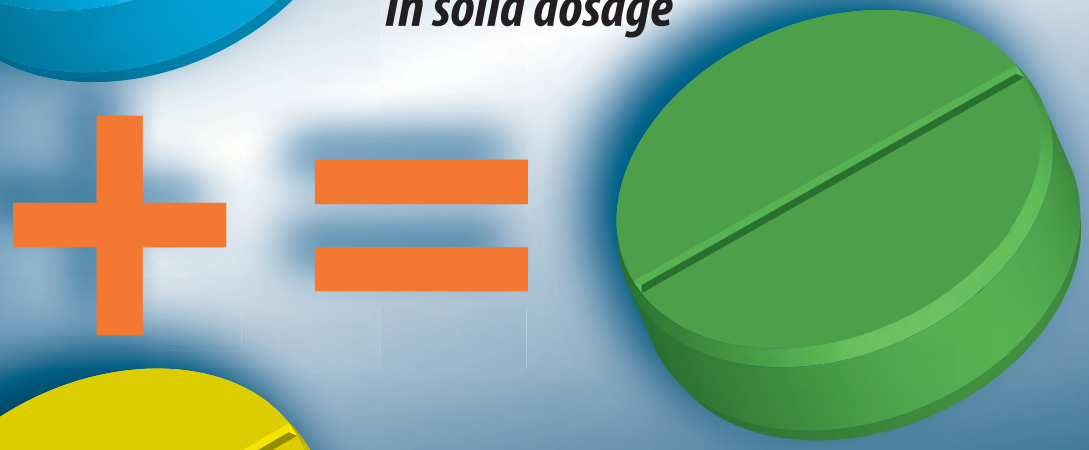
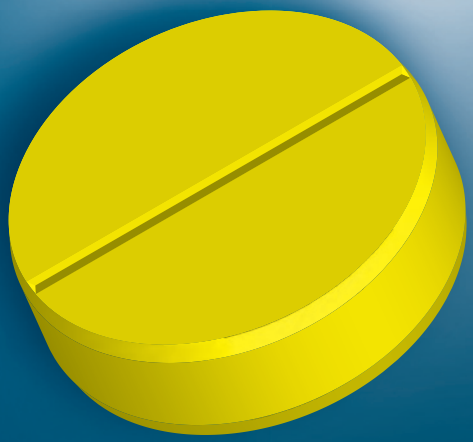


Combination Drugs

Adding up the opportunities in solid dosage





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On the cover

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Patricia Van Arnum

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Illustration by Dan Ward

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A World without R&D

Angie Drakulich

Will the next US President support the backbone of our industry?

I've recently been inspired by a series of events, programs, and speeches on the importance of the discovery side of our industry. Over the summer, hundreds of individuals raised nearly $1 million in one week to save the laboratory site of Nikola Tesla, the late physicist and engineer whose work in the late 1800s and early 1900s formed the foundation for wireless and X-ray technology. The funds are to be used to purchase the land where Tesla worked and to build a museum in his honor. The interest and initiative taken by donors to keep a scientific legend's work alive is more than moving.

New legendary scientists are being discovered every day. In September, I was lucky to be able to attend the PhRMA Research & Hope Awards ceremony in Washington, DC, where nine individuals were honored for their work in the fight against Alzheimer's disease, a disease that is not only plaguing healthcare systems and distressing caregivers worldwide, but that also presents complex scientific challenges. Also in September, 10 major biopharmaceutical companies formed a nonprofit called TransCelerate BioPharma, with the aim of accelerating the development of new medicines, with an initial focus on clinical trial execution.

This month, our Executive Editor Patricia Van Arnum will be in Madrid to meet the winners of the CPhI Worldwide Pharma Awards, which recognize companies that are breaking new ground in the manufacturing of pharmaceuticals, drug delivery, and sustainable packaging. Across the Atlantic, I will be meeting the recipients of the AAPS Graduate Student, Innovation, and Research Achievement awards in Chicago. The recipients of the various awards are dedicating their studies to improving pharma analysis, formulation design, drug delivery, biotechnology, product performance, and more.

All of the individuals working to identify new disease diagnostics and therapeutics, whether or not they are recognized on the global stage, serve as the backbone to this industry. For without new products to manufacture for patients in need, where would we be?

Just where R&D lies in America's future may very well depend on federal spending and support. With the US presidential election around the corner, I thought it important to examine where the country's candidates stand on this issue. Much has been said along the campaign trails regarding manufacturing and innovation, but the candidates' specific views on R&D and related federal spending do not always make the headlines.

Here are a few goals from Obama's court based on his FY2013 presidential budget proposal, which calls for $140.8 billion in overall federal R&D spending, an increase of $2 billion over the FY2012 enacted level:

- Enhance innovation in the manufacturing sector by supporting investment in new products, processes, and industries, and by investing in cross-cutting technologies
- At NIH, level funding for biomedical research ($30.7 billion); focus more on translational studies; and to get more out of funds, aim to increase the number of new research grants by 7%
- Provide $2.2 billion for federal advanced manufacturing R&D at the National Science Foundation, and 23 other agencies, a 19% increase over 2012. This includes funding for the National Institute of Standards and Technology to advance research in smart manufacturing, nanomanufacturing, and biomanufacturing
- Improve the patent system and protect IP by giving the US Patent and Trademark Office full access to its fee collections and strengthening its efforts to improve and speed patent reviews
- Help small businesses obtain early stage financing.

Both President Obama and Governor Romney support basic stem-cell research (in addition, Obama removed the federal funding ban on broader embryonic stem-cell research in 2009), and both candidates support making the research and experimentation tax credit permanent. Obama would also like to increase the alternative simplified credit from 14% to 17%.

Romney's official website includes his plan for American jobs and economic growth. The 160-page document includes language on R&D and basic research, but that language largely focuses on clean energy spending and technologies. The core policy sections of Romney's plan—tax, regulation, trade, energy, labor, human capital, and fiscal management—do not include medical research or science policy (other than from an educational standpoint), and my email request to the Romney campaign team about his take on NIH and FDA spending was not answered.

Media reports from earlier this year note that Romney would like to shrink the NIH biomedical budget. As governor of Massachusetts, however, he did support the state's biotech and life-sciences industry.

It will be interesting to see how the winning candidate's goals are carried out given that Congress largely controls the final federal budget. Let's hope that, no matter how Election Day turns out, that R&D still has a significant role. **PT**

Angie Drakulich
is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to adrakulich@advanstar.com.

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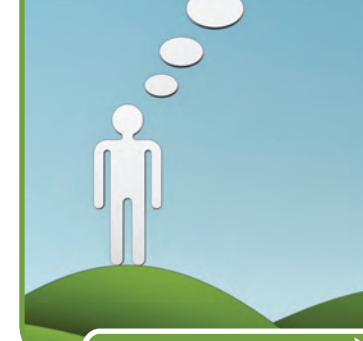

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Partnerships Remain Crucial to Future Development

David Mitchell, AAPS

Working together affords many unseen opportunities for pharmaceutical innovation.

With the nature of our industry shifting vastly, partnerships have become essential to continued success and productivity in the field. It is important that scientists and researchers establish these relationships within big and small pharma, academia, government, and professional organizations, such as the American Association of Pharmaceutical Scientists (AAPS), to help keep the industry moving forward. But, as with any relationship, there are bound to be challenges.

Managing partnerships with CROs, for example, is a necessity for many in the pharmaceutical sector. Pharma companies have a broad strategic rationale for clinical outsourcing and are still experimenting with different CRO relationship models. According to an April 2012 report from Booz & Company, "Nimble Partnerships in the Pharma Industry," there are four types of relationship models emerging: Qualified Talent Supplier, Preferred Capacity Partner, Preferred Capability Partner, and Strategic Partner. To develop sustainable value from these relationships, companies must align the design, structure, and performance measures of their relationships with their strategy. Companies that adopt a quick, capability-centered approach to partnerships are likely to be more focused, make better use of their distinct capabilities, and generate more value.

David Mitchell, PhD, is president of the American Association of Pharmaceutical Scientists (AAPS).

Much of consulting is about one's network. Partnerships with other consultants can broaden a consultant's network, provide more opportunities, and allow one to assemble a "complete package" for a given project. For example, if approached by a client to complete a clinical trial, I might design the trial, write the protocol, analyze the data, and write the report. But I need a partner to run and monitor the trial, complete the bioanalytical assays, possibly prepare regulatory documents, and provide a medical opinion on the safety aspects of the trial. By partnering with the right group of consultants, I can put together a "virtual project team" to complete the study with expertise in every required area.

In recent years, industry has also taken a more collaborative approach with academic research institutions. Academia holds a strong role in the advancement of drug discovery and has created great partnering relationships with companies. Tightening federal budgets have put a strain on academic laboratories, and the industry is trying to cut costs and improve productivity by outsourcing. This environment allows for the increased opportunity for collaboration from both parties and an increased acceleration in drug discovery.

AAPS recognizes the importance of partnerships in our field. During the past few years, the association has partnered and cosponsored events with numerous organizations, including FIP, FDA, ACCP, ASCPT, and GBC.

In addition, the association continues to partner with its members to bring them the information, both scientific and for professional development, they need. One area of focus during my presidency has been on the changing nature of our membership. Last year, AAPS created a Big Pharma/Small Pharma Task Force to identify the unique needs of the members from smaller pharmaceutical and biotechnology companies, CROs, and consultants, and to determine how AAPS could adapt to meet their changing needs.

The task force presented recommendations to ensure that members who are part of small pharma and biotech companies do not feel overshadowed by those employed in Big Pharma. These recommendations are particularly important to AAPS; nearly 50% of our members now reside at a small pharma/biotech company, CRO, or as a consultant. One recommendation was to allocate programming at this year's annual meeting (taking place Oct. 14–18 in Chicago) geared specifically towards members working at small companies, which has been completed. Additionally, we have learned that there is a need for more programming on discovery, a primary activity of small pharma, biotech, and academia. Lastly, we're organizing a summit of key pharmaceutical leaders to discuss the progression of the industry over the next 20 years. Our goal is to identify what industry, government, and academia need to be successful and how AAPS can help.

AAPS continues to take steps to adapt to shifting trends through partnerships with other organizations and our members. Part of adapting to our changing industry is continuing to provide the tools that members need to access the latest information and stay connected. Forming these partnerships is of utmost importance to us. **PT**

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Case Closed

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Cautionary Tales from the Files of "Control," a Senior Compliance Officer

Only the strong survive when it comes to pharmaceutical packaging and shipping.

Case by case

"We manufacture the same large volume parental product in two different factories; one in Europe and one in the US," explained our GMP Agent-In-Place. "They are filled into the same size bottle and sold around the world, sometimes in the same market. Each are packed into cases of 10 with crush zones around the edges. However, these zones make the case big and fewer fit onto a pallet. The European factory ships most of its product overseas, and so they wanted to minimize the number of pallets. For this reason, they designed the smallest possible case and used no crush zones. Both products are marketed in the same country, however, we had many complaints for breakage on the EU-manufactured product and almost none on the US-manufactured product. Now we either overpack the EU-made product, or replace the case with a more protective one. Someday we'll get the EU factory to start with a more protective case."

Forensics

"We found mold in our aseptic-filling rooms on a routine touch plate," complained our GMP Agent-In-Place. "This is a serious issue, because most cleaning and disinfection chemicals that we used do not kill mold. We immediately closed the room and quarantined the product that had been filled since the sample was taken. We then disinfected with a mold-killing agent, applied twice over two days, and then resampled. Only after a clean bill of health did we resume filling.

"We also needed to find the source. In a review of all the relevant data, we found the same mold on an employee's gown plate and on his glove touch plate. Following further sampling, we found more mold in the bulk tank staging room. The bulk tank had been stored for an abnormally long time in a cooler, and an employee noted that there was some condensation on it, which made it an excellent place for mold to grow. We found mold in the cooler as well, so we surmised that the mold grew in the cooler and the transport vector was the bulk tank exterior. The mold must have been transferred to the product hose, which is pushed through the opening from the bulk tank staging room into the fill room. The hose was disinfected in the fill room using ethyl alcohol, which doesn't typically kill mold typically. So the employee in the fill room transferred the mold around the fill room because it was on his hands from the hose.

We fully disinfected the cooler and bulk tank hold rooms. The two weeks' loss of use of the fill room could have been catastrophic if not for having sufficient capacity in two other fill rooms," our Agent concluded.

Guess which batch

"We got a telephone call from the Center for Biologics Evaluation and Research's lot-release branch," said our GMP Agent-In-Place. "They said they had received a container of unlabeled samples. Without a label, they could not tell which batch each sample came from, and therefore, could not test and release any of the batches that the container purported to hold. We had to replace the samples and chide the logistics staff, who were supposed to label them before shipping. It turned out that the regular logistics staff were on vacation, so it was a new-to-the-job person who did this and clearly didn't understand all the requirements."

All steamed up

"It started with a LAL (endotoxin) test failing for our clean steam system," our GMP Agent-In-Place grumbled. "The next day, the test passed, but then two days in a row failed. This intermittent LAL out-of-specification continued, and while it did, there were also intermittent total organic carbon and particulates failures. As part of the corrective action, we cleaned some condensate traps and found them to be full of junk, including many metal filings. This gave us a clue. There had been some piping replaced in the clean steam system and it had not been properly cleaned and passivated postinstallation. We lost a week of production, but finally got it cleaned up." **PT**

Pharmaceutical Technology's monthly "Agent-in-Place" column distills true-life cautionary tales from the files of Control, a senior compliance officer. If you have a story to share, please email it to Control at AgentinPlace@advanstar.com. We won't use any names, but if we do use your experience in the column, you'll receive a Pharmaceutical Technology t-shirt.

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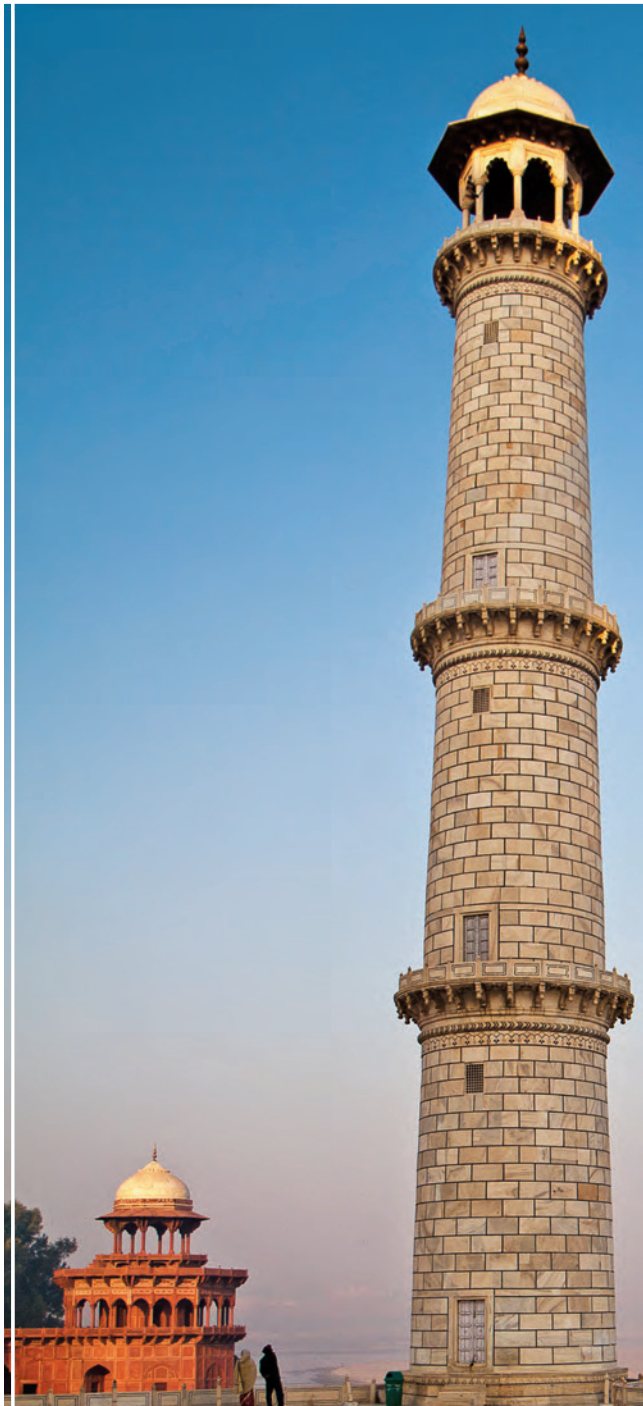

Report from: INDIA

Jane Wan

Foreign firms struggle against stricter patent laws, but all is not lost.

Swiss-based Novartis is taking India to court in a bid to seek patent protection of its leukaemia drug, Glivec (known as Gleevec in US). Novartis first applied for the patent in 2006 but was denied. In similar instances, Swiss-based Roche's anticancer drug Tarceva and US-based Gilead Sciences' HIV medicine Viread have failed to secure patent protection in India.

Looking back, patent laws in India have come a long way. India's patent history began in 1856 with Act VI, which encouraged innovations and sharing of creations between inventors. Based on the British Patent Law of 1852, Act VI was in effect for 30 years. When the British amended the laws in 1800s, India followed suit. In 1911, the Indian Patents and Design Acts came into effect whereby a Controller was installed to manage patent-related issues. When India gained independence from Great Britian, the Patent Act of 1970 was introduced to spur innovation and economic growth. It abolished the product patent system based on the "Ayyangar Committee Report, 1959," which examined the factors influencing the high prices of the drugs and pharmaceuticals in India. The Patent Act has been revised three times since then and made compliant with the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement in 2005.

contin. on page 20

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contin. from page 18.... India has since enforced a set of strict patent laws, and foreign players are facing obstacles in the review process, patent tracking, and pregrant and postgrant opposition, says Ajaykumar Sharma, associate director, pharma and biotech, healthcare practice of Frost and Sullivan (South Asia and Middle East). The interpretation of different sections of the Patent Act of 2005 and review of application remain the biggest challenge. This challenge is increased by the lack of trained manpower that further delays the review process. The Indian Patent Office, additionally, does not have an efficient database system to facilitate searchable full text databases of all patents and applications. Foreign players continue to face an increase in pregrant and postgrant opposition by generic-drug companies. Litigation and infringement cases usually take longer to resolve.

India has enforced stricter patent laws compared to other countries such as South Africa. For a drug to be patentable in India, the invention has to be novel (i.e., new to the industry), inventive, and industrially applicable. In contrast, weak patent standards and the absence of a patent agency in South Africa have resulted in the granting of a high number of patents yearly. In 2008 alone, South Africa issued a total of 2442 patents.

The Indian patent agency has set a higher bar for patent approval that is frustrating pharmaceutical manufacturers who are deeply concerned over the agency's standpoint of intellectual property in the country. In Novartis' case, the company is challenging the efficacy clause stated in Section 3(d) of the Indian Patent Law. However, the Indian agency views its decision as a move to curb the "evergreening" practice, whereby a drug is tweaked slightly in a bid to extend patent protection. Specifically, the Novartis patent application was denied on the grounds that the drug lacks innovation because it is considered a salt formulation of the drug and not a new drug altogether.

If Novartis gets its way with the patent, the decision could result in a flood of new patent applications and possibly threaten patients' access to essential drugs tagged at affordable prices. More significantly, it may upset India's position as a generic-drug manufacturer and role to provide affordable drugs to other developing countries.

The Indian Patent Law has also made provisions for the Controller of Patents to issue compulsory licenses to deal with extreme or emergency situations. Recently, it gave approval to Natco Pharma to produce the generic version of Nexavar. As a result, Natco is able to price the drug at $158 for a 120-tablet package.

Despite the concerted efforts to provide low-cost drugs, the problem of poor medical access is still prevalent in the country. To date, a significant number of infants (aged 12 to 23 months) have yet to be fully vaccinated against six major childhood diseases (tuberculosis, diphtheria, pertussis, tetanus, polio and measles) even though the Indian government has made these primary vaccination programs free across the country. Tapan J. Ray, director–general of the Organization of Pharmaceutical Producers of India, an association of R&D pharmaceutical companies in India, says: "Only a short focus on the rejuvenation of the fragile healthcare delivery system, healthcare financing, and rapid development of healthcare infrastructure by the government or public private partnership will address the access issue."

It is also impractical to envisage that the granting of compulsory license will resolve the issue of access to patented medicines on a long-term basis. Granting of these licenses should only be done after exhausting all access improvement measures, Ray says.

Sharma adds, "Compulsory license should not be a benchmark for possible future decisions taken by the government. But I foresee a need and evolution of a new business model that will reach out to the masses by foreign players. This can take place possibly in the forms of differential price launches, patient assistance programs, or state medical purchase policies."

Asked whether it is possible to strike a balance between maximizing profits and providing patient access to drugs, Sharma comments that this can be achieved through differential pricing. For example, GlaxoSmithKline's Ventolin asthma inhaler is priced at the lowest level possible for the lowest-income patients, Flixotide at a lower discount for those with higher incomes, and Diskus priced highest for citizens with the highest incomes. Roche is working on details to offer discounted versions of two cancer drugs, Herceptin and MabThera, in India by early next year.

Given the current restricted parameters, foreign companies should start looking for innovative engagement models to operate on Indian soil, Sharma says. In fact, mergers and acquisitions have taken place between foreign and Indian firms. In 2010, Illinois-based Abbott Laboratories' acquisition of Mumbai-based Piramal Healthcare for $3.7 billion has brought its market share in India to approximately 7%, and the company is expecting revenues to grow an estimated 20% a year to more than $2.5 billion by 2020, propelling the company to the leading position in the Indian market. In January 2011, Bayer Healthcare has inked a joint venture agreement with Mumbai-based Zydus Cadila in a bid to enhance its presence in India.

—Jane Wan is a freelance writer based in Singapore

CSR and sustainability forum

Pharmaceutical Technology's Sourcing and Management eNewsletter provides specialized coverage of the bio/pharmaceutical industry's activities in corporate social responsibility (CSR) and sustainability as well as developments from other business sectors, government organizations, professional, trade, and scientific associations, and NGOs. In the October issue (available at www.PharmTech.com/PTSM), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and BSR provide insight into global health partnerships. We welcome your ideas to learn about the work of your company or organization in CSR and sustainability. Contact Patricia Van Arnum, senior editor, at pvanarnum@advanstar.com.

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Regulation and Compliance Q&A

with David Elder and Richard Wright of Strategic Compliance Consulting, PAREXEL International. Both Elder and Wright formerly served with FDA.

David Elder is a principal consultant at PAREXEL and former senior official with FDA.

Richard Wright is a principal consultant with PAREXEL and former investigator with FDA.

Q. How should a company approach handling an FDA-483 observation with which they do not agree?

A. The best approach to deal with an observation with which a company does not agree is to prevent an FDA-483 observation in the first place.

During the course of an FDA inspection, there will be many opportunities to ascertain the areas of interest and potential areas of concern of the investigator. The clearest opportunity to understand the true concerns of the investigator will be during the periodic wrap-up sessions, which should occur on a daily basis per *Investigations Operations Manual* (IOM) Section 5.2.3: "… investigators and analysts should make every reasonable effort to discuss all observations with the management of the establishment as they are observed, or on a daily basis, to minimize surprises, errors, and misunderstandings when the FDA 483 is issued…" (1).

FDA investigators are human beings just like the rest of us and mistakes or misunderstanding can happen. The agency encourages the industry to use these communication opportunities to ask questions or request clarification, and if during the course of these communication opportunities it becomes apparent that there is an area of misinterpretation or misunderstanding, additional information or documentation should be presented quickly and clearly. It is highly encouraged that a professional posture be maintained, even when a company does not agree with the investigator. It is better for both the company and for FDA if any and all observations on the FDA-483 are understood, are factually accurate, and are grounded in law or regulation.

The ability to take prompt corrective action is another advantage of having periodic discussions during the inspection. While corrective action may not prevent an FDA-483 observation, it will mitigate the impact and demonstrate to the agency how the executive management is committed to compliance. Any corrective actions taken in response to a potential FDA-483 observation should be comprehensive in scope and should address the underlying system problem. The FDA-483 is not a final agency action and does not represent an agency level position. It is a list of objectionable conditions observed by the investigator(s) during the course of the inspection which are, in the in-

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vestigator's judgment, conditions or practices that may indicate that a drug has been adulterated (see IOM Section 5.2.3 and 5.2.7). The investigator owns the FDA-483; once issued, it would be a very rare exception to the rule to have it revised and reissued. In fact, the IOM limits such conditions to errors discovered prior to leaving the facility and errors discovered after leaving the facility (see IOM, Section 5.2.3.1.6). The only real fruitful areas of discourse are, therefore, factual inaccuracy and observations that do not accurately represent violations of law or regulation.

Once the FDA-483 is issued, the best opportunity to deal with an observation with which you do not agree (and which contains a factual inaccuracy or does not accurately represent violations of law/regulation) is within the FDA-483 response, which should be submitted within 15 days of the conclusion of the inspection. It is perfectly appropriate to present information and evidence in an FDA-483 response that repeats, and augments as appropriate, that which was provided during the inspection in addition to completely addressing all other observations, including those presented verbally by the investigator.

If all efforts undertaken do not achieve the desired result, keep in mind that it is only after further agency review that the objectionable conditions listed on the FDA-483 may be considered to be violations of the Food, Drug, and Cosmetic Act or other statutes (see IOM Section 5.2.7) and, therefore, subject to consideration for regulatory action.

Reference

1. FDA, *Investigations Operations Manual*, 2012, www.fda.gov/ICECI/Inspections/IOM/default.htm.

Have a common regulatory or compliance question? Send it to adrakulich@advanstar.com and it may be appear in a future column.

FDA Official to Speak at ISPE

The International Society for Pharmaceutical Engineering (ISPE) has announced that FDA's Deputy Commissioner for Medical Products and Tobacco, Stephen P. Spielberg, MD, PhD, will be discussing challenges and opportunities in advancing regulatory science in a plenary address at ISPE's Annual Meeting this November. Spielberg's address, "How the FDA is Advancing Regulatory Science through High Quality of Collaboration," will focus on FDA's current and future collaborations with ISPE and other organizations.

Part of a four-day conference program, the plenary session also includes an address by Murray Aitken, executive director of IMS Institute for Healthcare Informatics. Aitken's speech, "Top Priorities and Trends for the Pharmaceutical Industry," will provide a forecast of top trends through 2016 and a data-driven analysis of the industry.

ISPE's annual meeting is designed to provide pharmaceutical professions with opportunities to discuss technical and regulatory trends and challenges with colleagues. The meeting features a session in which industry leaders discuss key technical areas crucial to the pharmaceutical industry's future. Also of note is an International Regulatory Summit, where regulators from international organizations will discuss regional and global regulatory challenges.

The ISPE meeting will take place Nov. 11–14 in San Francisco.

—Susan Haigney

PhRMA's Research and Hope Award Recipients Honored at Newseum

On Sept. 12, 2012, the Pharmaceutical Research and Manufacturers of America (PhRMA) honored nine individuals for their research into and fight against Alzheimer's Disease (AD) as part of the association's new Research and Hope Awards. The statistics surrounding AD have been plaguing families for decades. The disease is the 6th leading cause of death in the US today, according to the Alzheimer's Association, with 5.4 million people currently affected. By the year 2050, one American will develop AD every 33 seconds.

The costs surrounding AD, from both a financial and time perspective, are also disheartening. The Alzheimer's Association notes that the US spends an estimated $200 billion on AD per year, and families across America and around the globe are all too aware of the intense care and attention that AD patients require.

These are just some of the reasons why PhRMA has focused on AD for its awards program, which launched this year, replacing the PhRMA Discover's awards program. In terms of the day-to-day work being done to find a treatment and improve care, the 2012 PhRMA Research and Hope Awards honor the following:

-*The Research & Hope Award for Academic Research in Alzheimer's:* Bradley T. Hyman, MD, PhD, Professor of Neurology, Massachusetts General Hospital/Harvard Medical School; and David Holtzman, Andrew B. and Gretchen P. Jones Professor and Chairman; Department of Neurology, Washington University School of Medicine.

Hyman's laboratory is looking to develop methods to examine clinical–pathological correlates and biomarkers in AD, as well as animal and cell models to explore the natural history of the disease. Holtzman's team has been focusing on how apoE influences Abeta metabolism and the risk for AD, the influence of synaptic activity and sleep on Abeta metabolism, the potential ability of anti-Abeta antibodies to act therapeutically and diagnostically in AD, and new methods to study protein metabolism in the CNS for both diagnostic and theranostic purposes.

-*The Research & Hope Award for Biopharmaceutical Industry Research in Alzheimer's:* The Merck BACE Team,

including Eric M. Parker, Senior Director and Neuroscience Site Lead; Andrew W. Stamford, Director, Discovery Chemistry; Matthew E. Kennedy, Associate Director, Neuroscience; Mark S. Forman, Director, Clinical Research; and Julie A. Stone, Senior Scientific Director. The BACE team is evaluating the safety and efficacy of the beta-amyloid precursor protein site cleaving enzyme, or BACE, inhibitors, including MK-8931, which is Merck's lead AD pipeline compound. Clinical trial results to date evaluating the safety and tolerability of MK-8931 in 40 healthy adults aged 18 to 45 associated single doses with marked reductions in amyloid beta peptide concentration levels.

-*The Research & Hope Award for Patient Advocacy*: Kate Maslow at the Keck Center Institute of Medicine (IOM). Maslow, a scholar-in-residence at the IOM National Academy of Sciences, is focusing on issues tied to the care of people with AD and other dementias Maslow previously spent 15 years at the Alzheimer's Association, directing practice and policy initiatives to improve the quality, coordination, and healthcare outcomes of long-term services and supports for AD patients and their caregivers.

-*The Research & Hope Award for Volunteer Champion:* Neha Chauhan at the AFA Teens for Alzheimer's Awareness. Chauhan, now an MBA student at Stanford, has been volunteering in the fight against AD since age 15 as the founder of AFA Teens, which is a branch of the Alzheimer's Foundation of America dedicated to youth advocacy.

The science award winners were selected by a special committee of the PhRMA Foundation. The advocacy awards were selected by a committee made up of PhRMA and cohost representatives. *Pharmaceutical Technology* was a media partner.

—*Angie Drakulich*

Editors' Picks of Pharmaceutical Science & Technology Innovations

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Shimadzu has added three new triple quadrupole mass spectrometers, LCMS-8040, LCMS-8080 and GCMS-TQ8030, to its UFMS series, which currently comprises seven systems. The LCMS-8040 combines improved ion optics and collision cell technology with proprietary ultrafast technologies, and provides an expanded range of ultra-fast, high-sensitivity applications. With the LCMS-8080, it is possible to conduct trace analysis of compounds in complex matrices as the system features high sensitivity with a large dynamic range and quantitation performance. The GCMS-TQ8030 achieves the highest sensitivity in its class for multiple reaction-monitoring measurements based on UFsweeper technology.

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New Era for Generic Drugs

Jill Wechsler

User fees aim to speed approvals and support timely plant inspections.

The promise of the Generic Drug User Fee Amendments of 2012 (GDUFA) is to end multiyear reviews of new generic drugs and the ever-growing queue of pending applications. After years of resistance, generic-drug makers agreed last year to provide funds to FDA to support speedier approval of abbreviated new drug applications (ANDAs) and prior approval supplements (PASs), as well as timely inspection of domestic and foreign manufacturers and suppliers of APIs.

To launch the new fee program on Oct. 1, 2012, FDA issued a wave of *Federal Register* notices and guidance documents in August 2012 that officially inform manufacturers of relevant procedures and obligations. The various fees authorized by GDUFA will provide $299 million in funding for FDA in fiscal year 2013 and $1.5 billion over five years. Application fees of approximately $50,000 will add up to almost $100 million, primarily from payments on an expected 750 to 900 ANDAs each year, plus some 750 supplements. Approximately $15 million will be levied on newly referenced (type II) drug master files (DMFs) on a one-time basis according to a fairly complex process; an FDA Q&A guidance spells out specifics on this and other issues and how fees will be calculated (1).

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Identifying facilities

Approximately $175 million in fees will be levied annually on facilities operated by manufacturers of both finished dosage forms (FDFs) and API producers, the majority (approximately $140 million) collected for FDFs. The payments will be $15,000–$30,000 higher for foreign facilities to reflect added inspection costs, and plants that produce both finished drugs and APIs will pay both fees. One tricky issue is how to account for facilities with several buildings at one site. Such complexes may owe only one fee if FDA determines that the site can be inspected at one time, based on activities and ownership structure. But one company with several distinct facilities most likely will pay fees for each location.

Various producers have to register with FDA, but do not have to pay fees, including repackagers, manufacturers of PET drugs, and sites conducting analytical testing.

This manufacturer "self identification" program expects to collect information from 3000 or so organizations, facilities, and sites utilizing existing electronic data submission processes and familiar file formats to reduce the data collection burden on the agency and industry (2). Manufacturers will provide Data Universal Numbering System numbers and Facility Establishment Identifiers plus physical addresses and contact details. Various producers have to register with FDA, but do not have to pay fees, including repackagers, manufacturers of positron emission tomography drugs, and sites conducting bioequivalence or bioavailability studies and other analytical testing.

In addition to determining who has to ante up, FDA expects the facility identification program will provide important information to promote global supply chain transparency. The data will go into new generic-drug facility databases, which will provide information to help FDA address global supply chain issues. Among other stated goals, FDA will conduct biennial GMP surveillance inspections of generic API producers and product manufacturers, with the aim to achieve parity in inspection frequency between foreign and domestic firms in 2017.

Cutting the backlog

FDA's Office of Generic Drugs (OGD) also will collect a one-time ANDA backlog fee this year on pending ANDAs, which will generate an expected $50 million to support the processing of almost 3000 ANDAs currently in the application queue. Many of these applications are categorized as "incomplete" or were hit with "not approvable" or "complete response" letters years ago, but were not withdrawn by the manufacturer. The initiative aims to clear out 90% of the ANDAs and amendments in the backlog by 2017.

FDA would like to whittle down the backlog before launching the GDUFA backlog program and announced in

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Hot-Topic Roundup

Tablet-splitting challenges

FDA officials are struggling to set standards for drugs that are scored to facilitate splitting by consumers, a practice that has become increasingly common as a way to reduce prescription drug costs. Ideally, the two halves of a split tablet would be identical, but there are no standards for ensuring that result. FDA issued draft guidance in August 2011 proposing criteria for evaluating and labeling scored brand and generic products. The *United States Pharmacopeia* also is examining the issue for a General Chapter on uniformity of dosage units. At issue is whether scoring yields consistent split doses and how to evaluate the stability and friability of the splits.

The agency sought advice on the recommendations in its draft guidance at the August 2012 meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Key topics discussed were how to assess ease of splitting, loss of mass, and variations in weight as an indication of content uniformity. Also on the agenda was whether to apply standards just to new products and to permit existing scored drugs to remain as is. The advisors agreed that a test for content uniformity should not involve tablet splitting by patients, as that would inject too much variability into the evaluation process. But there were questions about the value of stability data on split products and the status of marketed scored drugs. FDA is, therefore, headed back to the drawing board to clarify scoring and splitting test proposals.

Opportunities with orphan drugs

Pharmaceutical manufacturers are eyeing the orphan-drug market as a source of growth, as revenues and profits for widely used medicines fail to keep pace with new cancer therapies and other critical treatments for small patient populations. Despite limited markets, orphans accounted for $50 billion in global sales for 2011, according to an August report by *Thomson Reuters*. These select therapies benefit from extended exclusivity that can delay generic competition, as well as speedy FDA approvals based on smaller clinical trials. The analysts expect growth to continue for new orphan drugs, as well as expanded indications for initial therapies.

Fast track safety?

Despite pressure on FDA from patient groups and industry to moderate testing requirements and accelerate reviews of new drugs, particularly therapies for seriously ill patients, critics continue to complain that "fast track," "priority review," and "accelerated approval" policies permit harmful products to reach the market. The latest entry to the debate comes from Thomas Moore of the Institute for Safe Medicine Practice and Curt Furburg, professor at Wake Forest School of Medicine, who identify safety issues for three drugs recently approved under expeditious approaches. Their analysis in the Sept. 5 *Journal of the American Medical Association* cites one therapy for seriously ill cancer patients, which carries a limited distribution program. Another drug aims to prevent multiple sclerosis relapse and is subject to tight postmarketing review. More problematic is the blood thinner Pradaxa for stroke prevention, which has experienced serious adverse events since it was approved in 2010.

The remedy, according to Moore and Furburg, is longer clinical trials and extensive analysis to ensure that benefits outweigh risks of new therapies. Their conclusion contradicts efforts in Congress to expand expedited review for breakthrough drugs. And it runs counter to a main theme of the new FDA user-fee legislation (PDUFA IV), which calls on the agency to acknowledge patients' willingness to accept risk with new therapies.

More data on drug samples

FDA is implementing a new program that requires pharmaceutical manufacturers to submit data on drug sample distribution, a provision of the Affordable Care Act (ACA) of 2010 that aims to increase transparency in industry interactions with doctors and prescribers. Data submission officially began on Apr. 1, 2012, but FDA didn't issue guidance on how to submit data until Apr. 3, 2012 and, thus, said it would not enforce the requirements until Oct. 1, 2012. Under the new program, drugmakers have to file data that identify distributed samples and recipient physicians every April 1st for activities during the previous year, using the FDA Electronic Submissions Gateway and the XML data scheme.

The ACA program overlaps to some extent with policies set by the Prescription Drug Marketing Act (PDMA), which requires manufacturers to maintain records of all samples distributed by sales representatives to licensed practitioners. For PDMA, however, companies do not submit the data to FDA, but hold it for three years. The aim is to track theft or illegal diversion of drugs and to prevent adulterated medicines from reaching consumers, explained John Oroho of Porzio LifeSciences at CBI's Forum on Aggregate Spend in August 2012. The ACA program aims to identify which drug samples are going to specific healthcare professionals, similar to "Sunshine" provisions elsewhere in the health reform legislation that focus on disclosing which doctors receive payments and gifts from the pharmaceutical industry.

The PDMA and ACA programs are expected to "mesh seamlessly," according to FDA officials, but manufacturers are skeptical. Complicating the picture is a new drug sample disclosure program in Vermont that went into effect April 1. Definitions and data submission requirements differ for Vermont, the ACA transparency program, and PDMA. For example, Vermont specifies that manufacturers do not have to submit data on drugs provided for clinical trials or research, but there is no similar caveat under the ACA policy. Just what FDA or Vermont will do with this information remains to be seen.

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June that it plans to cancel backlogged applications that have not involved any communication with the sponsor since 1991. An August *Federal Register* notice further encourages manufacturers to withdraw backlogged applications that they no longer wish to pursue (3). The agency calculated that if 2000 applications remain in the backlog (of the 3000 pending in August), the backlog fee would be $25,000 per application.

FDA also promises to meet a range of GDUFA performance goals outlined in a commitment letter to manufacturers that is structured similarly to programs that have been in place for brand drugs for 20 years (4). Under a phased-in approach, FDA will "review and act on" 60% of ANDA submissions within 15 months by the third year of the program; the timeframe tightens in year five to review of 90% of submissions within 10 months. ANDA evaluation will take longer if a manufacturer files major amendments during the review process, and OGD won't accept an ANDA until the application fee is paid, a situation that could be important in determining which generic firm is "first to file."

OGD will strive to clarify review decisions by issuing complete response letters and DMF "completeness assessments," instituting rolling reviews, and holding first cycle deficiency meetings with sponsors. If minor problems crop up during a review, OGD staff will try to inform sponsors of "easily correctable deficiencies" that can be remedied quickly. OGD reviewers expect that issues raised in complete response letters will be addressed initially through teleconferences with the agency; eventually GDUFA will provide time and resources for sponsors to meet with OGD reviewers in person to discuss specific complete response letter issues.

Under a phased-in approach, FDA will "review and act on" 60% of ANDA submissions within 15 months by the third year of the program.

Sponsors still may file applications on paper, but FDA does not have to meet user-fee performance goals unless the ANDA is filed electronically, a process that FDA expects will become universal in the near future. FDA would like to see continued improvement in the quality of applications to reduce the frequent back-and-forth questioning that routinely delays approvals. OGD has been encouraging generic-drug makers to adopt quality-by-design (QbD) approaches by issuing sample pharmaceutical development reports with QbD principles for both immediate-release and modified-

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release solid oral dosage forms. The agency recently updated its Question-Based Review system to incorporate QbD models and has tightened initial criteria for filing ANDAs to discourage incomplete submissions. OGD has established a central system to track the progress and status of each application as it moves through the review process, and a broader OGD quality management system aims to clearly document procedures to provide more consistency across review divisions. Some of the GDUFA revenues also will support development of further guidance and research to facilitate development of more complex generic products, such as anti-epileptic drugs and inhaled products.

FDA held a public meeting in September to review with manufacturers these and other program implementation issues. GDUFA policies also were a prime topic at the PDA/FDA Joint Regulatory Conference on September 11, 2012 in Baltimore and at the fall technical conference on Oct. 2-3 sponsored by the Generic Pharmaceutical Association.

Implementing GDUFA will involve a significant expansion in OGD staff on all levels, along with extensive training for new hires and expanded IT systems. To provide the broader management structure needed to oversee this more complex generic drug program, CDER director Janet Woodcock recently announced plans to elevate OGD to a "super office" with other offices reporting to it. Instead of being part of CDER's Office of Pharmaceutical Science (OPS), OGD will be a parallel umbrella organization, similar to CDER's Office of New Drugs and Office of Compliance. New OGD director Greg Geba will head the super OGD, reporting directly to Woodcock and better positioned to work with CDER's Office of Executive Programs on GDUFA implementation.

The larger plan is to replace OPS with a new Office of Pharmaceutical Quality (OPQ), which will be responsible for overseeing drug quality throughout the product lifecycle. The new OPQ will absorb certain OPS functions as well as some activities performed by the Office of Manufacturing and Product Quality in the Office of Compliance. And, when we went to press, there was considerable anxiety that Congress would fail to enact an FDA appropriations bill by Oct. 1, which is needed for the agency to collect any 2013 user fees. Hopefully, that impass will be remedied by the time you read this report.

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Shifts in Pharma Capital Agendas

Andrew Forman

This year has been marked by flat to declining growth rates, but there are hopeful signs for 2013.

The long-awaited patent cliff that has loomed in the pharmaceutical industry for years has arrived in earnest in 2012, with more than $40 billion in 2011 brand sales facing loss of exclusivity (LOE). Although this year's LOEs were well-anticipated, a confluence of unexpected financial events and negative conditions in key global markets are creating additional challenges for a pharmaceutical industry seeking sustainable growth.

Declining first-half sales for top pharma

Among the leading (top 10 in global revenues) multinational pharmaceutical companies, first-half 2012 sales fell by $8 billion, or 3%, globally from the year-ago period. The Eurozone crisis contributed to this decline as European aggregate sales fell 6% in the first half of 2012, reflecting a weaker pricing environment for branded drugs as well as increased generic-drug substitution.

Emerging markets have been a growth driver for pharma in the last several years, with aggregate sales rising 12% in 2011. It is a different picture for 2012, however, as first-half sales growth for emerging markets decelerated to approximately 7%, principally due to slower growth in gross domestic product and declining transaction volume, particularly mergers and acquisitions. Although pharma's appetite for inorganic growth in emerging markets remains strong, those markets have become increasingly competitive, creating challenges to getting deals done. Also, government policies intended to support local industry are affecting market share and pressuring prices, albeit volume growth generally has remained strong. As a result, some pharmaceutical companies may be concluding that growth could be better realized in markets where uncertainty appears to be decreasing. For all the concerns about the United States, the "known unknowns" in the US may be better than the "unknown unknowns" that characterize some emerging market countries.

Andrew Forman, Transaction Advisory Services, Ernst & Young. The views expressed herein are those of the author and do not necessarily reflect those of Ernst & Young LLP.

Is the US a better strategic choice than emerging markets?

US bolt-on deals back in vogue?

Following the US Supreme Court's decision in June to uphold the *Affordable Care Act* and the US Federal Reserve reaffirming its stance to keep interest rates low through 2014, the US life-sciences industry could be moving into a new phase of heightened domestic deal activity. In the third quarter of 2012 in the US, there were several noteworthy mergers and acquisitions featuring Big Pharma: almost all were under $10 billion in value. These bolt-on deals are likely to continue as a core strategy given that overall industry growth is projected to remain anemic over the next several years.

Dividends and buybacks on the rise

As the pharmaceutical industry faces negative revenue growth, profit growth has waned even after waves of cost-cutting. Companies have responded to shareholders' demands by increasing dividends and buying back stock. The pharmaceutical industry's historic relatively unlevered balance sheets may be changing as debt-to-equity ratios rise to an estimated 18% this year versus 9% in 2007. Also, with payout ratios for many top life-sciences companies hovering around 40% and with less willingness to lever up, this constraints on financial resources mean that megamergers appear increasingly unlikely. For certain multinationals, the answer has been to "grow smaller," by optimizing growth by divesting noncore or underperforming operations. With most of the top pharmas facing similar strategic challenges—modest near-term growth prospects with increased investor scrutiny of capital allocation—we could see a continuation of the recent wave of divestitures.

Hopeful signs emerging

This year is likely to be remembered by new lows in growth rates. Although 2013 appears challenging, too, there are three reasons to view the glass as half-full:

- Several recent FDA approvals in obesity, cardiovascular, and oncology, after a dearth in brand pipeline approvals could revive domestic growth.
- The implementation of healthcare reform in the US could jumpstart growth in 2014.
- Restructuring and diversification into businesses with less exposure to patent cliffs (e.g., consumer, animal-health) are beginning to pay off. For the past several years, the industry has made difficult strategic decisions, cut costs, and expanded into more promising markets while exploring new business models with a goal of achieving more growth with less risk.

Most optimistically, pharmaceutical stocks have recently outperformed the major averages, and for 2012, have pulled even in performance after years of lagging. Forward-looking, investors may be signaling that the worst days are likely behind us. **PT**

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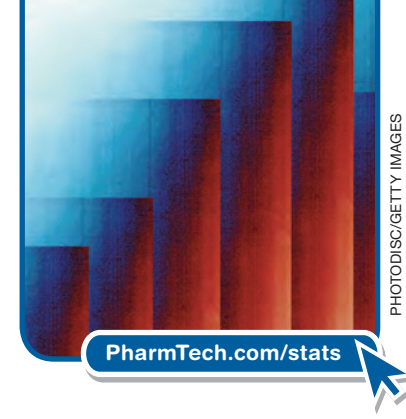

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Tools in Waiting: Time for Evolutionary Operation

Lynn Torbeck

Real-time experimentation may offer continuous process improvement.

Since the mid to late 1800s, statisticians and mathematicians have been developing increasingly useful statistical tools and statistical theory. Statisticians and nonstatisticians alike have readily adopted some of these tools and theories. Exploratory data analysis (EDA), for example, was quickly accepted within and outside the field of statistics (1). Other tools languish forgotten for years and even decades before being accepted by mainstream users. An example is the Plackett–Berman designed approach to experimentation. Published in 1946, the experiments were not appreciated and used until the early 1980s (2).

Evolutionary operation

Another valuable tool that has yet to gain wide acceptance is an optimization technique known as evolutionary operation (EVOP) (3). EVOP is experimentation done in real time on the manufacturing process itself. Small changes are made to the current process, and a large amount of data is taken and analyzed. The changes are small enough that the process still makes acceptable products and remains in a state of control. The small changes are compensated by the large amount of data collected. The designs are simple factorials which, when analyzed, direct the process to a new point of operation that is more optimal for the critical quality attributes. This process is repeated until no further optimization is achieved. Also, for processes that vary with input materials and environment, it is possible to track and maintain optimality over time. This achievement is the ultimate in continuous improvement philosophy.

George Box and Normal Draper, both highly regarded and pragmatic statisticians, stated the goal in the preface of *Evolutionary Operation*. "What originally motivated the introduction of EVOP, however, was the idea that the widespread and daily use of simple statistical design and analysis during routine production by process operatives themselves could reap enormous additional rewards" (4). And it should be said that there would be an increase in quality as well.

Why was this theory not wildly and immediately accepted in the 1970s? Companies had often spent years working to make their processes achieve a certain level of performance. Even if that level of performance was poor, management was not going to let anyone, particularly floor operators, start experimenting with an accepted process.

Are we still at that point today? Yes, but changes in the industry and at FDA may make EVOP a tool whose time has come. The combined intersections of process analytical technology (PAT), risk analysis, quality by design (QbD), the ICH troika of Q8, Q9, and Q10, and the strong emphasis of continuous improvement may provide a window of opportunity.

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Additional tools

The designs in Box and Draper are based on full and fractional factorials. A further discussion with an extensive example can be found in chapter 15 of Box, Hunter, and Hunter (5).

A second design approach uses a simplex or triangle as the basis of the data collection. (See reference 6 for a full textbook presentation.)

Finally, Charles Hendrix states, "Another popular method of optimization works very much like a game of leapfrog. It begins with a patterned set of experiments in all of the interesting variables. (For example, an eight-run Placket Burman or fractional factorial with seven factors.) The pattern is a triangle in two variables, a tetrahedron in three variables, or a simplex (i.e., a multidimensional triangle) in four or more variables. When this pattern of experiments has been run, the experiment that gave the worst result is identified. This experiment is then discarded and replaced by a new experiment according to a definite rule. When the replacement experiment has been run, the worst of the set is again identified and discarded. This continues until no further improvement is observed. This method is called … self directed optimization, or just SDO" (7).

Has EVOP's time arrived? The potential is enormous and worth a serious investigation.

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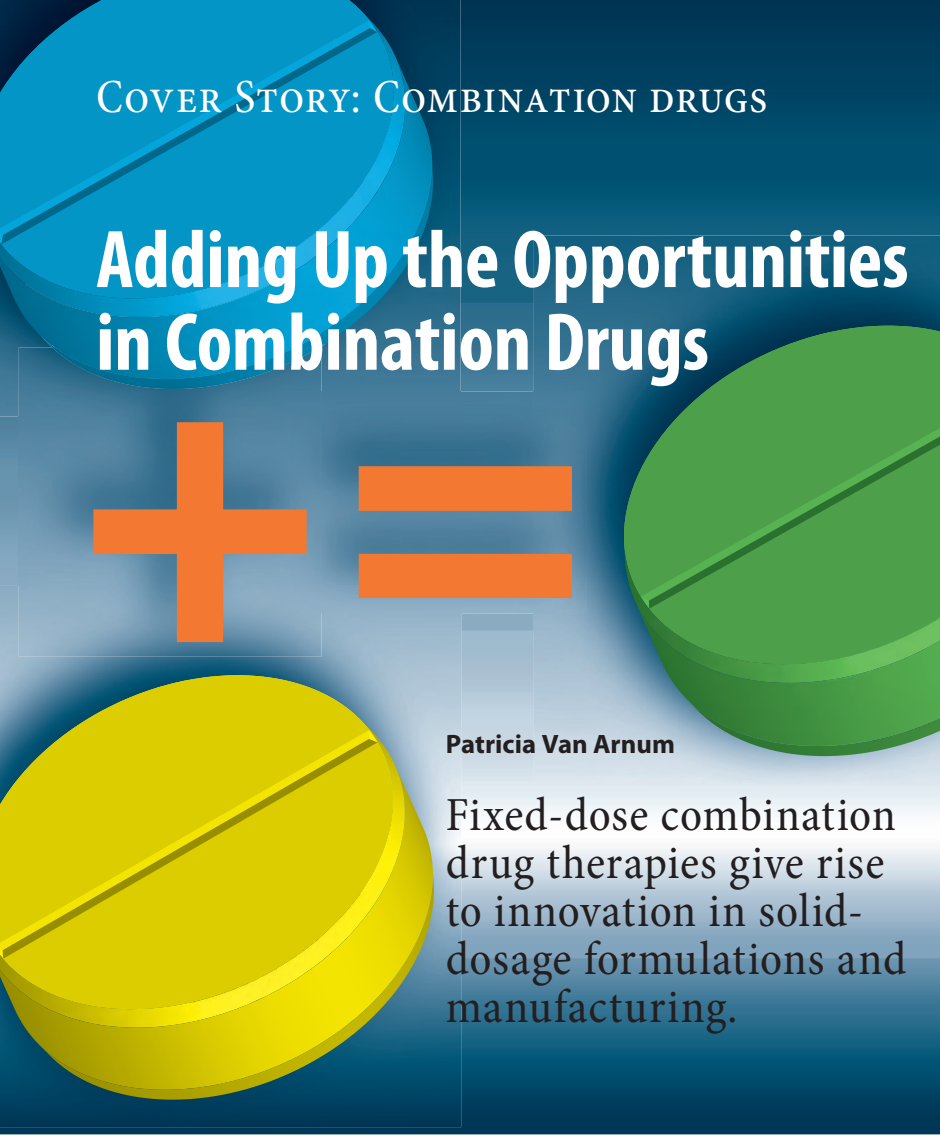

Patricia Van Arnum

Fixed-dose combination drug therapies give rise to innovation in solid-dosage formulations and manufacturing.

As pharmaceutical companies face shortfalls in R&D productivity and increased generic-drug incursion, product lifecycle management becomes increasingly important. Combination therapies provide an opportunity for innovator drug companies to extend the lifecycle of a given API by developing a fixed-dose combination product that may offer improved and synergistic efficacy, improved dosing regimes, and greater patient compliance. Combination drugs also allow specialty pharmaceutical companies to use specialized drug-delivery and formulation strategies for product differentiation. Challenges, however, exist in developing fixed-dose combination products compared with single API products, such as maintaining the physical and chemical stability of the APIs and modulating drug release.

Regulatory framework

Combination products encompass a wide range of products, including drug–device combinations. By regulatory definition, a *combination product* is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product (1, 2). Under 21 *CFR* 3.2 (e), a combination product is defined to include:

- "A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity" (e.g., a monoclonal antibody combined with a therapeutic drug, a device coated or impregnated with a drug or biologic, prefilled syringes, insulin injector pens, metered dose inhalers, and transdermal patches).
- "Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products" (e.g., drug or biological product packaged with a delivery device).
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and...the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose)."
- "Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect" (e.g., photosensitizing drugs and activating laser/light sources and iontophoretic drug delivery patches and controllers) (1–3).

In fiscal year 2011, FDA received 288 original applications classified into nine categories of combination products (see **Table I**). These applications included 26 new drug applications and 134 new investigational new drug applications, of which the majority were drug–device combinations (see **Table I)** (2).

Combination products also include oral fixed-dose combination drugs of two or more APIs in a single product form (i.e., tablet and capsule). According to 21 *CFR* 300.50, "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug" (4).

Market positions

Several high-profile solid-dosage fixed-

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combination therapies recently entered the US market (see **Table II**) with several large pharmaceutical companies either partnering on or singularly launching combination drugs (5). Earlier in 2012, Boehringer Ingelheim and Eli Lilly received FDA approved for Jentadueto (linagliptin and metformin hydrochloride [HCl]) for treating Type II diabetes. In January 2011, Boehringer Ingelheim and Eli Lilly formed a strategic alliance in diabetes, and Boehringer Ingelheim partnered with the CDMO Patheon, in a three-year deal announced in October 2011, for developing fixed-dose combination drugs to treat Type II diabetes. As part of their diabetes alliance, AstraZeneca and Bristol-Myers Squibb developed Kombiglyze XR (saxagliptin HCl and metformin HCl), which was approved in 2010. In August 2012, the companies expanded their alliance following Bristol-Myers Squibb's acquisition of Amylin Pharmaceuticals.

Merck & Co. received approval earlier this year for Janumet XR, an extended-release formulation of its fixed-dose combination of sitagliptin phosphate and metformin HCl (see **Table II**).

Gilead Sciences received FDA approval for two oral fixed-dose antiviral combination products—Complera (emtricitabine, rilpivirine HCl, tenofovir disoproxil fumurate) in 2011 and Stribild (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumurate) in 2012—and received a new indication of treating HIV infection in 2010 with Truvada (emtricitabine and tenofovir disoproxil fumurate). Novartis developed two fixed-dose combination products using aliskiren hemifurmate, the API in its antihypertensive drug Tekturna. In 2010, Novartis received FDA approval for Amturnide (aliskiren hemifurmate, amlodipine besylate, and hydrochlorothiazide) and for Tekamlo (aliskiren hemifumarate and amlodipine besylate). Daiichi Sanyko also used amlodipine with one of its APIs (olmesartan) for the combination product, Tribenzor (olmesartan medoxil, amlodipine besylate, and hydrochlorothiazide), which FDA approved in 2010. Bayer gained approval for several oral contraceptive fixed-dose combinations (see **Table II**).

Formulation strategies

Fixed-dose combination therapies are a challenge. The presence of an additional API or APIs adds complexity to the formulation in maintaining the physical and chemical stability of the APIs, mitigating interactions (i.e., API–API, API–excipient, excipient–excipient), reconciling incompatible pharmacokinetics, and addressing differing drug-release rates and targets in drug delivery. Some ways to address these problems in solid-dosage fixed dose combinations include monolayer tablets, bilayer tablets, trilayer tablets, inlay tables, and pellets or granules in capsules (6).

Recently approved fixed-dose combination products use various strategies. Merck & Co.'s Janumet XR is an extended-release metformin core tablet coated with an immediate-release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film (7). Merck's Juvisync is a bilayer tablet containing sitagliptin phosphate and simvastatin (8). Vivus's Qsymia

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Table I: Number and type of combination drug products for original applications for new drug applications (NDAs), biologics license applications (BLAs), premarket approval applications (PMAs), premarket notifications (510(k)s, investigational new drugs (INDs), investigational device exemptions (IDEs), and humanitarian-use exemptions (HDEs) received in fiscal year 2011 by FDA.

Application type	Combination product category*									Totals
	1	2	3	4	5	6	7	8	9	
Original NDAs	3	20	1	0	0	2	0	0	0	26
Original BLAs	0	0	0	0	1	0	0	0	0	1
Original PMAs	0	0	0	5	0	0	5	0	0	10
Original 510(k)s	2	2	0	62	3	0	2	17	6	94
Original INDs	11	37	10	3	5	29	3	34	2	134
Original IDEs	0	0	0	8	3	0	6	6	0	23
Original HDEs	0	0	0	0	0	0	0	0	0	0
Totals	16	59	11	78	12	31	16	57	8	288

Source: FDA, *FY 2011 Performance Report to Congress for the Office of Combination Products* (Ref. 2).

Combination product key:
1 = Convenience kit or copackage
2 = Prefilled drug-delivery device/system
3 = Prefilled biologic-delivery device/system
4 = Device coated/impregnated/otherwise
5 = Device-coated or otherwise combined with biologic
6 = Drug/biologic combination
7 = Separate products requiring mutually conforming labeling
8 = Possible combination based on mutually conforming labeling of separate products
9 = Other type of combination product.

is a capsule consisting of immediate-release phentermine HCL and extended-release topiramate (9). GlaxoSmithKline's Jalyn consists of one dutasteride soft-gelatin capsule, dissolved in a mixture of butylated hydroxytoluene and mono-diglycerides of caprylic/capric acid, and pellets of tamsulosin HCl with excipients of methacrylic acid copolymer dispersion, microcrystalline cellulose, talc, and triethyl citrate, encapsulated in a hard-shell capsule (10). Reckitt's Suboxone is a sublingual film (11).

Tablets are the main product form for fixed-dose combinations, but other technologies can be used. For example, Procaps, which recently partnered with Patheon in softgel development and manufacturing services, offers its Unigel technology, which provides various forms for fixed-dose combinations, such as a softgel in a softgel, a tablet in a softgel, granules in a softgel, or any combination to address challenges of multiactive formulation (6). The Indian drug manufacturer Cipla is partnering with the Drugs for Neglected

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Table II: Examples of FDA approvals of solid-dosage combination drugs, 2010–2012 (Ref. 5) (Contin. on page 47).

Trade name	APIs	Company	Dosage form (route)	Indication
Amturnide	aliskiren hemifurmate, amlodipine besylate, hydrochlorothiazide	Novartis	Tablet (oral)	Hypertension
Beyaz	drospirenone, ethinyl estradiol, levomefolate	Bayer Healthcare	Tablet (oral)	Contraceptive
Complera	emtricitabine, rilpivirine HCl, tenofovir disoproxil fumarate	Gilead Sciences	Tablet (oral)	HIV infection
Edarbyclor	azilsartan medoxomil, chlorthalidone	Takeda Pharmaceutical	Tablet (oral)	Hypertension
Jalyn	dutasteride, tamsulosin HCl	GlaxoSmithKline	Capsule (oral)	Hypertension
Janumet XR	sitagliptin phosphate, metformin HCl	Merck & Co.	Tablet, extended-release (oral)	Type II diabetes
Jentadueto	linagliptin, metformin HCl	Boehringer Ingelheim, Eli Lilly	Tablet (oral)	Type II diabetes
Juvisync	simvastatin, sitagliptin phosphate	Merck & Co.	Tablet (oral)	High cholesterol Type II diabetes
Kombiglyze XR	saxagliptin HCl, metformin HCl	AstraZeneca, Bristol-Myers Squibb	Tablet, extended-release (oral)	Type II diabetes
Natazia	estradiol valerate, dienogest	Bayer	Tablet (oral)	Contraceptive
Nuedexta	dextromethorphan HBr, quinidine sulfate	Avanir Pharmaceuticals	Capsule (oral)	Pseudobulbar effect
Qsymia	phentermine HCl, topiramate	Vivus	Capsule, extended-release (oral)	Obesity/weight management
Safyral	drospirenone, ethinyl estradiol, levomefolate calcium	Bayer	Tablet (oral)	Contraceptive
Stribild	elvitegravir, cobicistat, emtricitabane, tenofovir disoproxil fumarate	Gilead Sciences	Tablet (oral)	HIV infection

(Contin. from page 46) Table II: Examples of FDA approvals of solid-dosage combination drugs, 2010–2012 (Ref. 5).

Trade name	APIs	Company	Dosage form (route)	Indication
Suboxone	buprenorphine HCl, naloxone HCl	Reckitt Benckiser Pharmaceuticals	Film (sublingual)	Opioid dependence
Tekamlo	aliskiren hemifumarate, amlodipine besylate	Novartis	Tablet (oral)	Hypertension
Tribenzor	olmesartan medoxomil, amlodipine besylate, hydrochlorothiazide	Daiichi Sankyo	Tablet (oral)	Hypertension
Truvada	emtricitabine, tenofovir disoproxil fumarate	Gilead Sciences	Tablet (oral)	HIV infection

HCl is hydrochloride; HBr is hydrobromide.Janumet XR was approved in 2012; Janumet was approved in 2007. Suboxone (sublingual film) was approved in 2010; the tablet (sublingual) form was approved in 2002 and was voluntarily withdrawn from the market by Reckitt Benckiser in Sept. 2012. Truvada was approved in 2010 treat HIV infection and in 2004 for use in combination with other antiviral agents.

Diseases initiative (DNDi) to develop a four-in-one fixed-dose combination antiviral therapy using a "sprinkle" formulation of lopinavir and ritonavir, combined with one of two other antiviral APIs, abacavir/lamivudine or zidovudine/lamivudine. Cipla is developing a sachet product in which the four antiviral drugs will be in tastemasked and put in granular form for mixing into food or liquids with the aim of registering the drug by 2015, according to a July 20, 2012, DNDi press release.

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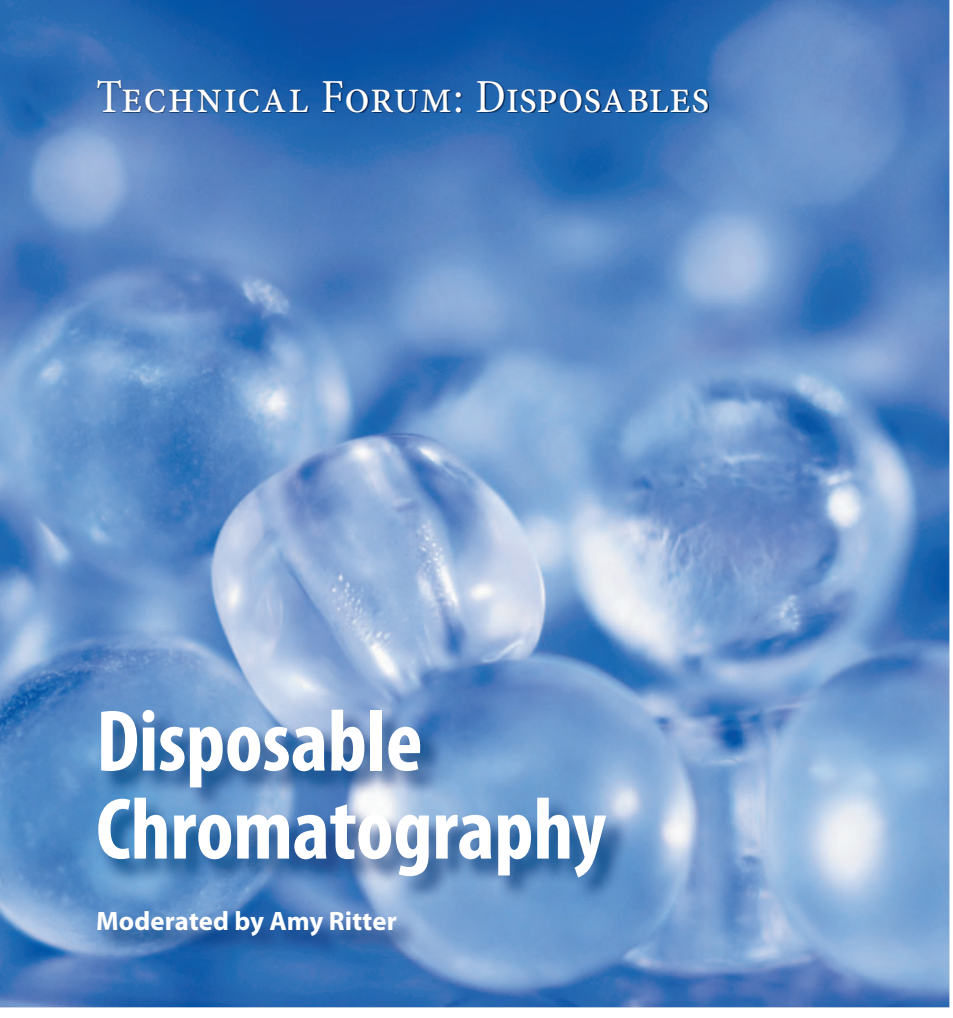

Disposable Chromatography

Moderated by Amy Ritter

Disposables have been widely adopted for commercial-scale bioprocessing, but use of these technologies for downstream processing has lagged behind that for other applications. PharmTech spoke with industry experts about the challenges of implementing disposable chromatograpy systems.

Participating in the roundtable are Eric Grund, PhD, senior director of biopharma applications at GE Healthcare, Marc Bisschops, PhD, scientific director at Tarpon Biosystems, Tracy Thompson, CEO of Polybatics, Fred Mann, PhD, program manager, biopharm process solutions at Merck Millipore, and Stephen Tingley, vice-president, bioprocessing sales and marketing at Repligen.

Barriers to implemetation

PharmTech: Chromatography has been one of the last components of the bioprocessing train to be adapted for single-use. What are the constraints of the chromatography process that have proved challenging to implement in single-use format?

Grund (GE Healthcare): The biggest constraint to single-use is probably a mental barrier based on a narrow view of the pros and cons. Chromatography media are often very tolerant to cleaning and withstand re-use, so it's tough to throw them away after single-use, especially if tests show they still perform well after many cycles. The benefits of speed, facility flexibility, facility output, and avoidance of cleaning are not yet fully appreciated.

Bisschops (Tarpon Biosystems): This statement is absolutely true for applications that involve capture of the product and/or some high resolution polishing steps. For flow-through applications (or negative chromatography), membrane adsorbers have already paved the way for disposable chromatography.

One of the most important reasons why chromatography has not been available in a disposable format is caused by the nature of the chromatography process itself: it is essentially a mass driven process, where the size of the column is governed by the amount of product that needs to be bound. For membrane processes and other flow-through applications, the most important system dimensions are determined by the volume that needs to be processed.

As a result, the successful introduction of disposable bioprocessing has largely been enabled by the process intensification that resulted from the increases in expression levels over the past decade. In essence, this has allowed us to produce the same amount of product with much less water and hence with a significantly reduced volume. All volume-driven unit operations have benefited from this, whereas the mass driven processes were not affected.

Everybody acknowledges that the costs of chromatography media currently are too high to justify a single-use application. These costs need to be depreciated over many cycles in order to make the economy work. This hampers the translation of batch-wise chromatographic processes into a single-use or disposable application, unless one uses a technology that would allow one to use the media over so many cycles in a single batch or in a campaign.

Thompson (Polybatics): Columns are very expensive systems, and the cost of buying these large chromatography systems is a cost that companies are reluctant to walk away from. Also, the cost of buying the resins themselves are fairly expensive, particularly Protein A. Protein A has been on patent until around March 2010, so there's been a monopoly on that particular ligand, which has maintained a very high price of the resin. I think those two factors have been a real impediment

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to going to a disposable chromatography system. And there hasn't been anyone out there who has come up with a format that is truly comparable to traditional packed-bed chromatography in terms of its ability to purify and capture the target.

In terms of implementation, packing of the columns is very fussy. You pump a slurry into the column, and have to let it settle. If it doesn't settle quite right, you can get voids in the column, and you have to pack again. There's a lot of art in packing the column to get it to perform right. One of the problems of implementing a disposable system is finding a medium that can either be pumped into fixed columns or finding a complete cartridge that is kind of plug-and-play. Until recently, there haven't been those kinds of plug-and-play systems.

Mann (Merck Millipore): Chromatography processes, while not fully single-use, have been operating in a hybrid way for some time with the implementation of single-use bags for buffers and product collection. Elimination of stainless-steel tanks and replacement with single-use bags is, together with the use of single-use bioreactors, the biggest contributor to cost savings when comparing single-use to traditional stainless-steel facilities. This is due to the elimination of clean-in-place (CIP) and steam-in-place (SIP) for tank/vessel cleaning. In contrast, the chromatography system is cleaned by process buffers including sodium hydroxide and does not need a separate CIP system.

Constraints of the chromatography process that make it difficult to implement as a disposable system include first, the greater complexity of the flow path in chromatography systems compared with other unit operations, for example the number of valves required to enable multiple buffer inlets, column flow reversal and bypass and fraction outlet. Coupled to this has been the greater number of different sensors deployed and the operating range and accuracy required of those sensors. Second, the cost of chromatography resins, especially the affinity resins such as protein A, has meant they tend to be used for multiple batches requiring cleaning and storage between times and so are not seen as single-use per se.

No one has come up with a format that is truly comparable to traditional packed-bed chromatography in terms of its ability to purify and capture the target.
— Thompson, Polybatics

Tingley (Repligen): If we take a look at the process as a whole, and we look at the adoption curve of single-use technologies, you can essentially split the process into functional and nonfunctional technologies. It's the nonfunctional technologies that have taken the lead because they've been easier to implement and easier to get to an economical cost point than the functional technologies. Examples of nonfunctional technologies would be replacing stainless-steel pipework with plastic tubing, or replacing stainless-steel tanks with plastic bags. When you start looking at the process, for instance, a bioreactor or filtration technology such as ultrafiltration or microfiltration, these are examples of functional technologies, which have to be disposable. Making functional technology costs money, and functional technologies are often reused to defray some of the costs.

It just so happens that one of the most complex of the functional technologies is purification. That includes capture, using Protein A which we know is an extremely expensive chromatography resin, and hydrophobic interaction or ion exchange or multimode resins which are also reasonably expensive. And processes use a lot of them—that's multiple tens of liters multiplied by multiple thousands of dollars. With chromatography, it's a very expensive, very critical functional technology that is hard to get into a single-use format. So, there are two parts of the problem: can you make a disposable or single-use container for the chromatography, that is, a column, and then, can you make a single-use media or functional element to go into that. That's the problem that's made it so intractable.

When people want to move to single-use technologies, they may be reducing column sizes and cycling them harder. What users are doing is making the media work harder, so it's less painful to throw it away. What you're seeing today is companies offering the easy part, the containment part, of the disposable chromatography, the column shells, and packing them. The difficult part of the technology is finding new ways to stretch the economics of running longer, running smaller batches, cycling the columns more often, and things like that.

Choosing a disposable platform

PharmTech: A few disposable chromatography platforms are currently available, including packed-bed, simulated moving bed (SMB), and membrane chromatography. What are the factors that would influence the choice of platform for a process?

Grund (GE Healthcare): Packed beds are used in steps following feed clarification, when binding capacity and resolving power are prioritized. Conventionally, the first step in downstream purification is product capture, in bind/elute mode, and a packed bed is needed to achieve the objectives of the unit operation.

The question of whether or not to use SMB is different. Frequently, a small number of cycles is used to handle large volumes of feed. SMB takes this further by providing a continuous processing approach with several small columns cycled in sequence. Generally, SMB offers higher loading capacity, greater exploitation of resin life, and more efficient use of buffers. So, SMB can be a door-opener to using disposable chromatography columns because small columns are used for multiple cycles to handle material from the bioreactor. This helps address the cost equation because the resin is used for many cycles before disposal. Accurate control and synchronization of the different phases in the chromatography cycle is critical. Single-use components are attractive in SMB since they assure reproducible performance and avoid multiple column-packing in the production workflow. The downside in SMB is system com-

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plexity. Multiple columns require many valves and sophisticated control to assure accurate column switching without cross contamination.

Chromatography is also used in product flow-through mode to remove impurities. The further downstream you are in your process, the fewer the impurities. When there are only small amounts remaining, membrane chromatography is attractive for impurity scavenging. The low binding capacity and low resolving power is not an issue and the high flow rates that can be used can be fully exploited. Single-use components are often preferred for scavenging, especially because cleaning may be challenging for several reasons.

If the product is a monoclonal antibody, then likely there is a template already in place for purification. — Mann, Merck Millipore

For producing tons of product, the column volumes are large, several hundred or even thousands of liters, and at this size, single-use designs are not viable. In general, the smaller the scale, the more attractive single-use chromatography is.

Bisschops (Tarpon): First of all, disposable technologies will generally result in more flexibility in manufacturing and in a shorter change-over time. These features are particularly important for multiproduct facilities such as clinical manufacturing facilities and contract manufacturing organizations. For these types of operations, the advantage of disposable bioprocessing technologies is more obvious than for single-product facilities.

Prepacked chromatography columns fit very well in streamlining the workflow in a facility by taking away the packing operations. The costs for prepacked columns were, until recently, cost prohibitive to consider them as a single-use or disposable product for other applications than clinical manufacturing. The scale limitations of prepacked columns also restricts the application of this technology to clinical-scale manufacturing.

SMB enables manufacturing of large amounts of product with reasonably small columns, which are cycled many times during a batch. As a result, this technology can make prepacked disposable chromatography a viable alternative, especially when you pair disposable columns with a fully disposable, simplified valving system. Disposable valving is the missing link in providing economically viable, fully disposable downstream processing for bind/elute applications. Another feature of continuous chromatography is that it allows the entire cascade of downstream processing unit operations to be operated as a fully continuous train. This continuity eliminates or significantly reduces interstage product hold steps and allows multiple unit operations to be operated simultaneously. Thus, the time in facility can be shortened by a factor of two, which in many cases translates into a significant increase in facility throughput.

Mann (Merck Millipore): Probably, the specific application is the first criterion, in so much as to how much freedom there is to pick and chose a chromatography platform. For instance, if the product is a monoclonal antibody, then likely there is a template already in place for purification, typically protein A affinity chromatography, followed by cation exchange bind-elute and then anion exchange flow through. Both the protein A affinity and cation exchange are almost certainly going to be conventional packed-bed columns. Although traditionally the anion exchange was also a packed-bed column, anion exchange flow through membrane adsorbers are being deployed because of convenience (i.e., no column packing) and buffer savings (i.e., no cleaning/reuse).

Membrane adsorbers are also finding application elsewhere when used in flow through mode for capture of impurities. Generally, they are less competitive with conventional packed columns for bind-elute applications because of lower capacity compared with resins.

SMB is relatively new to biotech. While frequently used for small molecule purification, it has not found adoption in protein separations primarily due to the greater complexity of the flowpath and the difficulty with engineering it in a sanitary manner. The new single-use systems coming onto the market may address that aspect, but the added complexity of operation compared to conventional batch chromatography will likely continue to be a hurdle to adoption. One attraction of SMB or similar multicolumn approaches is that, compared with batch, it uses smaller columns that make it more amenable to prepacked columns and coupled to the fact that the resin is cycled more times per batch. This has benefits especially for clinical-scale batches where, conventionally, the resin may be thrown away after only a few batches and so is nowhere near its end of life point. Multicolumn approaches enable better resin utilization, getting closer to the lifetime of the resin and thus saving cost.

The second criterion is probably scale, which is linked to cost. Although single-use implementation shows clear cost benefits at the smaller pilot/clinical scale manufacturing, at large commercial scale, stainless-steel installation can be more cost-effective. In addition, larger scale will require larger columns than currently available in a prepacked, disposable format.

Tingley (Repligen): In stepping back a little bit, you can ask—why do people want to adopt single-use technologies? I don't think the answer has changed as we've changed the technologies—it's speed—getting through the process quicker, being able to develop multiproduct facilities, being able to put more molecules through a facility in a short period of time. This is the reason why the disposable trend has developed and has been so successful over the past 15 or 20 years.

When you look at chromatography and ask what do people want to do with a disposable system, there are two answers. At one end of the continuum are users who really want to use chromatography columns the way they've always used chromatography columns, they just don't want to pack them any more. At the other end of the continuum are companies that have built truly single-use platforms, and don't have any capability to manage hardware. These companies are buying disposable

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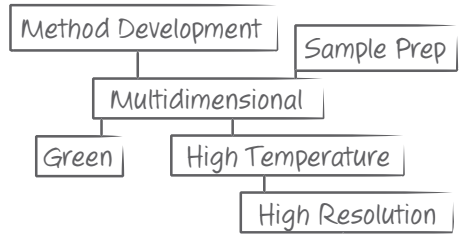

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columns and they're throwing away the columns and the media, because although on a per-process basis it may seem expensive, in terms of the overall operation, they get the economy of scale. Users operate on a continuum, and you see systems ranging from pure disposables to hybrid facilities. So, when you ask what factors influence the choice of platform, the answer for me is that the traditional process and the traditional technologies are the number one drivers. How do people get the convenience of disposables doing what they do today?

In addition to packed columns, there are also alternate technologies such as membranes that are good for some of the flow through applications. I think it's still early days, but some of these technologies are working well and tend to be in smaller processes.

Barriers to adoption

PharmTech: What barriers do you see to more widespread adoption of single-use chromatography?

Grund (GE Healthcare): Weighing up the pros and cons will give a different answer from case to case and it really depends on the application in question. Not all applications are best suited to disposable chromatography columns, speed is not the only goal. Operational efficiency can be addressed in other ways and many hybrid solutions are possible. Another factor is obviously that large, hard-piped facilities in existence around the world—dedicated to a small number of products—can operate very economically and there is little motivation to refurbish them. There are also many smaller facilities based on conventional stainless-steel approaches and these will probably only be replaced with single-use components when the pressure on flexibility and facility throughput is high.

The strongest push towards single-use is in multiproduct facilities that switch products frequently, especially at small scale, for example, in process development, production for clinical trials, or contract manufacturing. Here the barrier is more related to a conservative attitude with general reservations about using disposables. Manufacturers are concerned with issues such as risks from leachables, poor documentation, and increased risk of operator error.

Bisschops (Tarpon): One of the most important barriers to introducing disposable chromatography is most likely the sunk capital in legacy facilities.

We do see, however, a growing trend in even existing legacy facilities moving to disposables in process steps where the facility design itself becomes a limitation either because of increasing titers, holding tank capacity, or water-for-injection capability. This is where disposable continuous processing can have a huge impact.

A second barrier is the availability of true single-use devices or prepacked columns. While single-use membrane adsorbers are being adopted, especially for flow through applications, the relatively lower capacity compared with resins limits its application for bind-elute applications. Consequently, higher capacity membrane or similar device format could facilitate adoption. Alternatively, or in combination, lower cost, prepacked columns would make single-use operation more attractive.

At one end of the continuum are users who really want to use chromatography columns the way they've always always used chromatography columns.
— Tingley, Repligen

Thompson (Polybatics): I think one of the challenges that equipment suppliers haven't really addressed is the cost issue. Single-use manufacturers haven't really addressed the cost aspect—they've just shifted them from one-time upfront to ongoing operational expenses. I think you have to get to a 30% savings or more before manufacturers will take the investment they have in existing processes and systems and shift them. Otherwise, there just doesn't seem to be the economic incentive to shift to disposables.

Will there ever be a completely disposable system? There will still be some components of any system, whether it's membrane or resin-based, that will be reusable. I do believe there will be systems on the horizon as technologies evolve that are truly disposable. Whether that means systems that are single-use, or say, 10 uses for a campaign… My suspicion is that it will be more along the lines of using a unit for a campaign, then once the campaign is done you get rid of it. So you still get the benefits of disposablility but leverage some of those costs over 10 or 20 cycles.

Mann (Merck Millipore): One barrier is the availability of systems, including systems that have gradient capability. Greater capability and system choice will likely drive adoption.

Tingley (Repligen): For me, the way to get adoption of these chromatography products is to make them easy to adapt to what people are doing now. If they can get a prepacked column that's prepared in exactly the same way as their glass column, that's used exactly the same way as their glass column, and gives exactly the same results as their glass column, that will be the first step in making chromatography disposable. With that, I think, will come pressure to look for alternatives to make chromatography truly single-use.

From a vendor's point of view, for years we've been having great conversations with the biopharma industry about introducing new technologies and making changes. But, the actual adoption rate of game-changing technology is poor. Just because of the way we do things in this industry, we're more likely to be evolutional than revolutional. As long as people can think about how they can use the product as a disposable or semidisposable step and it makes sense to them, then they can easily see it fit within the confines and contraints of their own company's regulatory philosophy and guidance, and it's an easy step to make. This is what will take us down the path to truly game-changing technology in the years to come. **PT**

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Outsourcing Pharmaceutical Infrastructure Operations

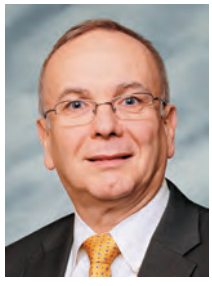
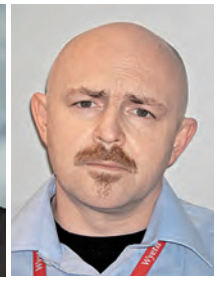
Mel Palmer and David Lyons

Key considerations for outsourcing energy services.

Today's pharmaceutical companies are striving to reduce costs and maximize efficiencies, while simultaneously working to advance the core business as quickly as possible, and must make decisions on the best way to deploy their limited resources. The job of an operations manager for a modern pharmaceutical facility includes operating and maintaining outlying building services and the utilities required to create and sustain on-site manufacturing capabilities, energy management, and essential non-manufacturing services, such as cleaning, building maintenance, catering, and other ancillary services. Outsourcing some or all of these services is a proven solution to optimize efficiency.

Outsourcing rather than out-tasking

In out-tasking, pharmaceutical technology and manufacturing companies utilize third-party vendors to carry out various maintenance tasks on specialized equipment, such as water-for-injection (i.e., stills) or compressors and boilers, while leaving the responsibility for the quality and scope of the work and the internal documentation in the hands of the client. In contrast, when the operations and maintenance program includes regular, preventive, and predictive work, as well as corrective tasks and technical support, then the client is operating under the outsourcing model. In other words, outsourcing involves contracting a whole function, rather than a specific task. Greater savings and efficiencies are found in outsourcing, rather than out-tasking.

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Greater savings and efficiencies are found in outsourcing, rather than out-tasking.

Outsourcing energy services

Implementing highly reliable energy solutions at research and manufacturing facilities is a significant challenge for pharmaceutical companies. The traditional model has been to run a facility with the company owning, operating, and maintaining all equipment itself, thus assuming exposure to risk on issues such as equipment durability, fuel volatility, and maintaining the expertise required to keep the system working properly in-house. Pharmaceutical facilities, however, are increasingly embracing the outsourcing model.

The outsourcing service provider can be contracted to operate and maintain complex energy plants and ancillary equipment, such as:

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- Plumbing/sanitary systems
- General building maintenance.

After the outsourced service provider has been selected, the client and service provider should agree on a well-defined scope and clear objectives, which should be captured in a service level agreement (SLA). Using a risk-based approach, the scope and responsibility of the service provider can be built up over time, which will ensure client satisfaction, specifically around regulatory compliance. However, it is important that the client does not relinquish all responsibility, as the ultimate regulatory responsibility lies with the product manufacturer.

Identifying a key subject matter expert to serve as a liaison between the service provider and client will ensure compliance to quality and regulatory systems. The expert should also design escalation and process flows for change controls and equipment deviation, which pose the most risk to the pharmaceutical manufacturer. For the service provider, customer satisfaction and adherence to quality systems in this highly regulated industry are essential.

The client and service provider can develop a performance scorecard that is linked financially to the service agreement contract. Key performance indicators (KPIs) can include areas such as safe systems of work, system availability, and performance against schedule. Each line item can be linked to a performance metric, and each metric can be weighted with agreed-upon scoring criteria that is reviewed and scored on a periodic

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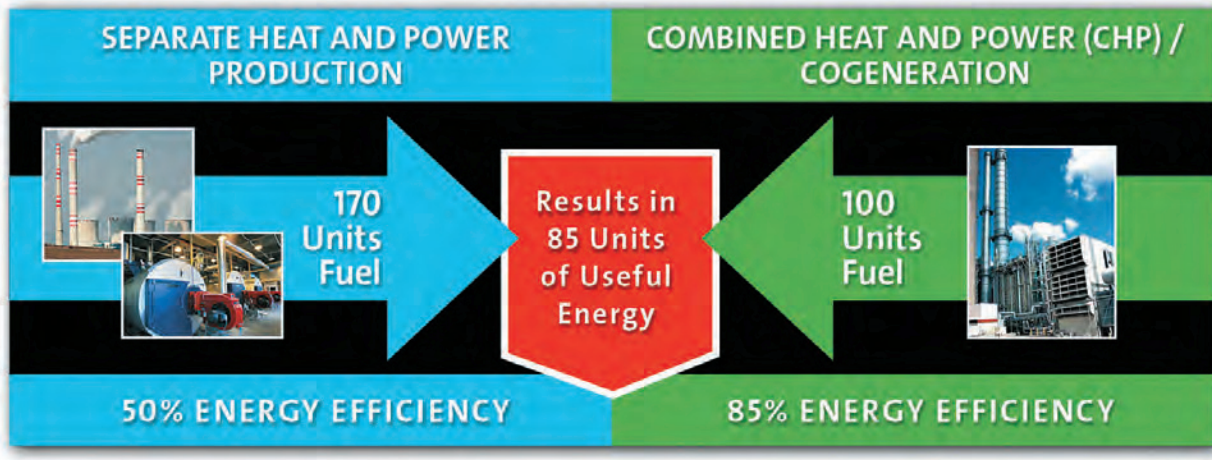
Figure 1: Comparison of separate heat and power generation with cogeneration.



basis (e.g., monthly, quarterly). Linking the score to contract payments, by withholding an agreed-upon percentage each quarter, drives performance from the service provider's point of view and ensures client satisfaction. As the relationship between the service provider and client evolves, or as business expands, it is common to review and adjust the KPIs.

Outsourcing maintenance allows the client to reduce costs without reducing core-business company headcount and, as the pharmaceutical company becomes the customer of the service provider, to more easily drive change and continuous improvement. Outsourcing also allows management to focus on developing and manufacturing the product rather than on the non-manufacturing activities involved in facilities engineering.

Leveraging combined heat and power

Another key advantage of outsourcing energy management is that full-service outside providers possess the expertise to evaluate, design, build, and then operate technologies such as combined heat and power (CHP) to optimize energy efficiency. CHP, sometimes referred to as cogeneration, is an efficient energy technology that simultaneously generates power (i.e., electricity) and thermal energy, which is used for heating, cooling, and production of high-pressure process steam, while typically consuming only 60% of the fuel required for separate processes (1). **Figure 1** illustrates the higher energy efficiency of CHP compared to separate heat and power production. CHP technology is currently experiencing a resurgence in pharmaceutical facilities due to its many operational benefits. CHP can provide increased energy reliability, greater fuel flexibility, and market responsiveness. CHP can also mitigate lost products and research projects due to utility grid failures. CHP reduces greenhouse gas emissions; the waste heat generated during the power production process can be captured, recycled, and used for process applications without the need for boilers within each building.

CHP is a proven solution for industrial manufacturing environments, in which reliable power is crucial. According to the US Environmental Protection Agency's (EPA) Combined Heat and Power Partnership, 88% of existing CHP plants are utilized for industrial purposes (2). The other 12% are used by commercial and institutional entities such as hospitals, municipal and state governments, colleges, and universities. With a full-service outsourcing provider, designing, building, and operating complex energy infrastructure may be achieved seamlessly.

Customers that implement CHP typically experience the following benefits:

- Cost savings. Burning less fuel generates cost savings. CHP users avoid buying from the market at peak price periods. CHP can also be configured to use locally-sourced renewable fuels.
- Reliability. Utility power outages will not interrupt CHP operations, so critical processes continue uninterrupted.
- Environmental benefits. Greenhouse gas emissions and criteria air pollutants are reduced when less fuel is combusted.
- Fuel diversity. CHP plants may be designed for input of multiple sources of fuel. This multi-fuel ability increases energy security and can also mitigate volatility in fuel commodity prices.

Conclusion

Outsourcing may seem like a simple concept, but the potential benefits are significant, especially when complex energy infrastructure must be operated and maintained at the highest levels of reliability. Pharmaceutical research and manufacturing processes are costly to operate, so outsourcing the facility's energy plant operations and management can be a solution to control costs, reduce fuel and energy consumption, and evaluate and implement energy solutions and technologies that can ensure the integrity of the underlying processes.

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1. EPA, "Efficiency Benefits," www.epa.gov/chp/basic/efficiency.html, accessed June 20, 2012.
2. EPA, "Combined Heat and Power FAQ," www.epa.gov/chp/documents/faq.pdf, accessed June 22, 2012. **PT**

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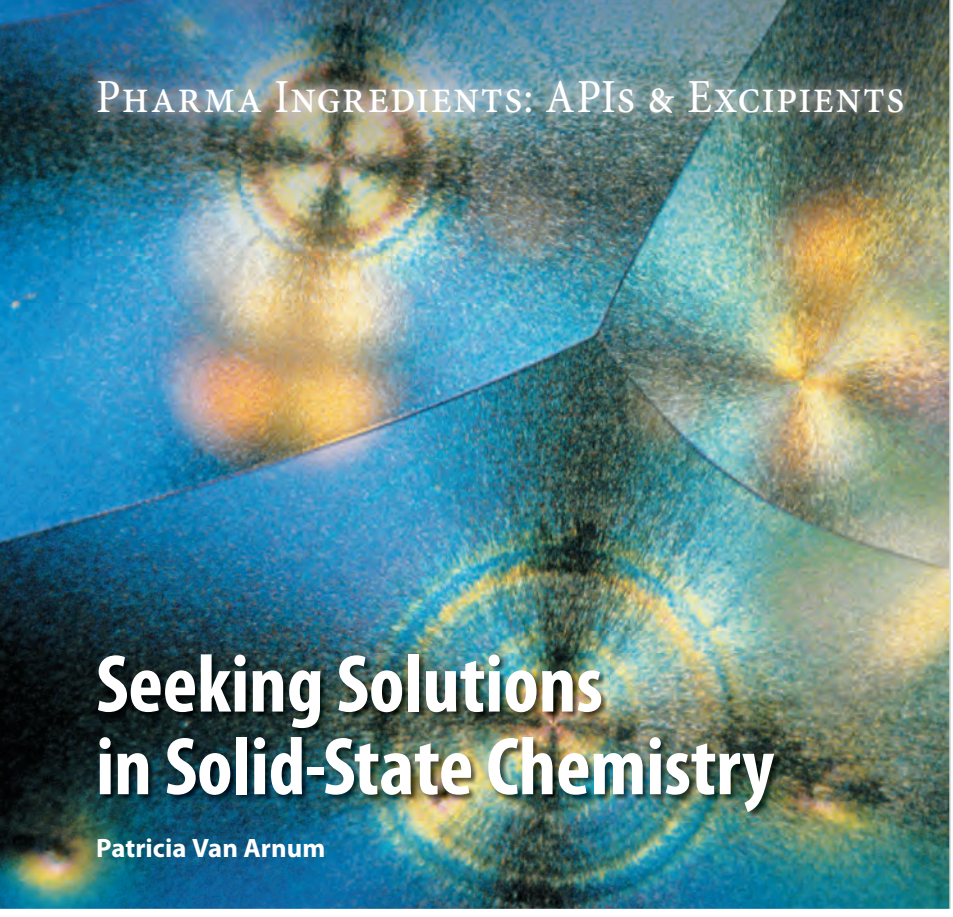
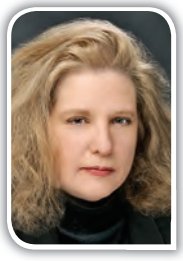


Seeking Solutions in Solid-State Chemistry

Patricia Van Arnum

Particle-engineering technologies, such as crystal design for controlling crystallization and producing cocrystals, particle-size reduction, and amorphous solid dispersions, help to optimize delivery of a drug.

The physical form of an API is important in formulation development for resolving issues in bioavailability and solubility. Particle-engineering technologies can be applied in various ways: crystal design for controlling crystallization and producing cocrystals; particle-size reduction, achieved through jet-milling, wet polishing and nanoparticle generation; and amorphous solid dispersions, produced by several approaches, such as spray-drying (including as inclusion complexes), hot-melt extrusion (HME), and spray-congealing. *Pharmaceutical Technology* discussed these issues with Colin Minchom, vice president, of the Particle Design Business Unit at Hovione.



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Crystallization

PharmTech: Under what type of situations would crystallization be used? How does it facilitate the delivery of poorly soluble drugs?

Minchom: Interest in cocrystals has increased in recent years, and the recent FDA guidance on a proposed classification of cocrystals has prompted further discussion and counter proposals from the industry. The proposed US FDA classification of cocrystals as crystalline materials containing two or more molecules in the same crystal lattice is limited but can serve as a starting point for discussion.

The addition of a cocrystal former into the crystalline structure of the API changes its physical and chemical properties. It is possible, in some cases, to improve bioavailability to adequate levels while preserving the stability of a crystalline form. For APIs with low glass-transition temperatures, a cocrystal may be favoured over the amorphous form. As such, the use of a cocrystal may be an attractive platform to overcome the solubility limitations of Biopharmaceutics Classification System Class II and Class IV drugs.

Cocrystal formation is a favored approach for increasing apparent aqueous solubility for poorly water-soluble molecules that have no ionizable groups, and for which salt formation is not possible, or for where the physical properties of the salts formed are not desirable. Solvates and hydrates are well-accepted crystal forms. In many ways, a cocrystal can be thought of as a solvate, but one whose components are solid at room temperature. The cocrystal will form if the resulting crystal is thermodynamically more stable than the components. Resulting cocrystal properties are dependent upon many factors, including the starting properties of the API, the physical properties of the co-former and the mechanism by which the cocrystal is formed. To increase the probability of success, we [Hovione] recommend that at early-development stages to test other proven platforms, such as solid dispersions, micronized and nanosized crystals and inclusion complexes.

PharmTech: Controlling nucleation during crystallization is an important task. What are the mechanisms for controlling crystallization?

Minchom: Where milling techniques can be thought of as top-down sizing techniques, controlled crystallization is where the desired particle-size distribution is achieved from the bottom up. The objectives of a crystallization process are twofold. On the one hand, the aim is to isolate the API in the right crystal form, typically a polymorph that provides the required level of exposure and stability. On the other hand, crystallization may also be a purification stage, whereby the impurities remain mostly dissolved in the mother liquors.

The kinetics of crystallization (nucleation and crystal growth rates) are driven by the imposed supersaturation levels. The degree of supersaturation,

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temperature ramp, mixing, filtration and final drying process all contribute to the final particle-size distribution. Moreover, the relative importance of each factor can change at each scale.

Particle-size reduction

PharmTech: What factors determine particle size? What are the differences in particle size achieved through jet-milling, wet polishing, and nanoparticle generation?

Minchom: Particle-size reduction is not a simple phenomenon. The mechanism of generating the material of the prescribed particle size has a profound effect upon a range of physical properties that may have a significant effect on the resulting pharmaceutical behavior. The final particle size of a material subjected to a comminution process is dictated by particle attributes, such as crystal hardness, morphology, and original crystal size, as well as the size-reduction method and energy applied. Jet-milling and wet polishing may generate materials with equivalent median particle sizes; however, the resulting span from jet-milled material is likely to be wider than the wet-polished material. Amorphous material and highly reactive surfaces also may result from jet-milling while a higher level of crystallinity is maintained with wet polishing.

Dry methods, such as jet-milling, tend to be more cost-effective (mainly because they do not require sophisticated isolating techniques), but they are more aggressive, less reproducible, and more limited in terms of the achievable size reduction.

Amorphous solid dispersions

PharmTech: What factors determine which method (i.e., spray-drying, HME, spray-congealing, and inclusion-complex generation) to use to produce the amorphous solid dispersion?

Minchom: Amorphous solid dispersions represent a tremendous opportunity for solubility enhancement of oral drugs. The resulting supersaturation levels (and hence bioavailability) and the physical stability of the final dosage form, however, depend on the manufacturing method applied. Many approaches are available to generate amorphous solid dispersions.

Spray-drying, being a solvent method, is the most versatile technique to obtain solid dispersions due to its gentle process conditions and much wider formulation options. Spray-drying is a technology that works well in nearly every compound. Another advantage of spray-drying is that it can be effectively operated using much smaller quantities of drug substance, thereby making it the most cost-effective option during early-stage development.

Melt methods, such as HME and spray-congealing, on the other hand, are more cost effective at the larger scale manufacturing and have the additional advantage of being solvent-free techniques. To use these methods, however, the compound needs to be soluble in the polymer/matrix and physically stable complexes need to be created. These methods are also limited to drug substances that can sustain relatively high heat loads. All these techniques are relatively well-established within the pharmaceutical industry, although spray-drying is a step ahead in terms of maturity.

Although challenging at a very small scale, the rationale design of an HME formulation is viable when the API is available in pilot-scale quantities. Where an API has low solubility in all preferred spray-drying solvents or retains extensive solvent following drying, HME may represent the best way forward for the development of a stable amorphous solid dispersion. Spray-congealing can uses a number of lipophilic excipients, which are useful in formulating poorly water-soluble compounds that will form self emulsifying drug-delivery systems (SEDD) or self micro-emulsifying drug-delivery systems (SMEDDS) on administration, as well as the polymers commonly used in spray-dried amorphous solid dispersions. **PT**

Applying acoustic levitation for elucidation of amorphous material

Researchers at the US Department of Energy's Argonne National Laboratory have discovered a way to use sound waves to levitate individual droplets of solutions containing pharmaceuticals (1). The research facilitates the process for placing drugs from solution into an amorphous state.

The researchers applied an acoustic levitator that uses two small speakers to generate sound waves at frequencies slightly above the audible range at approximately 22 kilohertz (1). With the proper alignment of the top and bottom speakers, the speakers create two sets of sound waves that produce a standing wave. At certain points along the standing wave, there is no net transfer of energy. The acoustic pressure from the sound waves is sufficient to overcome the effect of gravity, thereby allowing light objects to levitate when placed at these points in the standing wave (1). A video showing the technology may be found at the laboratory's website (www.anl.gov/videos/acoustic-levitation).

The technology now can produce only small quantities in an amorphous state, but it is considered a useful tool in elucidating the conditions that optimize producing amorphous material.

Argonne National Laboratory's Technology Development & Commercialization Division is developing a patent for the method and is evaluating the technology for licensing for commercial development with pharmaceutical industry partners (1).

Chris Benmore, an X-ray physicist at Argonne National Laboratory, led the study and teamed with various scientists for adapting the technology for drug research. These scientists include Professors Stephen Byrn and Lynne Taylor in the Department of Industrial and Physical Pharmacy in the College of Pharmacy at Purdue University (US) and Professor Jeffrey Yarger of the Department of Chemistry and Biochemistry at Arizona State University (US) and director of the university's Magnetic Resonance Research Center. The researchers also are now working on identifying drugs most suited to applications with the acoustic levitator.

Source

1. J. Sagoff, "Real-world Levitation to Inspire Better Pharmaceuticals" (Argonne National Laboratory Information, Argonne, IL), Sept. 12, 2012.

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Advancing protein crystallization: microgravity effects and predictive models

Elucidating the structure and sequence of proteins is an important task in understanding the biological properties of a protein and its potential as a therapeutic target. Producing a well-ordered crystal, particularly for proteins, which can be studied through crystallography, however, is not an easy task. Recent research involves examining the effects of microgravity on protein crystallization and a computational model for protein elucidation.

Protein crystallization and microgravity effects

The Center for the Advancement of Science in Space (CASIS), manager of the International Space Station (ISS) US National Laboratory, is collaborating with Merck & Co. to conduct research on protein crystallization on board the ISS in 2013. The research will examine the effect on protein crystallization using microgravity.

In July, CASIS announced its first request for proposals (RFP) focused on advancing protein crystallization using microgravity. Additionally, in early September 2012, CASIS announced an RFP focused on materials testing in the extreme environment of space. Proposals for this RFP will be accepted until Oct. 24, 2012. The final agreement with Merck is dependent on approval by CASIS' evaluation and prioritization process, a requirement for all ISS projects. If approved, the research will begin in mid-2013.

"We at Merck are excited to work with CASIS and explore the microgravity effects on several bioprocessing applications within the unique environment of the ISS National Lab," said Paul Reichert, chemistry research fellow at Merck Research Laboratories, in a September CASIS press release.

CASIS is the nonprofit organization promoting and managing research on board the ISS US National Laboratory, which includes a solicitation for proposals in relation to advancing protein crystallization using microgravity. The RFP seeks to identify projects within the field of crystallography that CASIS will support through grant funding, facilitation of service provider partnerships, and flight coordination to and from the ISS. Crystallography is the technique used to determine the three-dimensional structures of protein molecules. Protein crystallization, when performed in space, may produce large, better-organized crystals, thereby allowing for more focused drug development. CASIS believes that its RFP will lead to the production of better crystals in the microgravity environment than can be grown on Earth.

"CASIS has evaluated research performed to date in the life sciences and believes it is time to formally test the promising hypothesis that microgravity may produce greater internal order in protein-crystal growth," said CASIS acting Chief Scientist Timothy Yeatman, in a June 26, 2012, CASIS press release. "This could potentially lead to sharper resolution of crystals and their cognate proteins, which could produce more effective drugs for cancer and other debilitating human diseases."

In 2005, the US Congress designated the US portion of the ISS as the nation's newest national laboratory to maximize its use for improving life on Earth, promoting collaboration among diverse users, and advancing science, technology, engineering, and mathematics education. The laboratory environment is available for use by other US government agencies and by academic and private institutions to provide access to the permanent microgravity setting, vantage point in low-earth orbit, and varied environments of space.

Computational approaches for protein elucidation

Determining the structure and sequence of proteins is an important part of understanding the protein's biological properties and potential utility as a drug. Designing predetermined crystal structures, however, can be subtle given the complexity of proteins and the noncovalent interactions that govern crystallization (1). Researchers at the University of Pennsylvania recently reported on a computational approach for the design or proteins that self-assemble in three dimensions to yield macroscopic crystals (1).

"People have designed crystals out of smaller, much less complex molecules than proteins, but protein design is much more subtle," said Jeffrey G. Saven, associate professor of chemistry and biological and theoretical physical chemistry at the University of Pennsylvania, in a university press release. Saven conducted the research and recently reported on its results (1). Protein crystals are attractive as a nano-scale building material because their properties, particularly their exterior surfaces, are highly customizable, according to the university release.

The researchers targeted a crystal built using a relatively small protein containing a sequence of 26 amino acid positions. The researchers assigned specific amino acids to eight of the positions, but with 18 different types of amino acid to choose from for each of the remaining 18 slots, the algorithm addressed well more than 1022 potential combinations. The researchers accounted for other characteristics, such as the spacing between proteins and their orientation with respect to one another, increasing the variables being considered, according to the release.

"We worked on synthesizing both of those steps, doing the characterization of structure and the sequence at the same time," said Saven said in the university release. "As we move through this process, we eliminate things that will never work, such as proteins where atoms overlap in space or where amino acids don't fit into a given site. At the same time, we identify proteins that, as you vary the structure, are likely to yield a crystal."

Specifically, the research used a three-helix coiled-coil protein designed *de novo* to form a polar, layered, three-dimensional crystal having the P6 space group, which had a "honeycomb-like" structure and hexameric channels that spanned the crystal (1). The approach involved creating an ensemble of crystalline structures consistent with the targeted symmetry, characterizing this ensemble to identify "designable" structures from minima in the sequence–structure energy landscape and designing sequences for these structures, and experimentally characterizing candidate proteins. This approach to crystal design has potential applications to the *de novo* design of nanostructured materials and to the modification of natural proteins to facilitate X-ray crystallographic analysis.

The target crystal the researchers produced is a proof of concept. "There's still much we don't know about the interactions that govern crystallization," Saven said, in the university release. "With this technique, we can explore what those interactions are or how we might take an existing protein and engineer those interactions so we get much better structures."

Source

1. J.G. Saven et al, *PNAS*, **109** (19), 7304–7309 (2012).

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Obtaining Stable Homogenous Mixtures with Micronized APIs

H. Leonhard Ohrem, Roberto Ognibene, and Thorsten Wedel

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Micronized APIs help to improve solubility and are appropriate in low-dose formulations. Wet or dry granulation is typically used instead of direct compression (DC) in solid-dosage formulations to achieve homogenity of micronized APIs and excipients. The authors examine the use of various grades of DC-mannitol in a DC-tableting process to evaluate the content uniformity of micronized APIs and excipients in a solid-dosage formulation.

H. Leonhard Ohrem* is a technical manager, hans-leonhard.ohrem@merckgroup.com, **Roberto Ognibene** is head of the formulation laboratory, and **Thorsten Wedel** is a pharmaceutical engineer, all with Merck KGaA, Darmstadt, Germany 64271.

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There are several reasons to micronize APIs in a solid-dosage formulation. Many new drug molecules are poorly soluble, and one means to enhance solubility is to enlarge surface area by micronizing the API. Obtaining a homogenous mixture of the micronized API and excipients in a solid dose and maintaining product stability, however, can be challenging. Additionally, micronized APIs are used in the formulation of highly potent drugs that require low dosage. In this case, content uniformity is crucial and difficult to achieve when seeking to evenly distribute content of less than 1% API in a solid formulation.

The pure physical mixture based on statistical distribution often has no stability of homogeneity. For this reason, many formulators switch to more expensive wet- or dry-granulation processes instead of direct compression (DC) or sachet formulations. A mixture has the best chance for stability if the particles of the API and excipients are of the same size range (1). For handling reasons, the mixture of excipients and API should be in a granulate form rather than in powdered form.

The purpose of this study was to evaluate whether such APIs could create stable mixtures with larger excipient particles and support a DC-tableting process with good content uniformity. An earlier study demonstrated the stability of so-called "ordered mixtures" with spray-dried sorbitol and much smaller API particles (2, 3). Hersey first introduced the concept of ordered mixtures to explain the behavior of interacting particles in a powder mixture (4).

These examples from the literature dealt with spray-dried sorbitol, which at the time, was a rare example of a DC excipient. Today, mannitol is used as a DC excipient due to its inertness, its low hygroscopicity and its fast-release qualities. The study in this article focuses on different DC-grades of mannitol available on the market.

Materials and methods

Two types of spray-dried DC-mannitol were used, respectively named in this study as DC-Mannitol A and DC-Mannitol M, and one type of granulated mannitol, DC-Mannitol B (see **Table I**). The model APIs used were ascorbic acid as an example of a hydrophilic compound and riboflavin as a hydrophobic compound. Both APIs were micron-

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Table I: Physical characteristics of applied excipients and APIs*.

Excipient/API	Supplier	Particle size (µm) Laser-light diffraction Dv50	Crystal modification	Surface area (m2/g) (According to BET-method)
DC-Mannitol M DC-Mannitol M 200	Merck KGaA	196.8	β	2.89
DC-Mannitol A spray-dried	A	143.6	α	0.60
DC-Mannitol B granulated	B	286.0	β	0.50
Ascorbic acid*	Merck KGaA	4.52	N/A	Not determined
Riboflavin*	Merck KGaA	1.72	N/A	Not determined

DC is direct compression. N/A is not applicable.
* Ascorbic acid from Merck KGaA, Catalog Number 500078. Riboflavin from Merck KGaA, Catalog Number 500257.

ized on a pin mill before using them for this case study (see **Table I**).

API–mannitol mixtures (batch size 300 g) were prepared using a shaker-mixer (Turbula T2C, Willy A. Bachofen AG Maschinenfabrik). To evaluate the quality of mixing, the homogeneity was measured by taking six samples from the mixtures and applying a sample divider (Retsch Type RT 6.5, Retsch AG) after a specified period of mixing time (2, 5, 10, 20 and 30 min). The procedure was repeated three times.

The API content in each sample was analyzed (n = 18). For ascorbic acid, the content was determined through a volumetric analysis by titration with an iodine solution (TitriPUR, Merck KGaA), which provided an accuracy of measurement with a relative standard deviation (RSD) of 0.12%. The riboflavin content was determined spectrophotometrically at 444 nm according to the *European Pharmacopoeia* (5). The RSD of the API concentration was examined as a function of mixing time (see **Figures 1 and 2**).

To challenge the mixture stability and to show the strength of adsorption of low-dose formulations, API–DC-mannitol mixtures with a drug content of 1% and 3% were applied to an Alpine air jet-sieve (A 200 LS, Hosokawa Alpine) and analyzed for their drug content after 15 min of airflow. The applied mesh size was 40 µm, and the vacuum pressure was 2000 mPa. Separately, the capability of

Figure 1: The relative standard deviation (RSD) of the API content in relation to the mixing time of the API–direct compresson (DC)-Mannitol M samples (drug load 1% w/w).

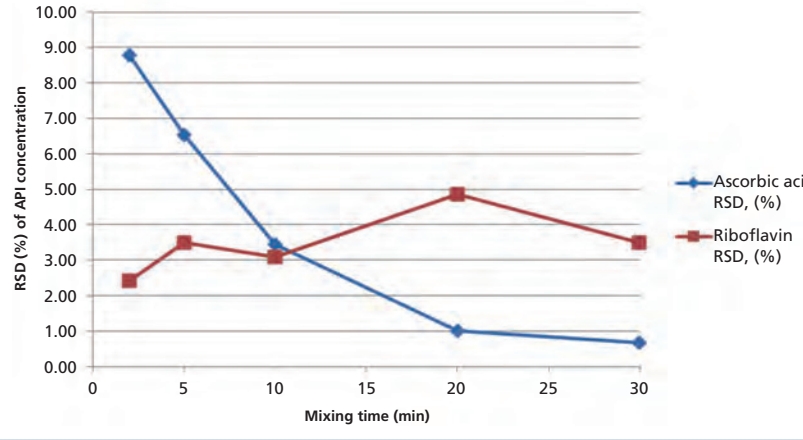
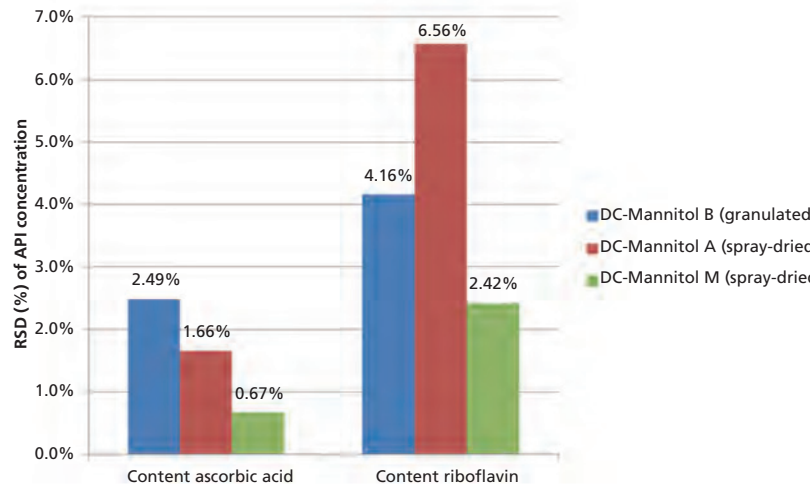


Figure 2: Relative standard deviation (RSD) of the API concentration (1% ascorbic acid/riboflavin, micronized) in samples containing a model API and different direct-compression (DC)-mannitols as excipients.



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a stable, direct-compression process was further investigated using a water-sensitive low-dose drug in a pharmaceutical formulation. The results of this investigation are later discussed under the "Results of field testing in a R&D case study" portion of this article.

Results

The reduction of the RSD of the measured API concentrations shows how the mixture approaches homogeneity with rising mixing times (see **Figure 1**). A time of 30 min was chosen as sufficient to view the mixture of DC-mannitol with micronized ascorbic acid as homogeneous (RSD = 0.67%). The mixing behavior of a blend is dependent on the API and the excipient, as well as on mixer type, scale, and the degree of filling of the mixer. As the latter parameters were constant for all assessed blends, differences in homogeneity must be due to either the API or the excipient. In this case, the micronized hydrophobic particles of riboflavin tend to re-agglomerate during mixing. This re-agglomeration is why at first the homogeneity decreases before the mixture reaches a steady state (see **Figure 1**).

The resulting mixing time of 30 min seems to be rather high. It has to be taken into account that this small laboratory-scale mixing unit is certainly not optimized. More importantly, however, the micronized API granules have a tendency of agglomeration to each other due to their high surface energy. This binding force has to be broken up and replaced by an alternative binding force—adsorption and van der Vaals interaction–with the carrier surface. This is a dynamic equilibrium process and takes more time than just a statistical distribution of different particles in space.

The comparison of different DC-mannitols at optimum mixing time reveals differences in the homogeneity of such a mixture with micronized ascorbic acid and riboflavin (see **Figure 2**). Clearly, for a hydrophilic API, the achievable homogeneity is greater than for a hydrophobic API. In this case, the different attraction forces of the hydrophobic API to a hydrophilic carrier cause more API particles to re-agglomerate rather than bind to the carrier surface. This is not a surprising observation because this relationship would be true for all excipients. There are, however, differences in the achievable blend uniformity among the compared carriers. The best homogeneity for both API cases was found for the excipient with the highest surface area, DC-Mannitol M (see **Table I**). This observation gives a hint for a correlation of BET surface area and/or pore volume to the achievable homogeneity. There also are significant differences between spray-dried and granulated DC-mannitol even having similar BET-surfaces (see **Figure 3**). The quality of the surface structure, not only the quantitative size of the surface area, seems to be relevant.

Figure 3: Comparison of the surface area and pore volumes of different excipients available for direct compression. DC is direct compression. Parkteck M 200 is a proprietary product of DC-grade mannitol (Merck KGaA). Sp is specific.

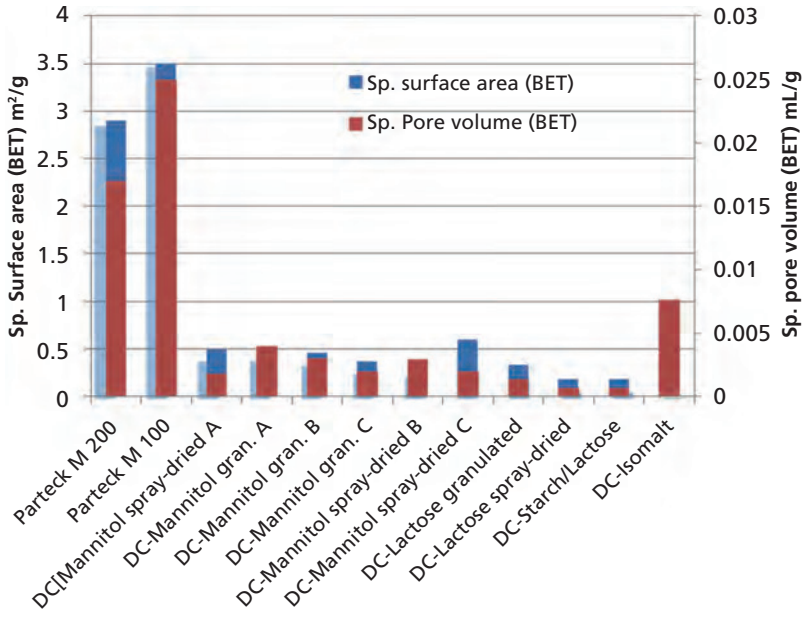
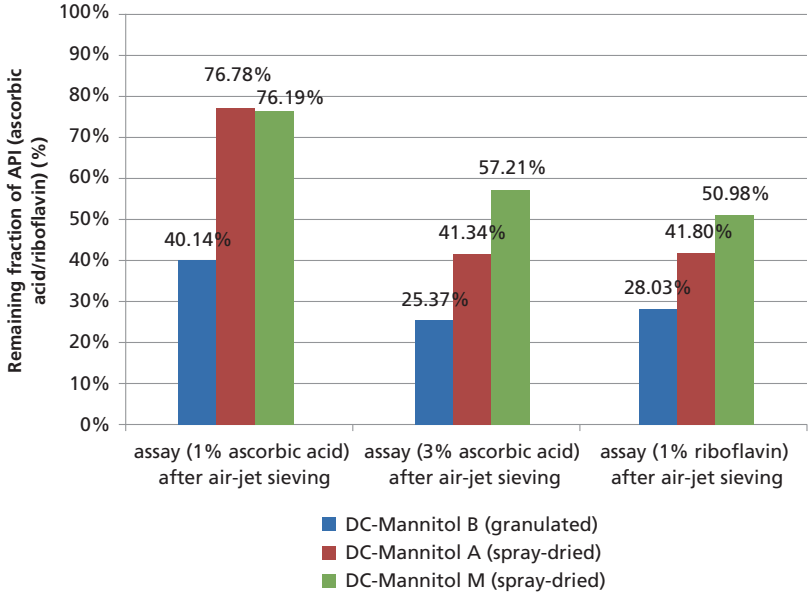


Figure 4: Comparison of the API concentration measured after 15 min in an air-jet sieve using either granulated direct-compression (DC)-Mannitol B, spray-dried DC-Mannitol A, or DC-mannitol M as excipients for the model drugs of ascorbic acid or riboflavin.



To prove an adsorption of the API to the excipient surface with a certain force, the remaining concentration of ascorbic acid and riboflavin was measured after 15 min on an air-jet sieve. By this procedure, a separation of fine API particles from the carrier can be expected if they were not strongly adsorbed. A recovery of 100% would mean a perfectly strong adsorption of the API to the carrier while a recovery of 0% shows no absorption to the carrier.

A much stronger adsorption was found for the spray-dried DC-mannitols in comparison to the granulated quality (see **Figure 4**). For low API concentrations of a hydrophilic drug, both spray-dried mannitols show similar results. Using higher API loads, it was demonstrated that the higher surface area of DC-Mannitol M shows advantages of a higher binding capacity. This effect was confirmed with a hydrophobic API, riboflavin. This finding may again result from the different surface structure of the investigated excipients. The lower recovery of hydrophobic API again confirms a weaker force of surface adsorption by this class of API.

To visualize the API distribution on the excipients' surface, a scanning electron microscope (SEM) was employed. **Figure 5** shows the SEM image of a mixture of ascorbic acid and DC-mannitol M. The micronized API particles are readily identifiable due to the different crystal structures of API and carrier (colorization performed manually). The API crystals were found within the pore structure of the much larger excipient particles. **Figure 6** shows the SEM image of spray-dried DC-Mannitol A and ascorbic acid. In this case, less areas are present that are suitable for the absorption of the API. The overall surface is less structured. A similar distribution on the excipients' surface was determined for the hydrophobic model drug riboflavin (see **Figure 7**).

The importance of the surface area and the pore volume of an excipient for the homogeneity of the mixture was demonstrated. In the next step, the surface area and porosity of various excipients available for direct compression were analyzed using the BET method (nitrogen adsorption). As the API is adsorbed to a porous surface, the observed differences of the excipients may give rise to a different behavior in the adsorption of the micronized APIs (see **Figure 3**).

Table II: Comparison of tablets manufactured at different speeds of the rotary press.

	40,000 tablets/h	80,000 tablets/h
Tablet weight	120.1 mg (RSD 0.6%)	118.8 mg (RSD 0.9%)
Tablet hardness	178 N (RSD 4.1%)	173 N (RSD 4.1%)
Disintegration time	3 min 25 s	3 min 22 s

RSD is standard deviation.

This study showed that stable mixtures of much smaller micronized API particles with DC-excipients can be achieved. The next question examined was whether this approach was suitable for the DC process for an actual formulation.

Results of field testing in a R&D case study

The question whether low-dose pharmaceutical formulations with micronized APIs are suitable for a DC process was challenged using a water-sensitive R&D API at only 0.4% in the final dosage form (0.5 mg API in a 120-mg tablet). Wet granulation could not be applied because of the water-sensitivity of the API. The micronized API (Dv50 10 µm), therefore, was premixed for 30 min using a shaker-mixer (Turbula T2C) with 15% of the total amount of DC-grade mannitol DC-Mannitol M (Dv50 200 µm) and mixed with the rest of the formulation using a Turbula T20P (Bachofen AG) (see **Figure 8**). A test run of 2 h on a rotary press (Korsch Pharmapress PH230, Korsch AG) was performed at two different rotation speeds (40,000 and 80,000 tablets/h). The tablets were assessed for their weight, hardness, and disintegration time

This result was surprisingly good as constant values were detected for tablet weight (RSD 0.6–0.9%), tablet hardness (RSD 4.1%), and disintegration time (see **Table II**). Content uniformity was measured to be ± 1.8 %.

Conclusion

Although the concept of ordered mixtures has been extensively studied and reported, little was known about the mechanisms and reasons behind ordered mixtures (6–9). The results clearly show that the effect of ordered mixtures can be found with DC-mannitols as a function of surface area and structure. To a greater extent, this functionality can be found for spray-dried qualities with a porous surface structure. A large surface area is helpful for good binding capacity. Stable mixtures are not only achieved with components of similar particle sizes as the literature suggests. It is also possible to achieve a stable

Figure 5: Scanning electron microscope (SEM) image showing a mixture of direct-compression (DC)-mannitol M 200 and micronized ascorbic acid (drug load 1% w/w).

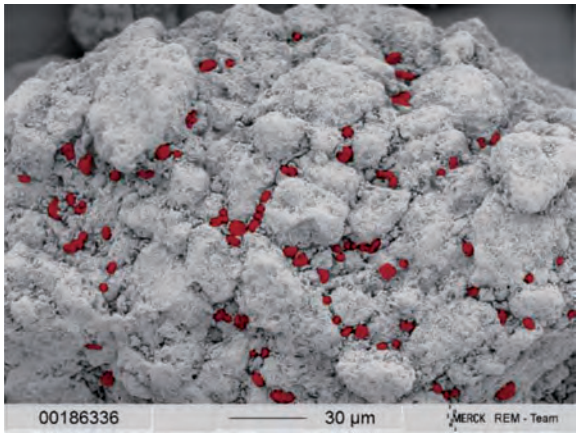


Figure 6: Scanning electron microscope (SEM) image showing a mixture of spray-dried direct compression (DC)-Mannitol A and micronized ascorbic acid (drug load 1% w/w).

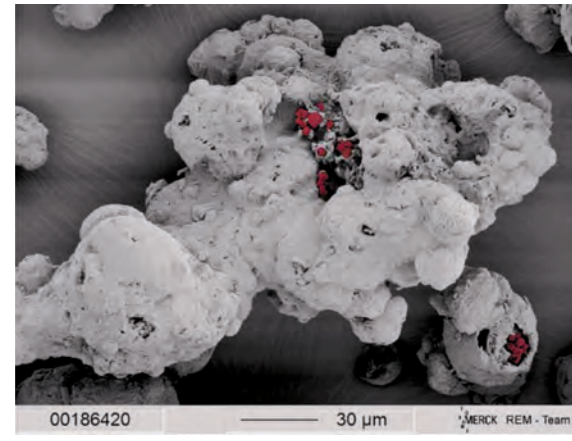


Figure 7: Mixture of direct-compression (DC)- mannitol M 200 with micronized riboflavin (drug load 1% w/w). Light microscope with 40 x magnification. The yellow particles of the API are clearly visible in the porosity of the carrier surface.

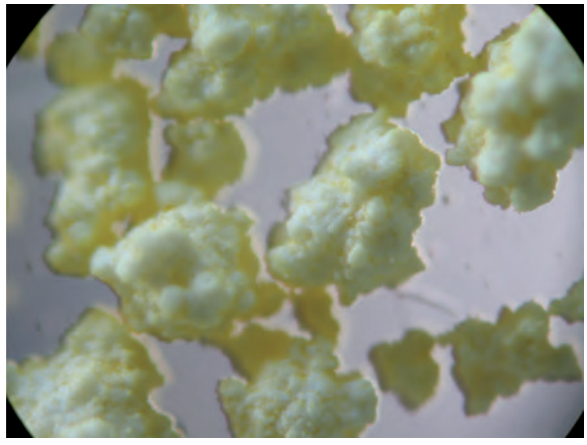
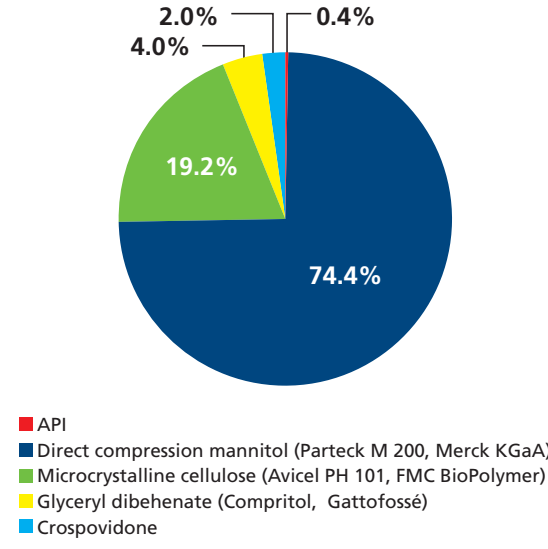


Figure 8: Composition of the investigated pharmaceutical formulation used for the R&D case study.



mixture of micronized API particles (< 15 µm) with a DC-mannitol with a mean particle size of 200 µm. The stability is caused by an adsorptive binding force strong enough to withstand the mechanical separation forces. This effect was successfully demonstrated for hydrophilic and hydrophobic APIs. This result confirms the feasibility of DC for low-dose applications with acceptable content uniformity as the example showed. It also helps to show that micronized APIs at higher concentrations can be applied in solid formulations to enhance their solubility. This approach can be applied for DC, sachet formulations, or in roller compaction.

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Overcoming Challenges with Pediatric Oral Solid Dose Development

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- Insights into the unique regulatory considerations to be addressed when formulating for the pediatric population.
- Opportunities to improve patient compliance by formulating specifically to meet niche group needs.
- Unique considerations, including excipient selection, dosage form and patient compliance.

Presenters

Dr. Jenny Walsh, PhD
Director,
Jenny Walsh Consulting Ltd
BioCity, Nottingham

Kevin Hughes
Formulation Technologies Manager
Colorcon Limited

Moderator

Angie Drakulich
Editorial Director
Pharmaceutical Technology

EVENT OVERVIEW

Pediatric drug products require specialized consideration in formulation development. This niche field has gained attention among regulatory authorities in Europe, North America, and beyond, thereby providing new perspectives on and expectations of pharmaceutical drug formulators. Unique considerations must be addressed when formulating for this population, including excipient selection, dosage form, and patient compliance.

This webinar will provide an overview of current strategies and opportunities in pediatric oral solid dosage formulation development as well as insight into potential delivery options for this niche group. Technical advances and global regulatory expectations will be discussed, as will specifics in multidose and controlled release oral solid dose presentations. Strategies to improve compliance through palatability, inclusion of color for brand recognition, and single daily dose vs. multiple daily dose products will be presented.

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Quality by Design for Analytical Methods

Implications for Method Validation and Transfer

Phil Nethercote and Joachim Ermer

Adoption of quality-by-design (QbD) concepts in pharmaceutical development and manufacture is becoming increasingly well-established. QbD concepts are aimed at improving the robustness of manufacturing processes based upon adopting a systematic and scientific approach to development and implementing a control strategy based on the enhanced process understanding this provides. Many pharmaceutical companies have also recognized that QbD concepts can be used to improve the reliability of analytical methods. The authors describe how traditional approaches to analytical method transfer and validation also may benefit from alignment with QbD concepts and propose a three-stage concept to ensure that methods are suitable for their intended purpose throughout the analytical lifecycle: method design, method qualification, and continued method verification. This paper represents a refinement and enhancement of the concepts originally proposed in an article written by P. Nethercote, T. Bennett, P. Borman, G. Martin, and P. McGregor (1).

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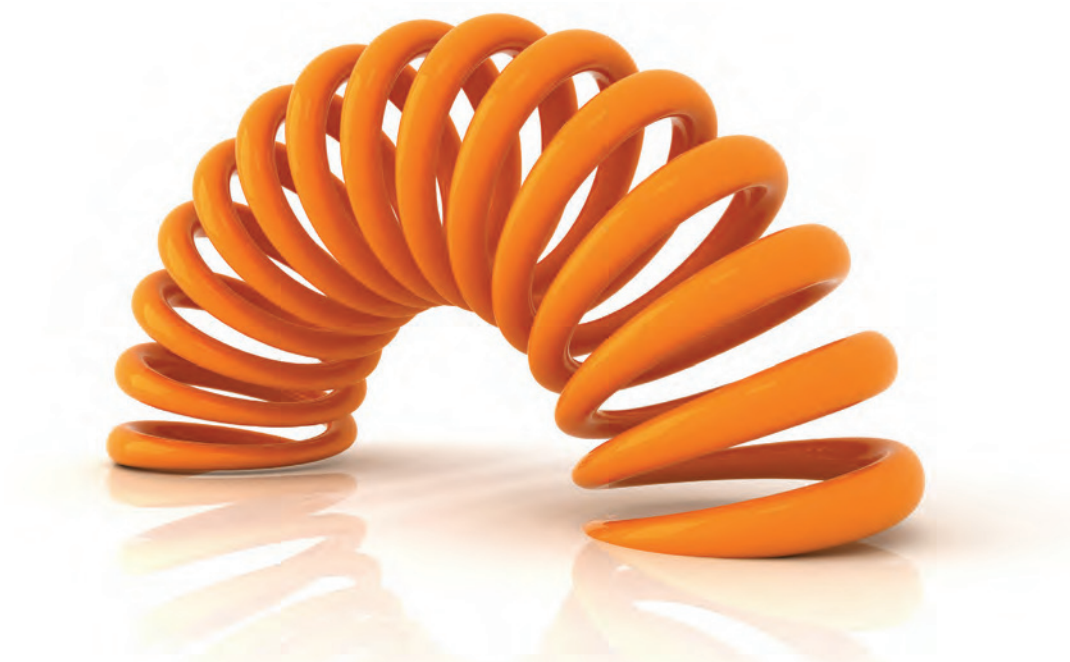
To help in implementation of the goals of FDA's *Pharmaceutical cGMPs for the 21st Century–A Risk-Based Approach* (2), FDA recently issued guidance for industry describing the general principles and practice of process validation, which seeks to align process validation activities with product lifecycle concepts. This guidance (3) addresses some of the issues with traditional approaches to process validation where a focus on a one-time, three batch approach, with the use of the best talent during the day shift with the same lot of raw material does little to ensure that the manufacturing process is and will remain in a state of control. The traditional approach to process validation encourages a "do not rock the boat" mindset since the product is approved and the process is validated and fails to foster continuous improvement in quality or efficiency (4).

These issues have parallels in analytical method validation. Analytical methods for pharmaceutical products are validated in accordance with the International Conference on Harmonization (ICH) Q2 Guideline, *Validation of Analytical Procedures: Text and Methodology*, usually by the experts who have been involved in developing the method (5). Method validation is often treated as a one-time event with no guidance on how to ensure continuing focus on consistent method performance. There also is lack of guidance on how to demonstrate in practice that a method is fit-for-purpose (i.e., what are suitable acceptance criteria). There is potential for the validation process to seem more focused on producing validation documentation that will withstand regulatory scrutiny than on ensuring that the method will actually perform well during routine application. There is a risk that both regulatory authorities and industry use ICH Q2 in a check-box manner rather than its intent, which is to provide guidance on the philosophical background to method validation.

After the method has been validated by the developing group, it may be transferred to another laboratory, which involves transferring the knowledge of how to operate the method to those who will use it routinely and documenting that both parties obtain comparable results. The routine operating environment, however, is not always considered during the method-development and validation exercise. The lack of an effective process for capturing and transferring the tacit knowledge of the development analysts can cause methods to fail to perform as intended in the receiving



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laboratory. Much effort is then expended on identification of the variables that are causing the performance issues and the exercise is repeated. As in the case of the initial method validation activity, the transfer exercise is typically performed as a one-off process. There is a risk that the exercise will focus more on producing the method-transfer report than on ensuring the ability of the receiving laboratory to run the method accurately and reliably and ensuring the continuity and integrity of analytical results.

The recognition that an analytical method can be considered a process that has an output of acceptable quality data led Borman *et al.* to take the QbD concepts designed for manufacturing processes and show how these could also be employed for analytical methods (6). It follows, therefore, that the concepts of lifecycle validation being developed for manufacturing processes might also be applicable to analytical methods. This concept aligns well with the lifecycle concept of equipment qualification in the *United States Pharmacopeia* (USP), consisting of equipment design, followed by operational and performance qualification, and with analytical method validation activities proposed by Ermer and Landy (7, 8).

A QbD framework for analytical lifecycle management

QbD is defined as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management" (9). FDA has proposed a definition for process validation that is "the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products" (3). When considering a lifecycle approach to method validation a similar definition could be adopted, "the collection and evaluation of data and knowledge from the method design stage throughout its lifecycle of use, which establishes scientific evidence that a method is capable of consistently delivering quality data" (1). A method, as defined in this article, is a synonym for analytical procedure and includes all steps of the procedure (e.g., sample preparation, analytical methodology, calibration, definition of the reportable result, and specification limits). From these definitions, it can be seen that there are a number of key factors that are important in a QbD lifecycle approach. These include:

- The importance of having predefined objectives
- The need to understand the method (i.e., having the ability to explain the method performance as a function of the method input variables)
- The need to ensure that controls on method inputs are designed such that the method will deliver quality data consistently in all the intended environments in which it is used
- The need to evaluate method performance from the method design stage throughout its lifecycle of use.

In alignment with the approach proposed in the FDA guidance for process validation, it is possible to envisage a three-stage approach to method validation.

- *Stage one: method design.* The method requirements and conditions are defined according to the measurement requirements given in the analytical target profile and the potential critical controls are identified.
- *Stage two: method qualification.* During this stage, the method is confirmed as being capable of meeting its design intent and the critical controls are established.
- *Stage three: continued method verification.* Ongoing assurance is gained which ensures the method remains in a state of control during routine use. This includes both continuous method performance monitoring of the routine application of the method as well as a method performance verification following any changes.

Measurement requirements

Before commencing method validation, it is key to understand what the product critical quality attributes and process control requirements are. These requirements form the basis for the development of an Analytical Target Profiles (ATP) (10). While the paper in reference 10 introduced the concept of an ATP and described how it could have potential as a tool to facilitate regulatory oversight of change, its principal aim is to act as the focal point for all stages of the analytical lifecycle including method validation, which is the focus of this paper.

To build the ATP, it is necessary to determine the characteristics that will be indicators of method performance. These should include all of the characteristics that will ensure the measurement produces fit-for-purpose data and are likely to be a subset of those described in ICH Q2 (e.g., accuracy, precision) (5).

Once the important method characteristics are identified, the next step is to define the target criteria for these (i.e., how accurate or precise the method needs to be). After ensuring safety and efficacy, a key factor in selection of the appropriate criteria is the overall manufacturing process capability. Knowledge of the proposed specification limits and the expected process mean and variation is helpful in setting meaningful criteria. To draw a parallel to qualification of new analytical equipment, the ATP is similar to a user requirement specification that would be produced to support qualification of new analytical equipment.

Stage one: method design

The method design stage involves selecting appropriate technologies and developing a method that will meet the ATP requirements. Appropriate studies are then performed to understand the critical method variables that need to be controlled to ensure the method is robust and rugged.

Method development. Once the ATP has been defined, an appropriate technique and method conditions are selected that will likely meet the requirements of the ATP as well as business needs. This step can range from developing a new method to making a change to an existing method. While method development is obviously a very important part of the method lifecycle, it is not necessary to elaborate here because it has been extensively addressed in the literature.

Method understanding. Based on an assessment of risk (i.e., the method complexity and potential for robustness or ruggedness issues), an exercise focused on understanding the method (i.e., understanding which key input variables impact the method's performance characteristics) may be performed. From this, a set of operational method controls is identified. Experiments can be undertaken to understand the functional relationship between method input variables and each of the method performance characteristics. Knowledge accumulated during method development provides input into a risk assessment. Tools, such as the fishbone diagram and failure mode effects analysis (FMEA), can be used to determine which variables need studying and which require controls. Robustness experiments are typically performed on method factors using design of experiments (DoE) to ensure that maximum understanding is gained from a minimum number of experiments. The output from the DoE should be used to ensure the method has well-designed system-suitability tests, which can be used to ensure that a method meets ATP requirements (i.e., is operating in the method design space).

When developing an understanding of the method's ruggedness, it is important that variables that the method is likely to encounter in routine use are considered (e.g., different analysts, reagents, instruments). Tools such as measurement system analysis (i.e., precision or ruggedness studies) can be useful in providing a structured experimental approach to examining such variables (11). Precision or ruggedness studies may instead be performed as part of Stage two, particularly if a developer has sufficient prior knowledge to choose appropriate method conditions and controls.

Method design output. A set of method conditions and controls that are expected to meet the ATP should be developed and defined. These conditions should be optimized based on an understanding of their impact on method performance.

Stage two: method qualification

Having determined a set of operational method controls during the design phase, the next step is to qualify that the method will operate in its routine environment as intended, regardless of whether this is research and development or industrial quality control. Method qualification involves demonstrating that the defined method, including specified sample and standard replication levels and calibration approaches, will, under routine operating conditions, produce data that meet the precision and accuracy requirements defined in the ATP. This may involve performing a number of replicate measurements of the same sample to confirm that the precision of the method is adequate and to demonstrate that any potential interferences do not introduce an unacceptable bias by comparing results with a sample of known quality. If the respective experimental results have already been obtained during Stage one, they only need to be summarized for the final evaluation.

Stage three: continued method verification

The goal of this stage of the method lifecycle is to continually ensure that the method remains in a state of control during routine use. This includes both continuous method-performance monitoring of the routine application of the method as well as performance verification following any changes.

Continued method performance monitoring. This stage should include an ongoing program to collect and analyze data that relate to method performance (e.g., from replication of samples or standards), by trending system suitability data, assessing precision from stability studies (12), or by trending data from regular analysis of a reference lot. This activity aligns with the guidance in *USP* Chapter <1010> on system performance verification (13). Close attention should also be given to any out-of-specification (OOS) or out-of-trend (OOT) results generated by the method once it is being operated in its routine environment. Ideally, by using a lifecycle approach to method validation, laboratories should encounter fewer analytically related OOS results, and if they do, it will be easier to determine or exclude a root cause. Monitoring performance parameters also serves to control method adjustments (i.e., changes within the method design space).

Method performance verification. Method performance verification is undertaken to verify that a change in the method that is outside the method design space has no adverse impact on the method's performance. The activities required to be performed as part of method performance verification are determined through risk assessment of the impact of the

Table I: Comparison of traditional and lifecycle approaches to analytical method validation.

Traditional approach	Lifecycle approach
Methods validated in a check-box manner against generic criteria and characteristics defined in International Conference on Harmonization (ICH) Q2 guidance, *Validation of Analytical Procedures: Text and Methodology (5)*	Suitability of a method demonstrated against an analytical target profile, which defines the specific characteristics and criteria required by the process control strategy (method design and qualification stages)
Limited understanding of the impact of variation in method parameters on performance	Detailed, structured approach to identifying and exploring method variables and their impact (method design and qualification stages)
Method transfer seen as a separate exercise from validation	Method-transfer activities seen as components of the lifecycle approach and considered change-control exercises; appropriate method installation and verification actions determined by risk assessment (method performance verification stage)
Ambiguity in use of terms (e.g., method verification, method transfer, method validation and revalidation)	Improved clarity; lifecycle-approach terminology used; method terminology aligned with process validation and equipment-qualification terminology
Method validation used to describe one-time event performed on completion of method development	*Method lifecycle validation* used to describe all activities that ensure a method produces fit-for-purpose data during the whole lifecycle (i.e., from development through to ongoing routine use); *method qualification* involves demonstrating that a method will perform as intended in a routine operating environment
Method transfer includes activities performed to transfer a method from a sending unit to a receiving unit and to demonstrate equivalence between the two units	*Method installation* includes activities performed to ensure effective method set-up in the routine operating environment and includes knowledge transfer from a sending unit
Method verification involves ensuring pharmacopeial methods operate under actual conditions of use; revalidation is performed after changes for validation characteristics likely to be affected	*Method performance verification* involves demonstrating that a method performs as intended following a change in the method's operating conditions or operating environment

change on the ability of the method to meet the requirements of the ATP. These activities may range from a review to ensure that the post-change operation of the method continues to meet the system suitability requirements to performing equivalency studies aimed at demonstrating that the change has not adversely affected the method's accuracy or precision. (See Appendix 1 in the expanded, online version of this article at PharmTech.com/Nethercote for examples of how a risk assessment could be performed.)

Change control

During the lifecycle of a product, both the manufacturing process and the method are likely to experience a number of changes through continuous improvement activities or the need to operate the method or process in a different environment. It is essential that all changes to the method's operating conditions are considered in light of the knowledge and understanding that exists on the method performance. For all changes, a risk assessment should be carried out and appropriate further validation activities performed. (See Appendix 2 in the expanded, online version of this article at PharmTech.com/Nethercote for examples of actions for different types of changes.)

Method installation

If a change involves operation of the method in a new location, appropriate method-installation activities, including knowledge transfer, need to be performed in addition to a method-performance verification exercise. Method installation focuses on ensuring that the location at which the method is intended to be operated is adequately prepared to use the method. It includes ensuring that the analytical equipment is qualified and appropriate knowledge transfer and training of analysts has been performed. The method conditions and detailed operating controls along with all the knowledge and understanding generated during the design phase are conveyed to the location in which the method will be used. Performing a method-walkthrough exercise with the analysts in the original and new locations can be extremely valuable in ensuring all tacit knowledge about the method is communicated and understood. The extent of the method-installation activities should be based on an assessment of risk and should consider, for example, the level of preexisting knowledge of the analysts in the new location with the product, method, or technique. As part of the initial qualification of a method, a second laboratory may be involved in producing data to determine the method's reproducibility. In such a case, the second laboratory can be considered as being within the method design space, and any subsequent operation of the method in that laboratory would not be considered a change. Nevertheless, the described activities with respect to method installation would be performed before starting the reproducibility study.

Other scenarios

This approach to method qualification focuses on activities that would typically be performed for a method that is developed and used within a single company. Other scenarios exist in which a laboratory may need to use a method for which it has no access to the original method design or qualification information, such as in a contract-testing laboratory. In these situations, it is important that the per-

formance requirements of the method are considered and an ATP is defined and documented. An appropriate qualification study is then performed to demonstrate that the method meets its ATP.

Implications

Adopting a QbD approach to analytical-method lifecycle management would have significant implications for analytical scientists in the pharmaceutical industry. Industry and regulatory authorities will need to modify the way they use ICH Q2, which, ideally, would prompt a revision of this guidance to align it with the lifecycle-validation concepts promoted by ICH Q8, Q9, and Q10 (9, 14, 15). The need for a revision of ICH Q2 as a consequence of increasing adoption of QbD concepts and use of PAT has also been identified by Criuzak (16).

The activities that were previously defined as method transfer (i.e., knowledge transfer and confirmation of equivalence) would become intrinsic components of the lifecycle validation approach (i.e., they would be described as method installation and method performance verification activities) and would be traced back at all stages to the ATP requirements, rather than being treated as distinct from traditional method validation.

A key advantage of adopting the approach described in this article is the flexibility to perform all the validation stages against the specific ATP defined for the intended method use. This would eliminate the approach of creating a validation document against ICH Q2 in a check-box manner, which can lead to unnecessary and non-value-adding work. Because this approach could be adopted for all users of analytical methods, it also offers the potential to standardize industry terminology and create a harmonized method validation approach. This approach aligns terminology to that used for process validation and equipment qualification, supports a lifecycle approach, removes existing ambiguities in validation terms (e.g., method validation, revalidation, transfer and verification), and clarifies what is required for each part of the process. **Table I** summarizes this comparison of the traditional and lifecycle approaches to method validation.

Conclusion

The switch to a QbD approach to method development is already beginning to bring improvements to the performance of analytical methods. Opportunities also exist to modernize and standardize industry's approach to method validation and transfer. By aligning method validation concepts and terminology with those used for process validation as well as equipment qualification, there is an opportunity to ensure that efforts invested in method validation are truly value adding, rather than simply being a check-box exercise, and to reduce confusion and complexity for analytical scientists.

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PEER-REVIEWED APPLICATION NOTE

Integration of Less-Formal Risk Assessment Tools into Change Control

A Practical Approach to Risk Management

Kelly Waldron and Marissa Gray

Managing risk in biopharmaceutical operations is of utmost importance for patient protection, ensuring that only the highest quality products are developed and distributed. A quality risk-management program systematically identifies and analyzes the risks associated with a product or process, mitigates those risks deemed unacceptable, and monitors the overall risk profile as conditions change. These programs facilitate more informed decision-making within a company regarding a product's quality and provide greater assurance to a company's stakeholders of the ability to deliver the highest quality product to patients. In this paper, the authors describe risk-assessment tools used in change control.

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According to the International Conference on Harmonization (ICH) Q9 guidance, *Quality Risk Management*, all manufacturing processes carry certain, inherent risks (1). It is, therefore, essential that these risks are assessed and mitigated throughout the product lifecycle. Risk assessment is especially critical when changes are made to validated processes or systems to ensure the integrity of the product is preserved as the risk profile evolves. Not all risks pose a concern; it is important to distinguish between risks that are problematic and require mitigation efforts and those that do not. Thus, an effective risk assessment will ensure that maximal resources are directed towards products, equipment, and processes deemed high risk and minimal resources towards those deemed low risk.

Less-formal tools for managing change control

Risk management tools provide the necessary means by which risk can be successfully understood and controlled, making the entire process both efficient and consistent. While there are several well-known formal tools for risk assessment, such as failure mode effect analysis (FMEA), fault tree analysis (FTA), hazard operability analysis (HAZOP), and hazard analysis and critical control points (HACCP), ICH Q9 notes that the use of formal tools is not always appropriate or necessary to manage risk. It is, therefore, important to select the appropriate tool based on the objective and scope the assessment. The greater the risk and complexity of the system (or process) under review, the greater the level of formality and detail is required of the risk tool (see **Figure 1**). Less-formal tools, such as the comparison matrix (CM) and the risk estimation matrix (REM), which are designed to be easily implemented and broadly applied, are useful when assessing simple or well-understood systems or changes. Less-formal tools can also be used to make preliminary decisions about whether to stop or advance a given project or to employ more formal risk assessment methodologies.

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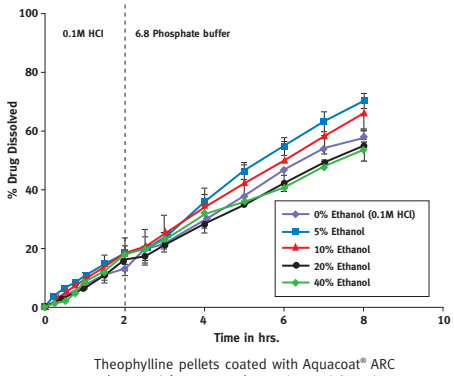

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additional risk by making the change, and to ensure the success and effectiveness of the change through the identification of risk mitigation activities to be implemented in parallel with the change. The risk tools selected to assess changes should also be simple enough to use in a fast-paced manufacturing environment and clearly communicate the scope and impact of the change to all stakeholders. CM and REM are two such tools.

Both the CM and REM have a foundation in critical parameters—that is, categories of attributes that are deemed critical to the proper functioning of a system and must be considered to fully characterize the implications of a given change. Critical parameters are system-specific and should capture such elements as critical quality attributes (CQAs), critical or key process parameters (CPPs/KPPs), critical aspects (CAs) of equipment, system capacity, process capability, raw materials, and product-contact materials. These critical parameters will serve as the input into the risk assessment process.

Figure 1: Risk assessment tool formality.

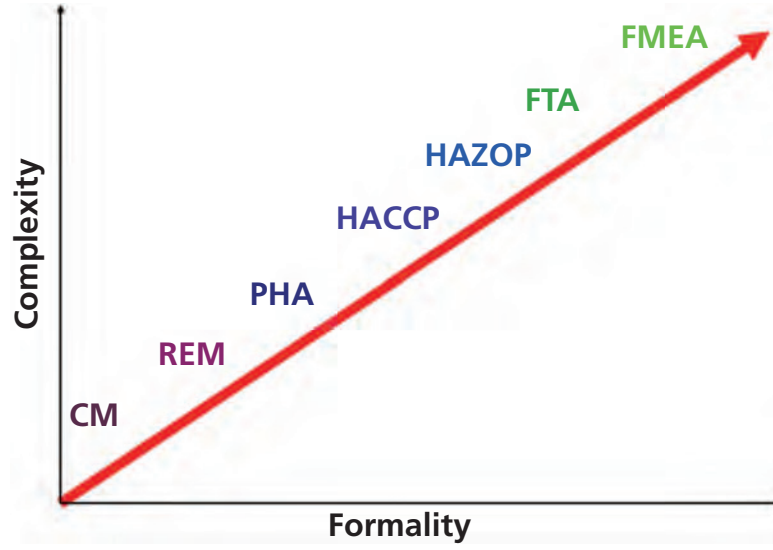

Table I: Comparison matrix: hypothetical scale-up of saline solution.

Critical parameter	Current state	Proposed state	Change to overall risk profile	Justification/ rationale
Bioburden spec	<10 CFU/mL	<10 CFU/mL	No change	Same bioburden spec
Environmental exposure	Semi-closed system, aseptic connections	Closed system, sterile connections	Reduced	Improved system maintains system integrity
Vessel type	316 SS	PVC	Increased	New product-contact material
Vessel capacity	50L	200L	Reduced	Scale-up ensures supply

Comparison matrix

The CM is a less-formal risk tool used to compare two different states in an effort to understand what the differences mean from a risk-based perspective. The primary objective of the CM is to determine if, overall, the change will lead to more or less risk exposure for the process or system. The CM is particularly helpful when making "go/no-go" decisions regarding individual change requests.

The process for the CM is as follows:

1. Identify critical parameters for the system under review.
2. Populate the CM with details for each critical parameter, for both the current and proposed states.
3. Determine what the differences between the current and proposed states mean from a risk-based perspective (i.e., the change to overall risk profile for each critical parameter).
4. Evaluate whether changes to overall risk profile are acceptable.

A hypothetical change request, for example, related to scaling up the production of saline solution may identify the following attributes as critical parameters: bioburden specifications, environmental exposure, vessel type, and vessel capacity. Once the CM is populated with details on how the current and proposed states fulfill each of these critical parameters, the potential impact of each change on the overall risk profile is assessed (see **Table I**). This assessment must take into consideration the nature (i.e., types of risk or potential failures), the gravity (i.e., frequency or severity of a failure), and the pervasiveness (i.e., where the failure might occur or what downstream impact it might have) of each risk.

The overall risk profile may be increased if the proposed change increases variability, reduces reproducibility or robustness, introduces a variable that is not well understood (such as a new technology), or cannot be quantified. Conversely, the exposure to overall risk may be reduced if the change decreases variability, improves reproducibility or robustness, or upgrades an element of the system in a way that is well-understood and controlled. Overall risk may remain the same if the change does not affect that particular critical parameter or if it is proven or expected to be equivalent to

FIGURE 1 COURTESY OF AUTHOR.

Table II: Risk action level.

Overall risk	Acceptability
Low	The risk associated with the critical parameter is acceptable. No mitigation is required prior to implementation.
Medium	The risk associated with the critical parameter may be acceptable provided additional actions are taken (e.g., risk control/mitigation measures, validation) or appropriate justification is documented.
High	The risk associated with the critical parameter is not acceptable. Additional risk control measures are required to reduce risk to within an acceptable level.

Table III: Risk matrix.

		Severity		
		Minor	Moderate	Critical
Likelihood	Certain	Medium	High	High
	Average	Low	Medium	High
	Remote	Low	Low	Medium

the current system. As with any risk assessment, available data should be cited as justification for the conclusions drawn.

The final step in the CM process is to assess whether the change is acceptable from a risk-based perspective. In general, the proposed change is acceptable if the overall risk profile has not changed or has been reduced for the majority of critical parameters. If the overall risk profile, however, has increased for the majority of critical parameters that were assessed, the proposed change should not be accepted until additional analyses are conducted or risk mitigation measures are pursued.

To continue the hypothetical example in Table I, the overall reduction of the risk profile suggests that it is appropriate to move forward with this change. The critical parameter surrounding the introduction of a new product-contact material, however, increases risk and should be examined more thoroughly.

Although the CM illustrates whether a given change should be pursued, individual risks associated with the proposed state (change) are not thoroughly explored through this tool. These individual risks are best assessed through another less-formal tool, the risk estimation matrix (REM).

Risk estimation matrix

REM is a simple risk assessment tool that assumes failure of each critical parameter and uses the likelihood and severity of that failure to determine the overall risk. REM is based on a 3 x 3 matrix, similar to a heat map. Like CM, REM is limited in that it is not a formal risk assessment tool; hence, it does not have the level of detail and rigor that more complex systems and processes may require.

The process for REM is as follows:

1. Determine qualitative scales for likelihood and severity rankings. Develop an action level table (see **Table II**).
2. Identify critical parameters for the system under review.
3. Brainstorm potential failures for each critical parameter.
4. Rank each potential failure for likelihood and severity using the criteria established in Step 1.
5. Determine overall risk using the risk matrix (see **Table III**). Propose mitigation for unacceptable risks.

In order to preserve objectivity and ensure consistency of the risk assessment to follow, the first step in the REM methodology involves the establishment of risk ranking scales. Two qualitative scales will be developed, each containing three potential scores. The likelihood scale addresses how likely is it that the failure will occur, given the current controls in place. This scale includes options ranging from remote (unlikely) through average (likely) to certain (very likely or unknown). The severity scale addresses the question: If that failure did occur, how severe would the consequences be? The severity scale ranges from minor (insignificant impact) through moderate (moderate impact) to critical (significant impact).

The final scale that must be established is an action level table that dictates the acceptability for overall risk, including whether mitigation measures are required. Low-risk items may not require any mitigation activities or resource expenditure, whereas high-risk items will require additional risk control measures to reduce risk to an acceptable level.

Returning to the hypothetical saline solution scale-up, the risk team would first brainstorm potential failures associated with each critical parameter for the saline solution process. For example, the batch could fail the bioburden specification, the closed aseptic system could be breached, the new material may not be biocompatible, or the vessel capacity may be insufficient for production needs (see **Table IV**). Each of these potential failures is then ranked for likelihood and severity and the overall risk identified using the risk matrix in Table III.

Table IV: Risk estimation matrix: hypothetical scale-up of saline solution.

Critical parameter	Potential failure	Likelihood/ severity	Overall risk	Justification/ rationale
Bioburden spec	Batch >10 CFU/mL	Remote/ Critical	Medium	Process capability OK
Environmental exposure	Breach of closed system	Remote/Moderate	Low	ISO Class 7, gowning, aseptic technique
Vessel type	PVC not biocompatible	Certain/ Critical	High	PVS characteristics unknown
Vessel capacity	200L capacity insufficient	Remote/ Minor	Low	OK at current capacity (50L)

Focusing on the new product-contact material, it may be difficult to assign a likelihood score if there is no available data on the biocompatibility or extractable/leachable profile of this material. In such cases, it is best to take a conservative approach and assign a likelihood score of "certain" to the lack of biocompatibility. Based on the potential patient impact of this failure, the severity would be given a score of "critical." The intersection of "certain" and "critical" in the risk matrix shows this risk to be high. Thus, the risk of changing the vessel type to a new material is not acceptable, and additional risk control measures must be taken. Because in this example the overall risk is driven primarily by a lack of data, mitigation efforts would focus on biocompatibility testing to better understand the implications of the new material on the product. Once this action is taken, it is expected that overall risk would then be reduced to an acceptable level.

Conclusion

To ensure that the quality system and associated processes remain in control over time, every company must understand how their risk exposure is affected as validated systems evolve. The application of quality risk management principles and tools facilitate this understanding, allowing for more comprehensive strategy development and informed decision-making. It is not always, however, necessary to perform lengthy, formal risk assessments to reach these goals. For simple systems and processes as well as for changes that are well understood, less-formal tools such as the comparison matrix and risk estimation matrix provide a comprehensive picture of the associated risk in an easily applied format. The consistent use of these tools can enable the pharmaceutical industry to prioritize resource expenditure and provide only the highest quality products to patients.

Reference

1. ICH, *Q9 Quality Risk Management* (Nov. 2005). **PT**

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Early Development GMPs for Small-Molecule Specifications

An Industry Perspective (Part V)

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The authors, part of the International Consortium on Innovation and Quality in Pharmaceutical Development (IQ Consortium), explore and define common industry approaches and practices when applying GMPs in early development. A working group of the consortium aims to develop a set of recommendations that can help the industry identify opportunities to improve lead time to first-in-human studies and reduce development costs while maintaining required quality standards and ensuring patient safety. This article is the fifth paper in the series and focuses on specifications.

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The International Consortium on Innovation and Quality in Pharmaceutical Development (IQ Consortium) was formed in 2010 as an association of over 25 pharmaceutical and biotechnology companies with a mission to advance science-based and scientifically-driven standards and regulations for medicinal products worldwide. In previous issues of *Pharmaceutical Technology,* papers written by the IQ Consortium's "GMPs in Early Development Working Group" described the desire and rationale for more clear and consolidated recommendations for Good Manufacturing Practices (GMPs) in Early Development (Phase 1 through Phase 2a) (1–4) . In this issue of *Pharmaceutical Technology*, the IQ Consortium presents a proposal for the analytical assessment and control of both drug substances (DS) and drug products (DP) in early development specifications. These recommendations take into consideration the differences in clinical trials in early development versus those in later development and provide a starting point to stimulate discussion on specifications in early development.

Previous industry position(s) on the topic of science-based specifications have not addressed early development needs or differentiated the role of specifications in early versus late development (5). During preclinical and early development, the primary focus is to progress the product into the clinic for safety and preliminary efficacy assessment. Due to the high attrition rate in early development, consistent specifications that ensure patient safety are desirable. During late development, specifications evolve as the clinical focus expands from safety to include efficacy, and as the product and corresponding synthetic and formulation process undergo significant transformations (e.g., synthetic route changes during scale-up, evolution of dosage forms from fit-for-purpose to robust formulations and processes suitable for commercial manufacturing). Therefore, early development specifications should also focus on those tests and acceptance criteria determined to be critical for the control of product quality with an emphasis on patient safety and supported by preclinical and early clinical safety studies.

Based on the cumulative industry experience of the members of this IQ working group, the authors of this paper have proposed standardized early phase specification tests and acceptance criteria for both DS and DP, which are discussed herein. In addition to

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release and stability tests, consideration is given to internal tests and acceptance criteria that are not normally part of formal specifications. These tests can be performed to collect information for product and process understanding, or to allow for tighter control (i.e., target criteria tighter than the release testing criteria), to ensure product quality will be maintained throughout the product's retest period. Based on the information obtained in early development, additional tests and acceptance criteria for other attributes (e.g., water content) can be included as the late development focus shifts to process and product performance and consistency; eventually aligning with the available ICH guidelines (6).

The scope of this position paper has purposely been limited to traditional small molecules that are formulated into solid oral dosage forms intended for US regulatory filings with the desire to build consistency across all worldwide regulatory regions. However, it is believed that the concepts presented can be easily adapted to other dosage forms and routes of administration. Although designed as an industry proposal, it is recognized that each company needs to evaluate these DS and DP specification recommendations based on their individual business needs.

Proposed drug substance specifications

The DS used in the first-in-human (FIH) enabling GLP drug safety studies, referred to in this article as the "tox batch," is a fundamental part of the product lifecycle in defining the specifications for an early phase clinical DS. For the DS used in the tox batch, internal targets rather than formal specifications are routinely used while gathering knowledge about impurities, structural identification, process purging capabilities, rework processing procedures, and potential impact to the safety study. The DS tox batch is typically subjected to a series of tests to confirm description, identity, potency, and purity. The main goals are to:

- Ensure that the correct DS is administered to the test animals (often done via a spectroscopic analysis such as nuclear magnetic resonance or infrared)
- Determine the correct potency value of the DS to ensure the proper dosing of the animals
- Quantitate impurities for toxicology qualification.

For DS intended for clinical studies, additional testing and controls beyond those used for the GLP toxicology lot testing may be required. The testing may be similar to the DS tox batch, but with established acceptance criteria. In early development, the depth of knowledge regarding the synthetic route is still evolving and the DS has not been fully characterized. Accordingly, the initial clinical acceptance criteria are often based on target specifications (see **Table I**), with the safety limits established from the tox batch being evaluated during the disposition process of the GMP clinical DS. If the tox batch is also intended to be used in a clinical study, there is an advantage in that the qualification of impurities for the clinical studies is inherently assured. In this case, the formal specification for clinical disposition of the DS may be established based on the results of tox batch testing. To further highlight the differences in expectations for early phase DS specifications, the authors propose a standardized set of clinical DS specification attributes in the following sections.

Table I: Proposed specification for clinical drug substance (DS) for use in early development.[1]

Attribute	Proposed acceptance criteria	Release testing	Internal testing[5]	Stability testing
Description	Range of color description (e.g., white to almost-white to light yellow powder)	X	–	X
Identification by spectroscopic method	Spectrum conforms to that of reference	X	–	–
Counterion	Report results	X	X	–
Assay	97.0–103.0% "anhydrous basis" or "anhydrous and solvent free basis" if compound is a solvate	X	–	X
Impurities/Degradation products[1]	Individual NMT 1.0% Total NMT 3.0%	X	X	X
Chiral impurity[2]	NMT 1.0%	X	X	X
Residual solvents[3]	ICH limits or other justified limits for solvents used in the final synthetic step	X	X	–
Mutagenic impurities	Follow the referenced guidance (Ref. 13) until ICH M7 is finalized	–	X	–
Inorganic impurities	NMT EMA limits/ADI	–	X	–
Water content	Report results	–	X	X
Solid form[4]	Report results	–	X	X
Particle size	Report results	–	X	–
ROI	NMT 1.0%	–	X	–

[1] In addition to the acceptance criteria, internal targets may be used to trigger action at the proposed 3X ICH identification (0.3%) or qualification (0.5%) limits. Table 2 provides qualification scenarios for individual impurities based on levels in the initial lot used for GLP safety studies versus lots produced for Phase 1 through Phase 2a clinical studies. [2] For a DS with two or more chiral centers, specific rotation may be used to monitor chiral purity in early development due to the complexity of the molecule. Chiral impurities can also be monitored and/or controlled upstream. [3] Solvents used in earlier steps of the synthetic process can be monitored as internal specifications. [4] Physical properties, such as polymorphic form and particle-size distribution, are typically monitored throughout development as non-specification characterization tests. As development progresses towards commercialization, specifications may be introduced. [5] Internal testing can be performed in addition or in replacement of release testing on the final DS. Internal testing may have target acceptance criteria tighter than the release testing criteria. Note: NMT is not more than. ICH is International Conference on Harmonization. ROI is residue on ignition. ADI is acceptable daily intake.

Description. Description, or appearance, is a test describing the visual attributes of the DS. Although technically simple in terms of the test, it can be the subject of much discussion due to potential discrepancies in visual observations from analyst to analyst. Important aspects of this specification are to ensure that there is no visible contamination or anomalous appearance within the DS. The recommended early phase acceptance criteria is often a somewhat broad range of colors (e.g., "white to almost-white to light yellow powder") because there is typically little batch history in early development related to the color of the DS. If it is known that the DS has an inherent color, the specification should be adjusted accordingly.

Identification. At least one form of discerning chemical identification (ID) testing is performed in the early clinical release DS specifications. This testing ensures that the drug being dosed is traceable to the same chemical entity that was qualified in the safety studies. A single ID test by a spectroscopic method such as IR is often employed. Often, the spectroscopic method compares the DS with a known batch that has been well characterized by several analytical methods.

Counterion. The counterion, if present, often is a relatively large percentage of the DS and as such is important to understand the overall potency. The recommended acceptance criteria is "report results" while batch data is accumulated and the variability of the analytical methods is assessed. If the DS is sensitive to extreme counterion levels (e.g., changes in hygroscopicity), internal targets may be implemented to prospectively alert the internal product development team of any potential issues.

Assay. Assay is a critical DS component used to determine the accurate dosing concentration for the corresponding clinical DP. The recommended range is 97.0% to 103.0% (wt/wt on a corrected anhydrous basis) based on typical assay variability for an HPLC-UV method and an acceptable accuracy range required for the early phase clinical studies. This range may be modified with justification for particular circumstances that require a wider acceptance range (e.g., elevated levels of a qualified impurity). In the absence of a reference standard, which may be the case for the initial DS lot, the assay value may be derived by using an assigned chemical potency factor that takes into account related substances, residual solvents, moisture, counterion, and inorganic impurities present.

Impurities and degradation products. Controlling organic impurities and degradation products through the DS specification is required during all stages of drug development, except in initial microdose studies. As discussed, understanding the profile of impurities qualified in the Tox batch is crucial to establishing acceptance criteria for impurities in early phase clinical DS. It is also important to monitor degradation products and impurities present in the clinical DS which may not have been qualified in toxicology studies.

Table II: Example of drug substance (DS) impurity scenario data in early development.[1]

Impurity	Lot A (DS used only for FIH enabling toxicology studies)	Lot B (GMP DS—used for clinical studies through Phase 2a)	Lot B Acceptability considerations
Impurity A (known ID)	0.40%	0.33%	Level of Impurity A is acceptable for early clinical use based on toxicology qualification
Impurity B (known ID)	0.83%	1.4%	Level of Impurity B may be acceptable for early clinical use based on toxicology qualification
Impurity C (known ID)	ND	0.45%	Level of Impurity C is acceptable for early clinical use based on proposed max 0.5% qualification limit
Impurity D (unknown ID)	ND	0.42%	Level of Impurity D is acceptable for clinical use based on proposed Max 0.5% qualification limit but requires ID prior to clinical administration
Impurity E (unknown ID)	NQ	0.22%	Level of Impurity E is acceptable for clinical use without need for ID
Impurity F (unknown ID)	0.05%	0.53%	Level of Impurity F may be acceptable for early clinical use based on internal company guidelines (e.g., safety margin) but requires ID prior to clinical administration
Impurity G (known ID)	ND	0.55%	Subject to disease category considerations, Lot B is not acceptable for use until toxicology qualification of Impurity G is completed

[1] For this table, the following limits were applied for Lot B: individual impurity (NMT 1.0%), qualification (3X ICH or NMT 0.5%), and identification (3X ICH or NMT 0.3%). The examples assume a maximum daily dose of < 2 g/day. ID is identification. ND is not detected. NQ is not quantitated (i.e., below limit of quantitation). FIH is first in human.

In early phase development, there is limited exposure to the clinical candidate and low numbers of individuals participate in these early clinical studies. The risk to patient safety is relatively low compared to late stage development (7, 8). Therefore, this IQ working group proposes controlling impurities in early stage DS at levels that are three times (3X) higher than those defined in ICH Q3 guidelines (9, 10). As clarified in the preamble of these guidance documents, the ICH impurity guidelines are intended for pharmaceuticals approaching the point of final commercial application submission. It is inappropriate to apply these commercial ICH expectations during early clinical development based on the shorter duration of exposure during these earlier clinical studies. This 3X ICH recommendation for DS impurities in early development translates to a qualification threshold for individual impurities being three times the commercial ICH Q3A limit. Specifically, the early phase DS impurity qualification threshold is proposed to be 0.5% or 3 mg per day intake, whichever is lower, for a maximum daily dose ≤ 2 g/day. It is recognized that individual companies within industry may choose to apply different impurity qualification thresholds in early development based on an assessment of safety in the context of the individual development program.

Similarly, an identification (ID) threshold of three times the ICH Q3A limit (0.3%) is proposed for unknown impurities that have not been qualified by toxicology studies. This ID threshold can be set higher for unknown impurities that have already been qualified. It is expected that as development progresses, impurities would be assessed from a toxicological perspective, appropriately qualified as necessary, and the relevant specifications updated accordingly. Later in development (Phase 2b and beyond), when a larger patient population is exposed to the clinical candidate for longer durations of time, the DS specifications for unqualified impurities should be narrowed to approach the limits outlined in the commercial ICH guidelines. **Table II** provides examples of various impurity scenarios to illustrate the utilization of the proposed early clinical identification and qualification thresholds and their potential impact on the acceptability of several example DS lots. All of the included examples assume a maximum daily dose of < 2 g/day and that the individual impurities are nongenotoxic.

For individual impurities that exceed the 0.5% threshold but are supported by toxicology data, an upper limit of not more than (NMT) 1.0% in the DS is appropriate for this stage of development. In some situations, an upper limit greater than 1.0% can be justified if the impurities are qualified at a higher level or if it is evident that the specific compound is also a known metabolite. In either case, a close review of the impurity profiles is required to ensure the quality of the clinical lot(s) is appropriate for the intended use and comparable based on projected exposure levels to the tox lot impurity profile. This may be triggered through the use of internal targets with alerts corresponding to the identification or qualification levels discussed above. For total impurities, the acceptance criterion often correlates with what is known about the individual impurities. An upper limit of 3.0% for total impurities is proposed as suitable for this stage of development. However, a higher upper limit for total impurities may be justified if there are a number of qualified impurities present in the DS.

Chiral impurities. Chiral impurities are usually held to the same criteria as any other impurity or degradation product with a known structural identification, leading to a proposed specification of NMT 1.0%. However, the target limit for the minor enantiomer can vary based on understanding of its pharmacological activity, toxicological qualification, metabolism pathway, and purging capabilities of the synthetic process. Sometimes it is difficult to determine the absolute chiral purity of a DS that has multiple chiral centers due to chromatographic separation challenges. For these molecules, specific rotation can be used to monitor the chiral purity in early as well as late development. Another accept-

Table III: Proposed specifications for powder-in-bottle (PIB) and powder-in-capsule (PIC).

Attribute	Proposed acceptance criteria	Release testing	Internal testing	Stability testing
Description	Same as DS for PIB Capsule shell description for PIC	X	–	X
Identification	Same as DS	X	X	–
Assay	90.0–110.0%	X	–	X
Degradation products	Use data from DS release (list degradation products only)	X	–	X
Uniformity of dosage units	Conforms per *USP* <905>	–	X	–
Disintegration or break test[1]	Disintegration: Per *USP* <701> for capsules, NMT 15 min	X	X	X

[1] For PIC formulations only. Note: DS is drug substance. NMT is not more than.

able approach to controlling chiral impurities in the DS is to monitor the chiral purity of the starting material or at an intermediate stage, where the corresponding isomers can be readily prepared and chiral chromatographic methods developed.

Residual solvents. The early development specifications for residual-solvent control are often set using the ICH established limits, including the consideration of maximum daily dose for Class 2 solvents (Option 2) (11). If the residual-solvent levels are likely to exceed the ICH limits, the specification limits in early development may be set higher than these ICH limits if they are realistically based on the manufacturing process capabilities and if there is low toxicity potential (e.g., Class 3 solvents that form solvates with the DS). In lieu of setting the standard ICH acceptance criteria, evaluation of known safety data are normally provided and justified by the appropriate drug-safety organization. It is also common practice to only set acceptance criteria on non-Class I solvents used in later steps of the synthetic process (e.g., final recrystallization and last synthetic steps) while assuring all solvents are purged through internal/characterization testing of intermediates and/or final DS.

Other internal/characterization tests

In addition to the specification tests already described, there are several tests routinely performed but not included in the specifications that are designed to gather information on the DS as the

Table IV: Proposed specifications for tablets and capsules.

Attribute	Proposed acceptance criteria	Release testing	Internal testing	Stability testing
Description	Describe color, shape and dosage form (e.g., white to almost-white round tablets)	X	–	X
Identification	Conforms to standard. For HPLC-based methods: "The retention time and UV absorption conforms to the standard"	X	–	–
Assay	90.0–110.0%	X	–	X
Degradation products[1]	Individual unspecified NMT 1.0%. Total NMT 5.0%	X	–	X
Uniformity of dosage units	Complies with *USP* <905>	X	–	–
Water content	Report results	–	X	X
Dissolution or disintegration	Dissolution: Report results	–	X	X
	Disintegration: Per *USP* <701> for capsules, NMT 15 min	X	–	X

[1] Does not include drug substance (DS) impurities unless they are also degradation products. In addition to the acceptance criteria, internal targets may be used to trigger action at the proposed 3X ICH identification or qualification limits. Note: NMT is not more than. HPLC is high-performance liquid chromatography.

compound advances through process and analytical development. These tests are often linked to process consistency, and in early phase development there is sometimes a temptation to set wide limits based on limited manufacturing experience. Instead, it is recommended to gather data through internal/characterization testing as manufacturing experience is gained. These tests may become part of the formal specifications when meaningful limits can be introduced based on experience with the compound. These additional characterization tests are discussed below.

Potential mutagenic impurities. Limits for mutagenic or potentially mutagenic impurities have been the subject of much discussion among the industry because ICH is currently drafting its M7 guideline on this topic (12). While the landscape for this class of impurities continues to evolve, the recommendation is to follow existing guidances, such as the 2007 CHMP Guideline on the Limits of Genotoxic Impurities, until ICH M7 is finalized (13).

Inorganic impurities. Inorganic impurities are typically monitored *via* Residue on Ignition (ROI) and heavy metals tests using *US Pharmacopeia* (*USP*) General Chapters <281> and <231>, respectively. The recommendation for ROI in early development is an internal specification of NMT 1.0% with the knowledge that this specification may be tightened as development progresses. The current *USP* heavy metals test is not typically sensitive to many of the metals used in an DS synthetic route and is also currently scheduled to be retired in the near future. As such, residual metals are often monitored internally by inductively coupled plasma–mass spectrometry (ICP–MS) or ICP–atomic emission spectroscopy (OES), or some other metal specific test. The recommended limits for these metals are those set forth in EMA guidance (14). This guidance provides classifications and permitted daily exposures (PDEs) for many of common metal catalysts and metal reagents. Limits for metals not contained within this guidance should be discussed with the internal product development team and appropriate drug safety organization.

Water content, polymorphic forms, and particle size. The proposed internal specifications for water, polymorphic form and particle size distribution (PSD) are all "report results" for compounds in early development. For water content, there is normally limited information available about a compound's sensitivity to moisture in early development. Although it is important that data be collected, initially the acceptance criteria should be "report results" unless the product quality is known to be sensitive to water. In the case where the DS is a known hydrate or shown to be hygroscopic, a target water content range is typically established in the DS specification.

X-ray diffraction, Raman, and solid-state NMR can be used to monitor the polymorphic form of the DS. Because the polymorphic form can impact on solubility, stability, and bioavailability, any change in form is typically monitored during stability studies.

Particle-size distribution (PSD) can be crucial to the ability to formulate the DS into the desired dosage form. In early development, many of the formulations are relatively simple (e.g., powder in a bottle) and the PSD information is normally gathered for development purposes only as an internal test. However in certain cases (e.g., low dose tablets, inhaled products), it is worth considering a suitable PSD target which is normally set in collaboration with the formulation development group.

Other tests to consider. Other tests may be considered as additional specification tests or non-specification tests for data collection purposes. For example, certain physicochemical properties of the DS, such as pH of an aqueous solution, melting point/range, and refractive index may be considered depending on the physical nature of the DS and its intended use. Similarly, there may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, Salmonella, *Pseudomonas aeruginosa*) in the DS. If so, these should be suitably determined using pharmacopeial procedures.

Proposed DP specifications

Quality attributes that affect DP performance are typically not known during the early stages of drug development. Regulatory specifications should focus on ensuring that accurate and reproducible dosing can be achieved in the clinic and that patient safety is not compromised. For many tests, it is important that charac-

terization data be acquired, reported, and monitored to gain an understanding of the DP in the context of characterizing chemical, processing, and packaging sensitivities. As product development continues, the DP formulation and process, along with the corresponding analytical methods usually undergo significant changes. The specifications evolve as additional knowledge is gained (e.g., tightening or widening acceptance criteria, adding tests).

As mentioned in the introduction to this paper, the authors have purposely limited the scope to oral dosage forms with an emphasis on US filings. The following sections outline proposed specifications for powder-in-bottle (PIB), powder-in-capsule (PIC), and tablets and capsules used in early development.

Powder-in-bottle and powder-in-capsule specifications. The PIB formulation is the simplest presentation of a DP for early clinical trials. It involves extemporaneous compounding of the DS into a solution or suspension for oral administration. The development of PIB requires a solubility assessment of the DS and selection of a pharmaceutically acceptable vehicle based on the expected clinical dose range. The DP is then manufactured by weighing the DS into appropriately sized bottles for reconstitution with the chosen vehicle at the clinical site. With the selection of PIB for clinical trials, the product development resources and timelines can be reduced significantly as there is no formal formulation development and thus additional analytical testing for stability, content uniformity, and dissolution are not necessary.

Because only neat DS is weighed into the bottles, the specifications for the release of the DS can be readily used to release the DP. Thus, the results of the appearance and identification tests used initially for releasing the DS can be used for the DP as well. Similarly, the initial impurity results for the DP are normally taken from the DS release data and the degradation products are monitored as part of the recommended DP stability assessment. For PIB assay, the 90.0–110.0% range covers the typical variability observed in fill weights for this formulation. A stability study of the reconstituted PIB is normally conducted to support its use at the clinical site within the recommended storage conditions, as well as holding and dosing times.

Verifying the uniformity of the dosage units is recommended as an internal specification test only. In PIB cases where it is intended to be weighed at the clinical site, a simple weight check during release testing assures that sufficient DS is contained in the bottle. This weight check may be omitted from the DP specifications if it is conducted as part of an in-process control. In cases where the entire contents of the PIB are to be used to make the clinical dosing solution and only a small amount of material (e.g., 1–2 mg) is provided in the bottle, then a more suitable quantitative analytical technique (e.g., a chromatographic method) may be required to verify the accuracy of the dosing concentration.

Similar to PIB, the PIC formulation is another simple presentation of neat DS in a capsule. PIC also provides dosing flexibility but has the added advantage of allowing easy manufacture of matching placebos. The only major difference in its development process compared with PIB is that a compatibility study of the DS with the capsule shell should be done to select a suitable capsule.

The typical PIC specification tests used in early development are comparable to those used for PIB formulations (see **Table III**). Specifically, appearance, identification, and assay all rely on the DS release results. Uniformity of PIC dosage units is performed according to *USP* General Chapter <905> but it can be omitted as a regulatory specification if it is part of an in-process control. In addition, disintegration test per *USP* General Chapter <701> is recommended to ensure that the capsules rupture to allow the release of the drug for absorption.

Tablet and capsule specifications. In early development, tablet and capsules for oral administration often employ "fit-for-purpose" formulation approaches designed to be suitable for wide classes of compounds, with the ultimate goal of facilitating rapid entry into FIH clinical trials. In the case of tablets and dry fill capsules (DFC), these formulations often employ a dry blend or granulations of a nonreactive diluent, a disintegrant, and a glidant to aid in pro-

cessing. As shown in **Table IV**, standardized specifications are frequently established for capsules and tablets that are used in early development that can be segregated into the following attributes:

Description and identification: Visual description of the dosage form and correct identification of the active dose are critical to the integrity of the clinical study and thus are important attributes to be included in the DP specifications. The appearance specification should note the external color and shape of the dosage form. A single discerning identification test is normally sufficient and may be derived from the HPLC test used for assay or impurities based on the comparison of the sample retention time or photodiode array spectrum to that of a comparator DS batch.

Assay: An assay specification of 90.0–110.0% is normally attainable and controllable for most tablet and capsule formulations used in early development and ensures dosage integrity and patient safety. Additionally, this acceptance criteria provides reasonable formulation process control while accounting for typical assay variability and formulation inconsistencies in early development given the higher levels of impurities/degradation products normally observed at this stage.

Impurities and degradation products: Similar to the earlier proposal for DS, it is proposed that identification and qualification thresholds of three times those listed in ICH Q3B guideline (regardless of maximum daily dose), be applied for both impurities and degradation products in DP in the early stage. The proposed limit for unspecified individual degradation products in early development is NMT 1.0%. The limit of 5.0% for total degradation products in early phase DPs is higher than the corresponding limit of 3.0% for total impurities in DS due to the additional variability contributed by the formulation excipients, DP manufacturing process, and DP analytical methods.

In early development, these limits are justified because clinical studies are of limited size and duration and stability information on early drug candidates with respect to sensitivities to moisture, hydrolysis, and oxidation is still being acquired. Later in development, process control, formulation design, and product protection strategies to minimize product degradation can be implemented after the compound sensitivities are better understood and thus tighter degradation product controls are justified.

Uniformity of dosage units: The uniformity of active material in dosage units is important to the integrity of the clinical trial and to patient safety. The guidance for acceptance values is defined in *USP* General Chapter <905>. These acceptance criteria set a minimum standard for batch homogeneity and should be attainable at all stages of development for both capsules and tablets.

Water content: As described for DS, a DP specification only needs to be established to control moisture levels in an investigational capsule or tablet dosage if the product quality or performance is known to be sensitive to water. As development progresses and additional knowledge is attained about product performance and stability in the presence of water, a specification may be applied, as necessary for release, shelf life, or both.

Dissolution and disintegration: For rapidly dissolving immediate release formulations, it is recommended to include disintegration as a regulatory filed specification. Dissolution may be performed as an internal specification (i.e., report results without defined acceptance criteria) to gather product knowledge during early development (e.g., for poorly soluble drugs). As additional knowledge is gained toward establishing an *in-vitro–in-vivo* correlation (IVIVC), dissolution acceptance criteria should be established in later development (i.e., Phase 2b and beyond).

Other tests to consider. Other tests may be added to the DP specification as required. For example, residual solvents should be tested if solvents are used in the DP manufacturing process. Similar to DS, microbial testing may be considered, although a risk assessment may be performed to justify not including this test in the specification for solid oral dosage forms in early development.

Some in-process control tests such as hardness and/or friability may have a critical impact on drug product quality (e.g., chewable tablets). In these cases, acceptance criteria should be included in the specification.

Conclusions

A standard, risk-based approach has been presented for setting DS and DP specifications in early development for conventional solid oral dosage forms intended for US regulatory submissions. The recommendations herein are aimed at ensuring patient safety while allowing the flexibility to adapt to the frequent product and process changes that occur early in development. The authors' goal is to promote clarity and consensus within the pharmaceutical industry and to establish a more detailed approach to specifications in early development that are aligned across the industry and regulatory agencies. To further stimulate discussions on these approaches within the industry and with worldwide health authorities, this IQ working group is planning on conducting a workshop in the near future to promote robust debate and discussion on these proposed specifications in early development. In closing, it is recognized that each company needs to evaluate these early development recommendations based on the objectives of their individual drug development programs and may choose not to adopt this industry proposal on phase appropriate specifications.

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Understanding Particle Coating

Considerations for Coating Polymers

Felix Hofmann and Harald Stahl

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Coating liquids, substrates, and the type of coating application all play a role in the difficulty of the coating process. The authors describe the coating process and propose a matrix to calculate the relative difficulty of a particular coating system, which can be used as a tool for choosing the optimal coating equipment.

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Coatings are applied to particles for various reasons. Cosmetic coatings are used to achieve an appealing appearance, to help differentiate between different dosage forms, and to help with blinding the samples in clinical trials. Functional coatings are required for the protection of the drug from moisture, to mask the bitterness or smell of drugs, and to modify the release of actives by, for example, providing gastric resistance, targeting certain regions in the gastrointestinal system, or prolonging the release. Another commonly used application is drug layering of particles. Here, the API is suspended or dissolved in a binder solution (e.g., polyvinylpyrrolidone) and sprayed onto the substrate. A coating with a functional polymer is often applied directly after the drug-layering step.

Common polymers used in coating have a range of properties and functions, and some examples are shown in **Table I**. The amount of polymer in the coating is given as a range because the actual amount depends on several factors, including:

- Surface area of the particles, with smaller particles requiring higher amounts of polymer to achieve the desired functionality.
- Solubility of the actives, with higher solubility requiring higher polymer weight gains, as in the case of sustained release coatings, in which the drug is released via diffusion through the coating layer.
- Surface structure of the substrate and mechanical stability.

The actual polymer amount should be calculated based on the measured, specific surface area. Specific surface area can be determined by using a BET gas adsorption method or by an image-aided, particle size and shape analysis method.

Coating liquids

Polymers for liquid coating are available as solutions or dispersions with a broad range of viscosities, and the liquids may contain suspended particles. Liquid properties should always be considered when choosing the right equipment for processing. **Table II** gives an overview of coating liquids and recommendations for stirring pump and spray systems. General considerations for processing coating liquids include:

- Suspend particles thoroughly during preparation of the spraying suspension, preferably with high shear forces
- Use low stirrer speeds
- Use larger stirrer diameters for good mixing
- Keep all coating liquids free of air bubbles

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Table I: Coating polymers; polymer amounts are guidelines for spherical particles with diameters in the range of 0.5–1.2 mm.

			Polymer amount	
Polymer (Eudragit, Evonik)	**Property**	**Function**	**% (w/w)**	**mg/cm²**
Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1 (Eudragit E types)	Cationic, soluble < pH 5	Moisture protection	10–30	1–6
		Taste masking	5–10	1–2
Poly(methacrylic acid-co-ethyl acrylate) 1:1 (Eudragit L 30 D-55 and L 100-55)	Anionic, soluble > 5.5	Enteric protection, targeting of duodenum	10–30	4–6
Poly(methacrylic acid-co-methyl methacrylate) 1:1 (Eudragit L 100 and L 12,5)	Anionic, soluble > 6.0	Enteric protection, targeting of jejunum	10–30	4–6
Poly(methacrylic acid-co-methyl methacrylate) 1:2 (Eudragit S 100 and S 12,5) and Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 10:1 (Eudragit FS 30 D)	Anionic, soluble > 7	Enteric protection, targeting of colon	10–30	4–6
Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1 (Eudragit RS types) and Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2 (Eudragit RL types)	Cationic, pH independent, swellable	Sustained release	5–20	1–4
Poly(ethyl acrylate-co-methyl methacrylate) 2:1 (Eudragit NE 30 D and Eudragit NM 30 D)	Neutral, pH independent, swellable	Sustained release	5–20	1–4

Table II: Recommendations for processing of various coating liquids.

Coating liquid	Stirring system	Pump system	Spray system	Remarks
Aqueous solution, low viscosity	–	–	Low atomizing pressure	Easy to process
Organic solution, low viscosity	Closed vessel			
Aqueous solution, high viscosity	–	Wide inner-tube diameter	High atomizing pressure	Sticking tendencies possible
Organic solution, high viscosity	Closed vessel			
Aqueous solution, low viscosity, suspended particles	Keep stirring	Narrow inner-tube diameter	Low atomizing pressure, prime guns shortly before processing	Liquid should be in movement to avoid settling of suspended particles
Organic solution, low viscosity, suspended particles	Keep stirring, closed vessel			
Dispersion, low viscosity	No high shear forces	–	Low atomizing pressure	High shear forces can lead to coagulation
Dispersion, low viscosity, suspended particles		Narrow inner-tube diameter	Low atomizing pressure, prime guns shortly before processing	High shear forces can lead to coagulation; liquid should be in movement to avoid settling of suspended particles

- Use peristaltic pumps for conveying
- Adapt the inner tube diameter to the characteristics of the liquid
- Keep tubes as short as possible
- Prime spray guns as briefly as possible before starting the coating if liquids with suspended particles are used
- Use a spray gun that can be removed during the coating process to ease troubleshooting, especially if handling dispersions.

Film formation and curing

The mechanism of film formation is different for dispersions and solutions. With dispersions, as shown in **Figure 1**, the polymer and the liquid phase are in a heterogeneous system. With solutions, the polymer and the liquid phase are in a homogeneous system, as shown in **Figure 2**. The film formation of dispersions is more complex, and the minimum film forming temperature (MFT) and the glass transition temperature

Figure 1: Film formation from dispersions, T is temperature, MFT is minimum film forming temperature, T_g is glass transition temperature.

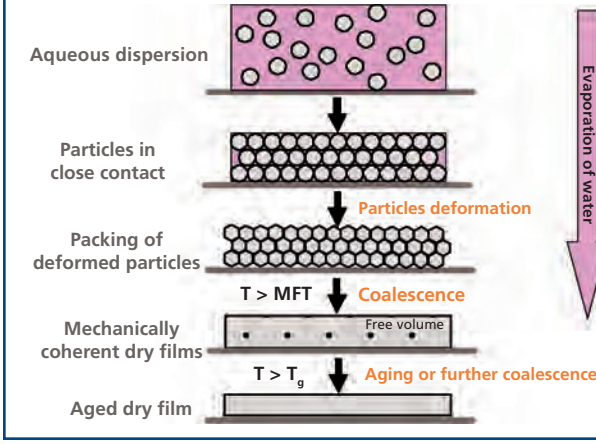

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Figure 2: Film formation from solutions.

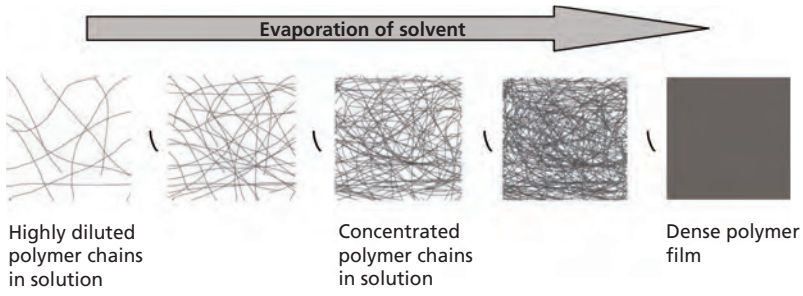

Table III: Input parameters for the application.

Application	Difficulty *	Remarks
Cosmetic coatings	1	Not difficult
Protective coatings	1–2	Water- or solvent-sensitive APIs require low spray rates until a thin uniform layer is applied
Taste masking	2	External filter system avoids incorporation of fine API particles in the coating
Drug layering	3	Sticking tendencies can occur if the API is soluble; optimize size ratio for suspension layering of API on substrate
Controlled-release coatings	4	Excellent film quality and high-yield process are necessary
Multilayer coatings	3–5	Difficulty increases with increasing number of layers and if nozzle cleaning is required

*1=least difficult, 5=most difficult

Table IV: Input parameters for the coating liquid.

Coating Liquid	Difficulty *	Remarks
Aqueous solution, low viscosity	1	Easy to process
Organic solution, low viscosity		
Aqueous solution, high viscosity	2–4	Sticking tendencies possible
Organic solution, high viscosity		
Aqueous solution, low viscosity, suspended particles	2–4	Liquid should be in motion to avoid settling of suspended particles
Organic solution, low viscosity, suspended particles		
Dispersion, low viscosity	3–5	High shear forces can lead to coagulation
Dispersion, low viscosity, suspended particles		High shear forces can lead to coagulation, liquid should be in motion to avoid settling of suspended particles

*1=least difficult, 5=most difficult

(T_g) are essential parameters. Film formation (i.e., coalescence) can only be observed at temperatures above the MFT. For fast film formation during coating, temperatures 10–20 K above MFT are recommended. Aging or further coalescence can occur if the film is stored at temperatures above the T_g. During aging, free volume is reduced, which typically leads to lower permeability and a reduced dissolution rate of the API. Such polymer films need special postprocessing to accelerate the aging process and ensure stable storage formulations if the storage temperature is not well below the T_g.

The film formation of solutions is simpler because they do not have an MFT. The film is formed by evaporation of the solvent, and the process temperature defines the evaporation speed. If the solvent is evaporated too fast, free volume in the polymer film will be generated, and aging effects can occur as described above.

In general, removing volatile substances (i.e., solvent) from the film can reduce the permeability of the film independently of the T_g. A drying process is recommended, therefore, for all coating liquids. This effect should not be confused with aging of the polymer film.

Types of coaters and associated process parameters

Top-spray systems. These systems were developed mainly for making agglomerates. With a spray nozzle placed above the product bed, particles are locally overwetted. Such particles will meet randomly and form larger granulates by sticking to each other. In the case of coating, exactly the opposite is required. No particles should meet in a wet state because of the risk of forming agglomerates. In a top-spray process, the only way to tackle this problem is by reducing the spray rate until unacceptable levels of agglomeration or picking (i.e., particles sticking for a short duration to each other and damaging the coating when they separate again) are eliminated. This reduction in spray rate will in turn increase overall process time.

Bottom-spray systems. Compared to top-spray coaters, the mechanical setup of the bottom-spray coaters is better for preventing agglomerates. The most commonly known bottom-spray system is the Wurster coater. It was invented in 1953 and continued to be the state-of-the-art for 35 years. For simpler applications such as cosmetic coatings, the Wurster coater was used successfully until the mid-1980s. By that time, however, companies commercialized more complex formulations that often faced serious issues with agglomeration, regular nozzle blockages, and necessity of splitting batches if higher weight gains were required. These problems sometimes led to significant product losses, extremely long processes, and difficult scale-up procedures, which drove demand for the development of a new generation of coaters.

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Table V: Input parameters for the substrate.

Substrate	Difficulty*	Remarks
Pellets	1–2	Narrow particle size distribution, best flowability, low tendency to break
Mini tablets	1–3	Narrowest particle size distribution, good flowability, tendency to break depending on tablet formulation
Granules, high shear	2–3	Variation in particle size, good flowability, slight tendency to break
Granules, fluid bed	3–5	High variation in particle size, good flowability, high tendency to break
Crystals	1–5	Difficulty of crystals is hard to predict as there is huge variability in size, shape, brittleness and hardness; suitability of crystals as substrate needs to be carefully evaluated

*1=least difficult, 5=most difficult

Table VI: Maximum score for which fluid-bed technologies should be used.

Performance	Cumulative difficulty score	Remarks
Top Spray	<4	High risk of agglomeration
Wurster	<30	Limitations possible in weight gain and overall process efficacy
Modern Bottom	<125	State of the art
Tangential		

Table VII: Set up and process data for the fluid-bed processor

Fluid-bed processor	MP 1	MP 2/3	MP 4/5
Number of spray guns	1	1	3
Nozzle bore (mm)	1.2	1.8	1.8
Gun-to-product distance (cm)	7	19	19
Tube diameter (mm)	1.6	4.8	6.4
Atomizing air pressure (bar)	2.5	2.5	2.5
Inlet air volume (m^3/h)	~150	~500	1750
Drying air capacity ($m^3/(min*kg)$)	1.0	0.9	0.5
Inlet air temperature (°C)	~43	~48	~48
Outlet air temperature (°C)	~23	~24	~23
Product temperature (°C)	~22	~23	~22
Spray rate (g/(min*kg))	6-14	5-13	3-7
Inlet air humidity (g/kg)	~4.5	~4.0	~3.0
Outlet air humidity (%])	52–74	56–78	45–79
Spraying time (min)	95	113	185

Table VIII: Curing conditions.

Fluid-bed processor	MP 1	MP 2/3	MP 4/5
Inlet air temperature (°C)	90-97	90-95	90
Outlet air temperature (°C)	38-40	36-40	34-36
Product temperature (°C)	42-45	42-45	40-45
Spray rate (g/(min*kg))	~21	~15	~11
Inlet air humidity (g/kg)	6.4	4.5	2.0
Outlet air humidity (%)	49-50	48-52	50-54
Inlet air temperature (°C)	90-97	90-95	90

Modern, bottom-spray systems. The Aeromatic-Fielder Precision Coater and the Glatt Wurster HS were introduced in the late 1980s. Both follow the principal idea of the Wurster coater but eliminate most of its limitations through mechanical optimizations and improved fluid dynamics. These machines eliminated many of the shortfalls in earlier systems and were technology leaders for the following decades. They allowed, for example:

- Running multitube installations, which made scale-up easier and processes faster
- Inspection or cleaning of nozzles without interrupting the process
- Weight gains up to 1:10 without the necessity of splitting batches.

Tangential-spray systems. Hüttlin's Kugelcoater and Aeromatic-Fielders FlexStream marked the next stage in development by eliminating the need for columns. Both systems use tangential spray and remove the risk of particles getting thrown into the highly moist zone in front of the nozzle tip(s) by introducing a protective air stream around the nozzle. The systems' performance is similar to the modern bottom-spray systems described above. Additionally, the tangential-spray systems can be used for granulation without using extra product containers. Their design allows easy scale-up.

Application matrix

Because particle coating is a highly complex process, thorough knowledge about the type of application, coating liquid, and substrate type is required. An application matrix was developed from the experience of numerous particle-coating projects to assist in rating the difficulty connected with coating. Difficulties for applications, coating liquids, and substrates are rated in **Tables III** to **V** and a cumulative difficulty score is calculated using the following equation, in which D=difficulty:

$$\text{Score} = D_{\text{Application}} * D_{\text{Coating liquid}} * D_{\text{Substrate}}.$$

Table VI shows the maximum difficulty scores for which different fluid bed processor technologies should be used.

BEST PRACTICES FOR ACHIEVING PRODUCT QUALITY IN STERILE MANUFACTURING

LIVE WEBCAST: Tuesday, November 6, 2012 at 11:00am–12:00pm EST

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EVENT OVERVIEW:

Product quality is the utmost consideration for pharmaceutical companies, who must successfully manage the technical and regulatory considerations to design, implement, and monitor manufacturing processes to consistently and reliably produce a safe and high-quality product. For sterile manufacturers, the quality bar is even higher as sterile manufacturing has become increasingly more complex due to the increase in the number of poorly stable compounds, new technologies, unit operations, and controls. This 60-minute webcast will provide practical guidance and insight on the strategies and practices for quality control and assurance in sterile manufacturing, including applying the life-cycle approach under FDA's *Guidance for Industry: Process Validation: General Principles and Practices* for process design, process qualification, and continued process verification. Our speakers will focus on sharing:

- Key elements/overview of FDA's process validation guideline
- Strategies for implementation and best practices
- Technical and quality considerations and responsibilities in the outsourced relationship

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- Managers, group leaders, or directors external or third-party manufacturing
- Managers, group leaders, directors of clinical supplies
- Managers, group leaders, or directors of R&D

PRESENTERS

Sandra Lueken
Director of Quality,
Baxter BioPharma Solutions

Scott Bozzone, PhD
Senior Manager, Quality Systems and Technical Services-Validation,
Pfizer
Co-leader,
Parenteral Drug Association's Process Validation Interest Group

MODERATOR

Patricia Van Arnum
Executive Editor
Pharmaceutical Technology

For questions, contact Sara Barschdorf at sbarschdorf@advanstar.com

Figure 3: Dissolution test of the coated and cured pellets produced in lab (2.5 kg), pilot (10 kg), and production (60 kg) scale.

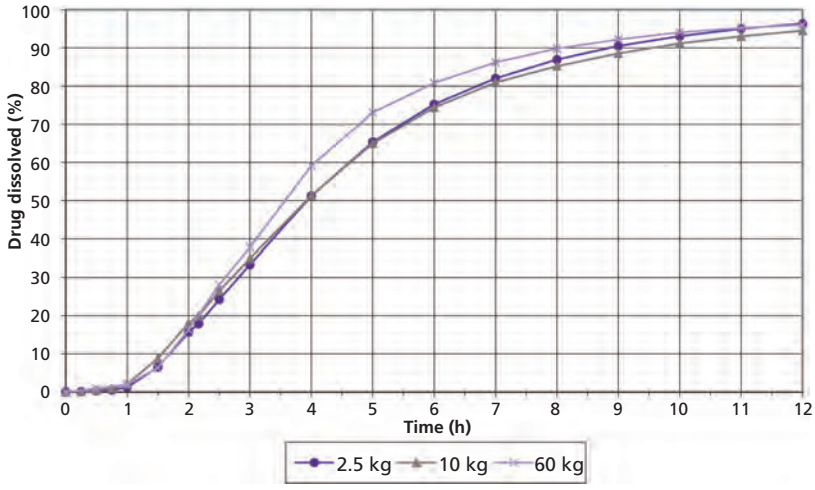
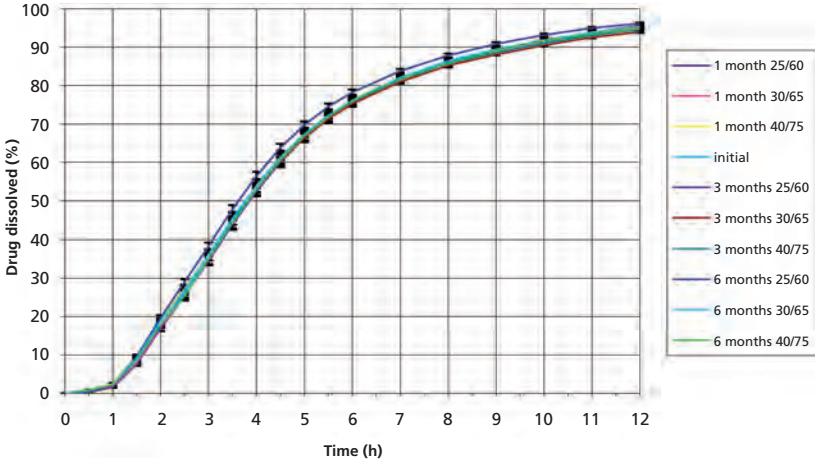


Figure 4: Six month storage-stability test of pilot-scale batch.



A working example for the application matrix is a scale-up study of a coating polymer (Evonik, Eudragit NE 30 D) on propranolol pellets, for which D=2. A multi-layer coating application, for which D=5, involved a functional coating followed by in-process curing with purified water, for which D=1. The coating liquid was a low viscous dispersion with suspended particles with D=3. The application matrix equation resulted in a cumulative difficulty score of 30.

With this score, the work could have been conducted in a Wurster or modern bottom-coating system, but a tangential system (Aeromatic-Fielders, FlexStream) was chosen because of its easier scale-up. Experiments were run with lab, pilot, and production scales using 2.5, 10, and 60 kg of core material, respectively, that was coated and in-process cured using three sizes of a fluid-bed processor (Aeromatic Fielders, Flexstream MP 1, MP 2/3 and MP 4/5, respectively). Process parameters are listed in **Table VII.** A coating of 12% dry matter of a polymer (Evonik, Eudragit NE 30 D) was applied on the core material for each batch. Coating excipients were 100% talc, 10% polysorbate 80, and 10% hypromellose (5 mPa·s) based on the dry matter (Evonik, Eudragit NE 30). Purified water was used as diluent; the solid content of the spraying suspension was 20%.

A silica suspension (Grace, Syloid 244FP, 10% w/w) was sprayed into the process to avoid pellet agglomeration. After heating to the desired product temperature, water was sprayed into the process to control the humidity level. Once curing conditions were reached, the process was kept steady for 30 min. The key parameters for in-process curing were product and outlet temperature and outlet air humidity (see **Table VIII**). Differences in drying air capacity and inlet air humidity were compensated by the spray rate and inlet air temperature. The dissolution test was carried out in a *United States Pharmacopeia (USP)* apparatus II (i.e., paddle apparatus) with 100 rpm in 900 mL 0.1N hydrochloric acid for 2 h followed by a full change to 900 mL phosphate buffer with a pH=6.8 (1). Storage stability of the pilot-scale batch was conducted according to ICH guidelines using high-density polyethylene bottles for packaging (2). An F-test (95% significance level) showed no difference between the release profiles of the different scales or during the six-month storage stability test (see **Figures 3 and 4**).

This example shows how a fundamental understanding of the process complexities and the appropriate choice of a fluid-bed processor led to successful scale-up of a particle coating.

Conclusion

From a processing point of view, most coating applications are similar. Nevertheless, the level of coating difficulty varies dramatically depending on the core materials, the type of coating fluid, and the amount of coating that needs to be applied. The application matrix helps identify the optimal coating process and equipment, which, along with an understanding of how the components interact, can ensure successful particle coating.

References

1. *USP* 35 General Chapter <711>, "Dissolution."
2. ICH, Q1A(R2) *Stability Testing of New Drug Substances and Products,* Step 5 version (2003). **PT**

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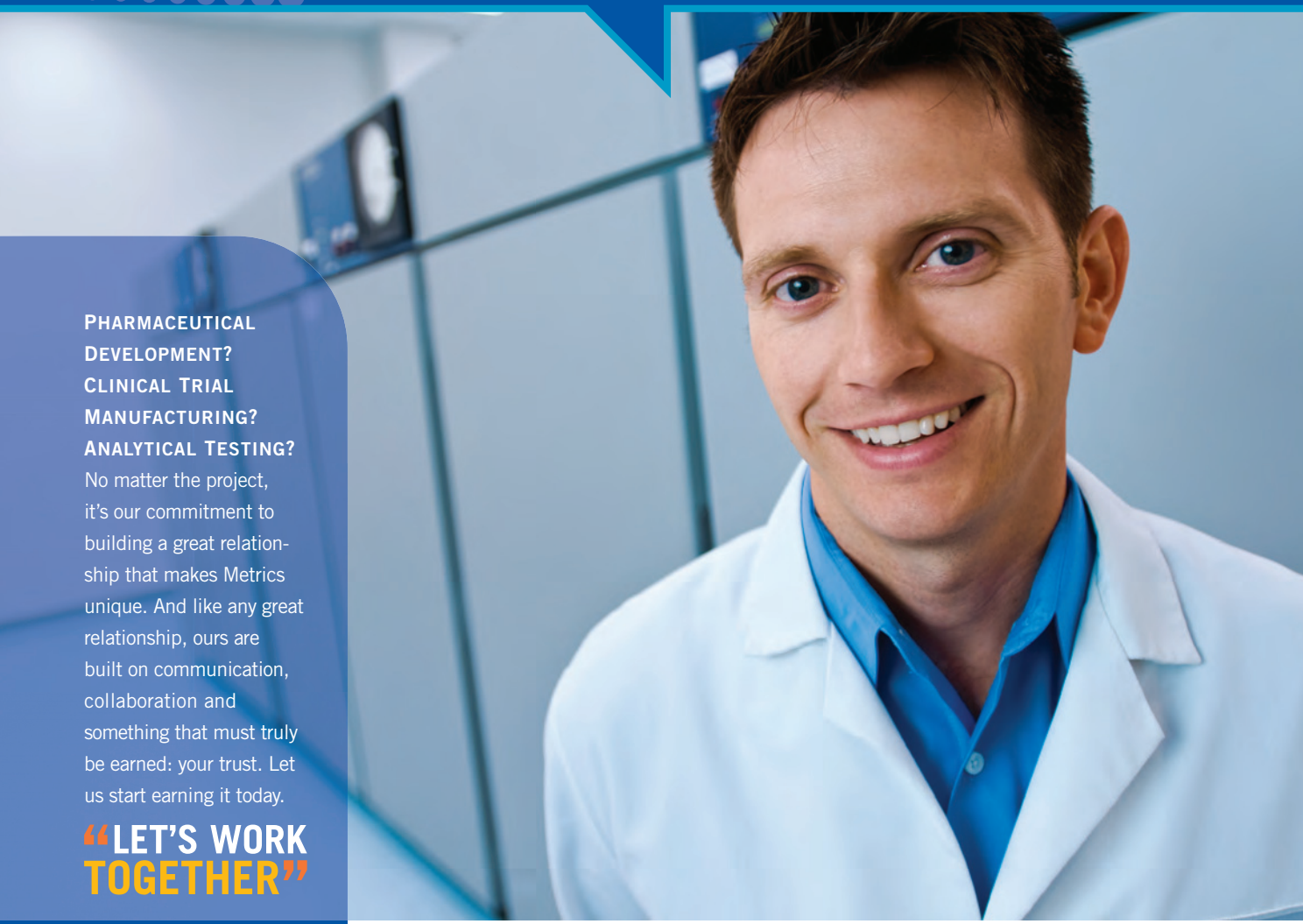

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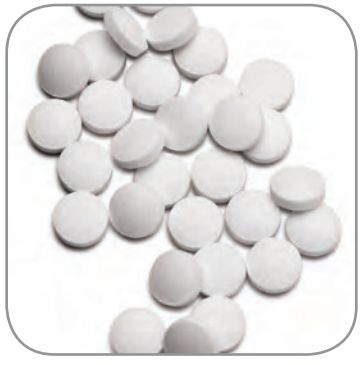
Applying Quality by Design

For Extended-Release Hydrophilic Matrix Tablets

Ian. A. Robertson, Sandip B. Tiwari, and Tim D. Cabelka



CREATIVE CROP/GETTY IMAGES

Understanding the effect of excipients' material attributes on the final drug product is integral to quality by design (QbD). The authors examine the effect and interaction of variations in the material properties of hypromellose on powder flow, the physical attributes of tablets, and *in vitro* drug-release profiles from two model formulations of extended-release hydrophilic matrix tablets using QbD principles.

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*To whom all correspondence should be addressed.

Quality by design (QbD) is a systematic approach to designing and developing pharmaceutical formulations and manufacturing processes to ensure predefined product quality (1). In the case of hydrophilic matrix tablets, it is important to consider potential variability in material attributes of the rate-controlling polymer in addition to variability in the API properties and processing conditions (2–4). This proactive and enhanced understanding supports efficient pharmaceutical product development.

This study examines the effect and interaction of variations in hypromellose physicochemical properties on powder flow, the physical attributes of tablets, and *in vitro* drug-release profiles from two model formulations of extended-release (ER) hydrophilic matrix tablets using QbD principles. This article presents a QbD approach to determine the effect of material attributes on both the physical properties and *in vitro* drug-release performance of the matrix tablets.

The excipient hypromellose *United States Pharmacopeia (USP)* substitution type 2208 (Methocel K15M Premium CR, Dow Chemical) was used as the rate-controlling polymer for two case studies with a soluble drug (propranolol hydrochloride [HCl]) and slightly soluble drug (theophylline). Normal variation of Methocel material attributes (apparent viscosity, percent hydroxylpropoxyl (HP) substitution, and particle size) was studied at polymer concentrations of 15% w/w and 30% w/w. The study demonstrated consistent physical properties for direct-compression blends and subsequent tablet cores, irrespective of the Methocel concentration or drug included. *In vitro* drug release, however, showed greater sensitivity to material-attribute variability at lower polymer concentration.

The importance of QbD

QbD is a systematic approach to pharmaceutical development that results in increased quality and reduced costs. QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality (1). Adoption of QbD principles for new-chemical-entity and generic-drug products is becoming an expectation by regulatory agencies to better ensure that high-quality medicines are available to the end-user, namely the patient. Building quality into drug products by design also benefits developers. Successful first-cycle approval, reduction of postapproval changes, and the potential of real-time release could offset initial investment associated with QbD implementation.

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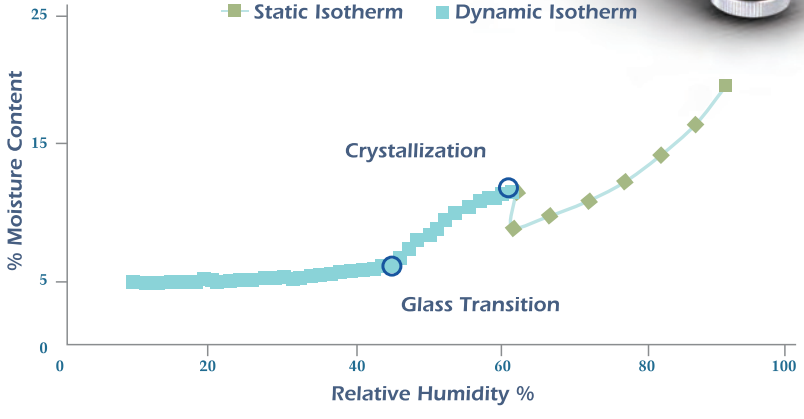

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Importantly, enhanced understanding of the product and manufacturing process also can lead to the elimination of production rejects and recalls due to quality issues. Before FDA introduced QbD into the chemistry, manufacturing, and controls (CMC) review process in 2004, the amount of product waste due to manufacturing mistakes was reported to be as high as 50% (5). Clearly, for the end-user, the patient, drug-product recalls associated with quality issues, and potential shortages of medicines are a risk to health. For the manufacturer, these problems can lead to severe financial penalties due to loss of market share and even litigation. Needless to say, adverse publicity also can erode consumer confidence and damage a manufacturer's reputation.

The foundations of QbD for drug-product development are contained within the International Conference on Harmonization (ICH) quality guideline ICH Q8 (R2) *Pharmaceutical Development* (R2) (6). This guideline for pharmaceutical development includes "determining the critical quality attributes (CQA) of the drug substance (and) excipients and selecting the type and amount of excipient to deliver drug product of the desired quality" (6). This determination is of particular importance for designing drug products for ER applications, where the performance of the rate-controlling excipient is crucial to precisely deliver the required amount of drug over time. Typically, for ER technologies, such as hydrophilic matrices, barrier membrane-coated multiparticulates and osmotic delivery systems, the dose of the drug within a single unit is much greater than in an immediate-release product. Understanding the primary rate-controlling excipients' physiochemical properties (i.e., material attributes) is important to ensure robustness of the finished product and to mitigate any risk of batch-to-batch variability and/or potential premature drug release that could impact the patient.

Hydrophilic matrix products

Hydrophilic matrices are a well-established ER delivery platform due to their flexibility in delivering a wide range of drugs, relatively simple manufacturing, and generally good product stability and shelf-life. The majority of marketed hydrophilic matrix products use high-viscosity hypromellose (HPMC) as the rate-controlling polymer. HPMC polymers are semisynthetic materials derived from cellulose with chemical modification to add both the methoxyl (CH3–O–) and hydroxypropoxyl ($CH_3CHOHCH_2$–O–) functional groups. In addition to the type and distribution of these functional groups, the polymer molecular weight (measured indirectly by apparent viscosity) and particle size are key material attributes that could affect drug-product manufacturability and performance.

Methocel for hydrophilic matrix applications uses two types of chemical substituent groups signified by either "E" or "K" designations (7). Methocel E chemistry is the *USP* substitution type 2910; K chemistry is the substitution type 2208. The number that follows the chemistry designation identifies viscosity in millipascal-seconds (mPa·s), measured at 2% weight/volume aqueous solution at 20 °C. The letter "M" is used to represent a multiplier of 1000.

Along with the polymer, ER matrix formulations typically consist of the API, filler, binder, glidant, and lubricant. Other functional ingredients also may be added, such as additional polymers to modify the release rate, buffering agents to mitigate the effects of pH-dependent drug solubility, stabilizers, and surfactants. Commonly, a matrix-tablet formulation also will be film-coated with a conventional immediate-release coating or may be coated with a functional modified-release coating system.

Accordingly, the matrix formulation can be designed to influence the mechanism and rate of drug release. The design can include polymer type and concentration, drug solubility and dose, polymer-to-drug ratio, filler type and concentration, polymer-to-filler ratio, the particle size of the drug and polymer, and the shape of the matrix (8–12). Drug solubility is an important factor in determining the mechanism of drug release from hypromellose hydrophilic matrices (i.e., diffusion, diffusion and erosion, or erosion) and guides the selection of other excipients as well as the viscosity and chemistry grade of the hypromellose.

Nevertheless, as the principal rate-controlling excipient, it is important to assess the criticality of both polymer concentration and the effect of material-attribute variation (within the manufacturer's sales-specification limits) on the final drug-product quality. This knowledge is important to justify development of a robust formulation and to set an appropriate control strategy for consistent manufacture of a high-quality finished product.

Materials and methods

Two case studies were designed to investigate the influence of material attributes: the percent HP substitution, viscosity, and particle size on the functional performance of hydrophilic matrix-tablet formulations (2–3).

The rate-controlling polymer in the model formulations was Methocel K15M Premium CR (*USP* substitution type 2208). The designation of "15M" describes a relatively high-viscosity material, and the "CR" grade is designed for controlled-release applications.

Polymer concentration can be an important factor for matrix robustness. Two polymer concentrations, therefore, were evaluated: 30% w/w, which has been shown to produce robust formulations, and 15% w/w, which was considered relatively low and could result in performance differences of the hydrophilic matrix tablet associated with variability in the material attributes.

For these case studies, Methocel K15M Premium CR batches were carefully selected. Six of the batches were selected on the basis of having two out of three material attributes (percent HP, particle size, and apparent viscosity) within the nominal manufacturer sales-specification values, with the third property at the "high" or the "low" extremes of the normal sales-specification range. In addition, one batch had all three properties close to the nominal specification values, denoted as "center point" (see **Table I**). A total of 14 matrix formulations (seven each for 15% and 30% w/w polymer concentration)

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Table I: Physiochemical properties of hypromellose (Methocel K 15 Premium CR , Dow Chemical) batches.

Hypromellose batch name	2% Viscosity[a] (mPa-s)	Percent through 230 mesh[b]	Percent (%) HP[c]	Percent (%) MeO[d]
High viscosity	24865*	57.7	9.1	23.1
Low viscosity	13462	55.0	9.6	22.9
High % through 230 mesh	17054	62.8	9.5	22.4
Low % through 230 mesh	20156	52.6	9.4	23.1
High % HP	16698	56.2	10.5	22.5
Low % HP	16833	56.2	8.4**	22.8
Center point	19036	57.5	9.4	22.6

HP is hydroxypropoxyl content. MeO is methoxyl content.
[a] Maximum/nominal/minimum *USP* specification (mPa • s): 24780/17788/13275.
[b] Typical maximum/nominal/minimum production range (% through 230 mesh): 70.0/60.0/50.0.
[c] Typical maximum/nominal/minimum production range (% HP): 10.5/9.5/8.5.
[d] Methoxyl content, for reference purposes only; not a variable in the experimental design.
* Outside high end of sales specification.
**Outside low end of sales specification.

Table II: Extended-release model formulation containing propranolol hydrochloride as the active ingredient.

Ingredient	Percent composition
Propranolol hydrochloride (Ipca Laboratories)	45.7%
Hypromellose (Methocel K 15M Premium CR, Dow Chemical)	15.0% (low) or 30.0% (recommended)
Microcrystalline cellulose (JRS Pharma)	38.8% or 23.8%
Magnesium stearate (Peter Greven GmbH)	0.5%
Total	100%

Table III: Extended-release model formulation containing theophylline as the active ingredient.

Ingredient	Percent composition
Theophylline (Medilom)	45.2%
Hypromellose (Methocel K 15M Premium CR, Dow Chemical)	15.0% (low) or 30.0% (recommended)
Lactose (FastFlow, Foremost)	38.8% or 23.8%
Magnesium stearate (Peter Greven GmbH)	0.5%
Silicon dioxide (Cabot)	0.5%
Total	100.0%

were prepared. The Methocel K15M Premium CR batches used in these studies will be referred to by the "batch name" listed in **Table I**.

The methoxyl substitution content could be considered another material attribute for Methocel that may affect the robustness of the formulation. Prior assessment of the methoxyl content variation (from the manufacturer's sales-specification) showed this to be precisely controlled, and therefore, it was not considered to be a significant variable and was excluded from the study.

Propranolol hydrochloride ER model formulations

For the first study, the model API was propranolol HCl (soluble drug, 50 mg/mL, 160-mg dose). The formulation is detailed in **Table II.**

Tablet preparation procedure. Propranolol HCl, hypromellose, and microcrystalline cellulose were passed through an ASTM #30 mesh (600 µm) screen and mixed in a four-quart V blender (Model B Lab Blender, Patterson–Kelley) at 26 rpm for 10 min. Magnesium stearate was screened through an ASTM #40 mesh (400 µm) screen and added to the powder mixture, followed by blending for an additional 3 min. The final powder mixtures were compressed at 5–20 kN (compaction pressure of 70–280 MPa) using an instrumented 10-station rotary tablet press (Piccola, RIVA) at 20 rpm using standard round 9.52-mm concave tooling and a tablet weight of 350 mg.

The formulated powder blends were analyzed for bulk and tapped densities using a VanKel density tester (Model 10705, Varian), flowability using a flow tester (Sotax FT 300, Sotax), and loss on drying (LOD) using an infrared (IR) moisture balance (Model IR-200, Denver Instrument). Tablet weight, breaking force, diameter, and thickness were measured with an automated tablet tester (Multicheck V, Erweka). Tablet friability was measured using a VanKel friabilator (Varian) at 100 revolutions and 25 rpm. A dissolution study was performed using an *USP* Apparatus II, 100 rpm, with sinkers, and 1000 mL of a pH 6.8 phosphate buffer. Propranolol release was detected at a wavelength of 289 nm using a ultraviolet (UV)-visible spectrophotometer (Agilent

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Figure 1: Propranolol hydrochloride release profiles—effect of viscosity.

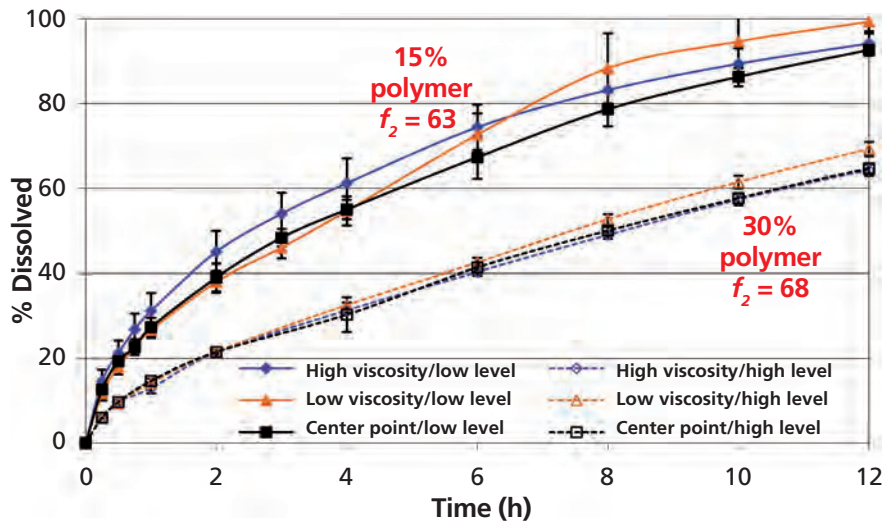
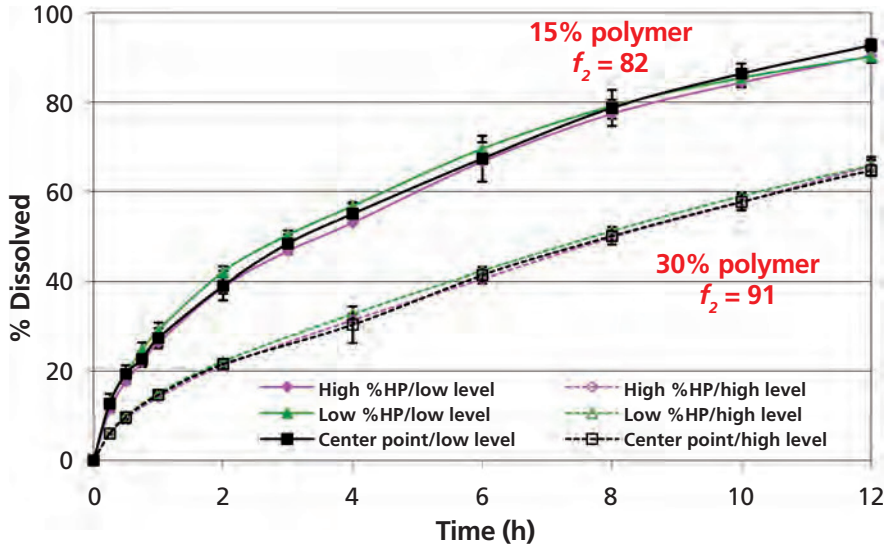


Figure 2: Propranolol hydrochloride release profiles—effect of percent hydroxypropoxyl (HP) content.



8453, Agilent Technologies) fitted with quartz flow cells of a 2-mm path length.

The similarity factor (f_2), which is a measurement of the similarity in the percentage of dissolution between two curves, was calculated by comparing the high versus the low end of the selected physicochemical property. Two dissolution profiles are considered similar when the f_2 value is > 50. In addition, the release exponent (n) and release-rate constant (k) were calculated by fitting the dissolution data to the Power Law equation $(M_t/M_{inf}) = k\,t^n$, where M_t is the amount of drug released at time t; M_{inf} is the amount of drug released over a very long time, which corresponds in principle to the initial loading; k is the kinetic constant; and n is the release exponent (12).

Theophylline ER model formulations

In the second study, the model API was theophylline anhydrous (slightly soluble drug, 8.3 mg/mL, 160-mg dose). The formulation is detailed in **Table III**.

Tablet-preparation procedure. Theophylline, hypromellose, lactose, and fumed silica (Cab-O-Sil, Cabot) were passed through an ASTM #30 mesh (600 µm) screen and mixed in a four-quart V blender (Patterson-Kelley) at 26 rpm for 10 min. Magnesium stearate was screened through an ASTM #40 mesh (400 µm) screen, added to the powder mixture, followed by blending for a further 3 min. The final powder blends were compressed at 15 kN (210 MPa) using an instrumented 10-station rotary tablet press (Piccola, RIVA) at 20 rpm using a standard round 9.52-mm concave tooling and a tablet weight of 350 mg.

All blends were analyzed for bulk and tapped density using a VanKel density tester (Varian) and LOD (Model IR-200, Denver Instrument). Tablets were examined for physical properties, including weight variation, thickness, and hardness as well as friability. Drug release was measured using an *USP* Apparatus II (VK 7000, Varian) at 100 rpm with sinkers and 1000 mL of deionized water at 37 ± 0.5 °C. Theophylline release was detected at a wavelength of 272 nm using a UV-visible spectrophotometer (Agilent 8453, Agilent Technologies) fitted with quartz flow cells of a 2-mm path length. The similarity factor (f_2) was calculated by comparing the high versus the low end of the selected physicochemical property. In addition, the release exponent (n) and release-rate constant (k) were calculated by fitting the dissolution data to the Power Law equation (11).

Results

Propranolol hydrochloride ER model formulations. The results indicated that at 30% polymer concentration, all propranolol

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EVENT OVERVIEW

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This webcast will provide you with insight into how to find the right signs and understand them to help you speed along the path to achieve the best outcomes. You will hear a detailed case study about the development of an insoluble compound that otherwise never would have made it to First in Man and lessons learned from that experience. These presentations and interactive Q&A sessions will provide you with insight into how to speed your molecule to First in Man studies with an optimal formulation strategy.

Jason Vaughn will present information on "Successful Dosage Form Development for First in Man," and Jim Wright will speak on "A Case Study on Getting an Insoluble Compound into Man."

Who Should Attend:

- Formulation scientists
- Formulation R&D managers, directors, and group leaders
- Process development scientists
- Process development managers, directors, and group leaders
- Section Heads
- Project Managers
- Technical personnel involved in process optimization
- Technical personnel involved in formulation and development
- Scientists, manager, directors, and group leaders involved with formulation

Key Learning Objectives:

- Learn how following the correct path by reading the signs in early development help you reach major milestones faster and with a more viable formulation.

Presenters

Jim Wright, Ph.D.
Chief Scientific Officer
BIND Biosciences

Jason M. Vaughn, Ph.D.
Director of Scientific Affairs
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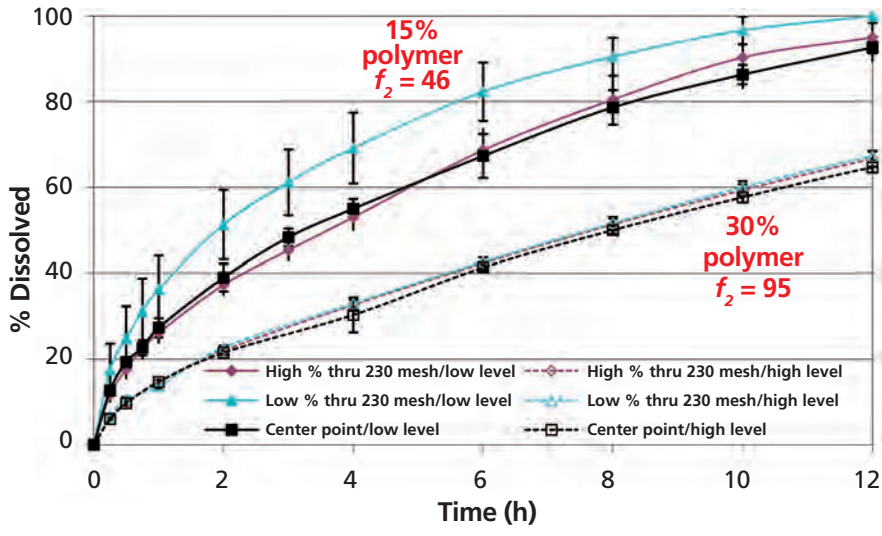
Figure 3: Propranolol hydrochloride release profiles—effect of particle size.



blends exhibited comparable bulk/tapped density and powder flow. All matrix tablets had comparable hardness, tensile strength, and friability values. Similar results were observed for all formulations with 15% w/w polymer concentration, indicating that the material attributes (i.e., percent HP, particle size, and viscosity) of Methocel K15M CR had minimal or no influence on the physical properties of the formulated powder blends or tablets. All matrices showed low friability (≤ 0.06%) and consistent content uniformity (97.8–101.5%).

Propranolol HCl release was slower when polymer concentration increased from 15% to 30% w/w (see **Figures 1–3**). At both 15% and 30%, drug-release profiles were similar (f_2 = 63 and 68, respectively) despite variations in Methocel viscosity (see **Figure 1**). Use of higher polymer concentration (30% w/w) resulted in lower tablet-to-tablet variability as indicated by the error bars.

The effect on drug release of the percent HP substitution of hypromellose on the drug-release profiles is shown in Figure 2. Here too, at both 15% and 30% polymer concentration, the drug-release profiles were similar (f_2 = 82 and 91, respectively) despite variations in percent HP content.

The effect of Methocel particle size on the drug-release profiles is shown in **Figure 3**. At 30% polymer concentration, the drug-release profiles were very similar (f_2 = 95) despite variations in particle size. At 15% polymer concentration, however, the batch with the larger particle size (low percentage through 230 mesh) gave a faster and dissimilar (f_2 = 46) drug-release profile compared with the batch with the finer particle size (high percentage through 230 mesh) of the polymer. In addition, tablet-to-tablet variability was higher in the formulation containing the coarser particle size in comparison to the center point and fine particle-size formulations. All formulations produced good results fitting to the Power Law equation ($R^2 > 0.99$). The release exponent (n) was in the range of 0.59–0.63 for 30% w/w polymer formulations and 0.48–0.56 for 15% w/w polymer formulations, indicating drug release mainly by diffusion (11).

Higher polymer concentration may decrease sensitivity of the formulation to minor variations in raw materials or the manufacturing process. The potential for particle-size variability to influence *in vitro* drug release was shown to be negated when higher concentration of Methocel K15M CR was used.

Theophylline ER model formulations. Study results indicated that comparable physical properties were obtained for theophylline powder blends and compressed tablets at both 15% and 30% polymer concentration. All matrices showed low tablet-weight variation (1.0–1.9%), low friability (≤ 0.14%), and consistent content uniformity (94.8–100.0%).

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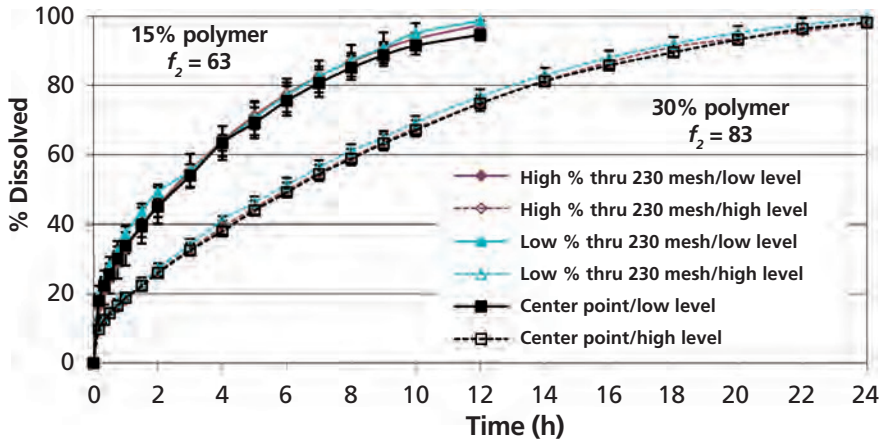
Accomplishments: Launch of 3 products, both biologic and small molecule

Figure 4: Theophylline release profiles–effect of particle size (n = 6; drug dissolution using *USP* Apparatus II at 100 rpm with sinkers and 1000 mL of deionized water at 37 ± 0.5°C).



Theophylline release rates were lower when polymer concentration was increased from 15% to 30% (w/w) as shown in **Figure 4.** At both 15% and 30% polymer concentrations, drug-release profiles were similar ($f_2 > 50$) despite variations in Methocel viscosity, percent HP substitution, and particles size. Results for all formulations fit to the Power Law equation ($R^2 > 0.99$). The release exponent (n) was in the range of 0.50–0.62 for 30% w/w polymer formulations and 0.39–0.48 for 15% w/w polymer formulations, indicating that diffusion is the principal mechanism of drug release (13).

The linear-regression model also was applied to examine the relationship between drug-release response (i.e., release constant (k), release exponent (n) or time for 80% drug release [$T_{80\%}$])and predictor variables (i.e., viscosity, percent HP, and particle size measured by percent through 230 mesh). Results indicated statistically an insignificant relationship (p value > 0.1).

Conclusion

The study demonstrated that evaluation of hypromellose materials-attribute variability on matrix formulation robustness can be readily determined. It was shown that material-attribute-variability effects can be dependent upon the rate-controlling polymer concentration. This observation has important implications for designing Methocel-based ER matrices.

Results indicate that the ranges studied for viscosity, percentag of HP, and particle size of Methocel K15M Premium CR had no significant effect on the physical properties of propranolol HCl or theophylline formulation blends and tablets. This finding is important for direct-compression processing because blend properties, such as flow and compactability, can impact CQA, such as content uniformity for a matrix formulation.

For both model formulations, the drug-release profiles from Methocel matrices were slower when the polymer concentration was increased from 15% to 30% w/w. At 30% polymer concentration, the drug-release profiles of propranolol HCl were similar ($f_2 > 68$) despite variations in viscosity, percent HP, and particle size. At 15% w/w polymer concentration, the drug-release profiles of propranolol HCl were similar ($f_2 > 63$) despite variations in viscosity and percent HP substitution; therefore, for these case studies, both material attributes were noncritical.

An early indication of risk associated with material-attribute variability is an important factor in formulation design and the subsequent manufacturing-process selection. The formulator can develop an enhanced understanding by building quality into its drug product by evaluating material attributes and "designing out" variability effects. Development of poorly designed and understood products can lead to manufacturing and cost inefficiencies, including customized excipient specifications and batch selection as well as producing out-of-specification drug products. The approach, presented in this study, provides a useful starting point for identifying and managing excipient material-attribute criticality when developing drug products through QbD strategies.

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Achieving Sensory Benefits and Mildness in Dermatology Products

ON-DEMAND WEBCAST

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EVENT OVERVIEW

Today, there is a growing need to develop topical dermatology formulations that provide sensorial benefit (e.g., pleasant feel during application, efficacy cues, and minimal irritation) for those with compromised and highly sensitive skin conditions. Dermatology companies have an increasing interest in the design of topical products that are pleasant to apply while also mitigating irritation, textural features, pain, and itch. These benefits can help patients overcome some of the negative side effects of severe skin conditions and also may drive patient compliance. This 60-minute webcast will provide insight from leading industry experts on:

- Sensory attributes and related research for dermatological products
- Formulation strategies to achieve mildness and mitigate the impact of skin disease
- Topical excipients and formulation strategies to provide sensorial benefits and minimize irritation.

Who Should Attend:

- R&D scientists, formulators, and managers of dermatological, topical and skincare product development
- Consumer, sensory and clinical scientists supporting topical healthcare products
- Toxicological and regulatory specialists

Presenters

Shannon Lu, PhD
Head, Sensory Guidance
Novartis Consumer Health

Nayan Desai, PhD
Assistant Director,
Formulation & Process Development
Dow Pharmaceutical Sciences

Norman Richardson
Technical Sales Manager,
Dermatology
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Uniformity of Dosage Units Using Large Sample Sizes

Ø. Holte and M. Horvat

New *European Pharmacopoeia* chapter aims to resolve problems with applying the harmonized UDU test to large sample sizes.

Recent development in analytical technology has made possible the fast determination of unit content in a large number of dosage units from a batch using nondestructive analytical methods during production. These measurement techniques are often referred to as process analytical technology (PAT). Using such methodology, a better understanding of the manufacturing process, in line with the quality-by-design (QbD) concept according to the International Conference on Harmonization (ICH) Quality Guidelines Q8–Q11, and a closer control of the drug product can be obtained compared with the use of traditional analytical methods. The increased process control that is achieved by PAT is attractive both from the patient's point of view (improved product quality) and from the industry's point of view (increased production efficacy, less batch rejection).

Acceptable batch quality is demonstrated by compliance with the drug product specification. Usually, several of the tests of a specification refer to pharmacopeial test methodologies and acceptance criteria. One such test is the *European Pharmacopoeia (Ph.Eur.)* General Chapter 2.9.40 on Uniformity of Dosage Units (UDU). To take full advantage of the increased batch control that is gained by PAT in general and large sample size in particular, there has been a demand for a test method that utilizes large sample sizes to demonstrate compliance with UDU. Such a test has recently been adopted by the European Pharmacopoeia Commission, and will be published as *Ph.Eur.* General Chapter 2.9.47. In this paper, the new test is presented and explained.

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M. Horvat is a leading scientist with Lek Pharmaceuticals. Both authors are representing the European Pharmacopoeia (Ph.Eur.) PAT Working Party.

Background

To ensure the consistency of dosage units, each unit in a batch should have an active substance content within a limited range around the label claim (1). *Ph.Eur.* General Chapter 2.9.40 on UDU addresses the recommended test to demonstrate this critical property in a batch of drug product. The general monograph was introduced in Supplement 5.2 of the *Ph.Eur.*, and is harmonized with the *Japanese Pharmacopeia (JP)*. The test is also included in the *US Pharmacopeia (USP)*, but with a reservation against the possibility to demonstrate UDU by mass variation rather than content uniformity, which is allowed in *Ph.Eur.* and *JP* under certain circumstances (2). When justified and authorized, acceptable dose uniformity may be demonstrated by compliance with *Ph.Eur.* General Chapter 2.9.5 Uniformity of Mass of Single-Dose Preparations (2.9.5) or General Chapter 2.9.6 Uniformity of Content of Single-Dose Preparations (2.9.6) instead of the UDU test (3).

With the harmonized UDU test, acceptable and nonacceptable batches, respectively, are more precisely judged than with the 2.9.5/2.9.6 tests, as the sample size is larger (n = 30, as opposed to n = 20, and n = 10, respectively). The UDU test returns a numerical measure of the dose consistency—that is, the acceptance value (AV). In addition, UDU takes into account sample mean: a stricter standard deviation requirement applies if the sample mean is more than 1.5% off-target. The performance of the old and the new General Chapters has been discussed by Limberg and Savsek (4).

Although it is assumed that the sample is representative for the batch, it is acknowledged that the evaluation of a small sample will only provide an estimate of the batch quality. There is always a risk that a highly variable batch would pass the UDU test and be released. Likewise, there is always a risk that a good quality batch can fail the UDU test and be rejected. Increasing the sample size leads to a more precise estimate of the batch variability.

Concerns have been raised that the UDU requirements discourage the use of modern analytical techniques that are fast and nondestructive (e.g., PAT techniques) (5–10). It was unfortunate that a pharmacopoeial requirement

could be regarded as a disincentive to the implementation of such analytical methods.

The main concern with the UDU test when applied to large samples was the requirement that no single result of the test sample is outside ± L2 % of the reference value M (M = "sample average"; L2 = 25.0, unless otherwise specified. For a precise definition of M, refer to *Ph.Eur.* 2.9.40). Such an unconditional requirement is included in both General Chapters 2.9.5/2.9.6 and the UDU chapter. The requirement was established to disclose batches with largely deviating units, even if the sample mean and the overall sample variance is acceptable. This "safety net" does not assume any distribution in the sample or in the batch (e.g., normality), and it seems reasonable enough not to allow any largely deviating unit in a small sample.

Even in normal distributed batches of good quality, a small number of largely deviating units is expected. As sample size increases, the probability to detect one of these units becomes significant. In the new General Chapter 2.9.47 (2.9.47), a small number of largely deviating units is allowed for large sample sizes. This allowance is not considered an acceptance of largely deviating units as such, but rather recognizes that the large sample has a greater probability to contain such units, even when the batch in total is considered to be of acceptable quality.

A proposal for 2.9.47 was published in *Pharmeuropa* 23.2 in March 2011, together with a background paper explaining the elaboration of the proposal in detail (9). During the public consultation period, several comments were submitted by industry and regulators. The feedback was fairly uniform, and the European Directorate for the Quality of Medicines (EDQM) PAT working party accordingly elaborated a revised proposal for Chapter 2.9.47. The revised text was adopted by the European Pharmacopoeia Commission in April 2012, and it will be published in Supplement 7.7 of the *Ph.Eur.* and implemented on Apr. 1, 2013.

Figure 1: Operations characteristic (OC) curves of the initial proposal for 2.9.47: Selected sample sizes (including the obsolete sample size n = 75) are compared with the UDU test (n = 30). The red oval represents the higher probability to pass the 2.9.47 test than the UDU test for certain batch distributions. The simulated batches follow normal distribution with a certain standard deviation (indicated along the X-axis).

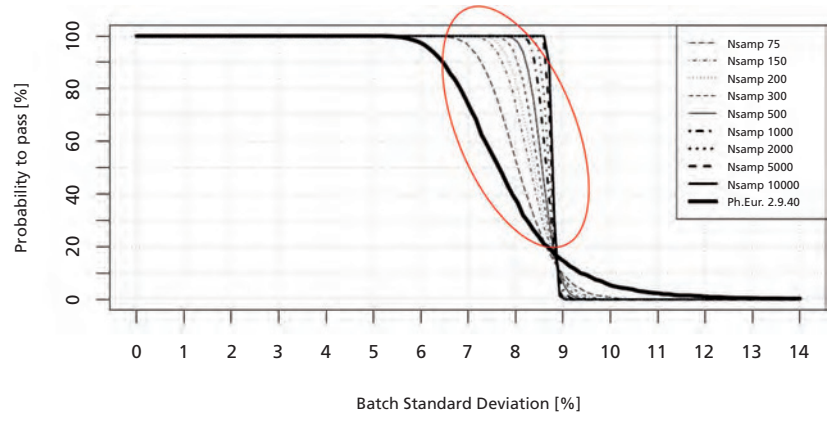
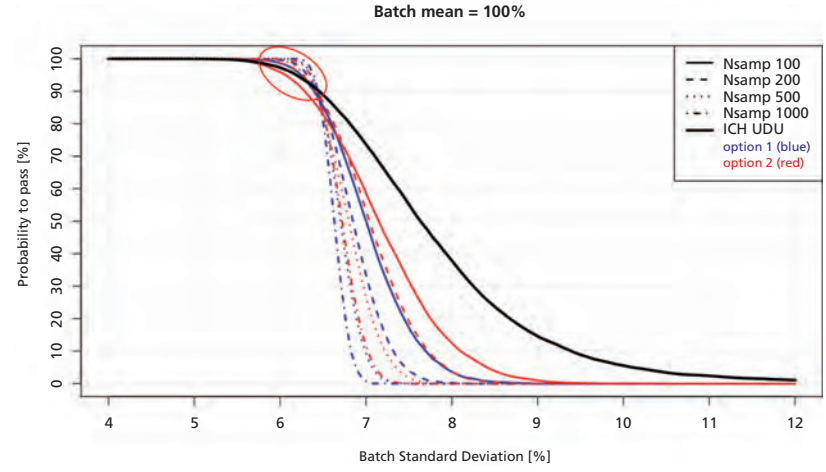


Figure 2: OC curves of selected sample sizes for the adopted 2.9.47 (Alternative 1 and 2, respectively), compared with the uniformity of dosage unit (UDU) test (n = 30). The red oval represents the higher probability to pass the 2.9.47 test than the UDU test for certain batch distributions. The simulated batches follow normal distribution with a certain standard deviation (indicated along the X-axis).



Industry comments and applied feedback

The following section summarizes the comments received during the public consultation, and explains how the industry feedback has been taken into account in the revised text. The primary concerns raised during the public consultation were related to four key issues, as outlined below.

"What is the relation between the Ph.Eur. new General Chapter 2.9.47 and the existing chapters (2.9.5, 2.9.6, and 2.9.40)?" Before the adoption of 2.9.47, there were already three general chapters in *Ph.Eur.* addressing dose variability. The new chapter does not represent a fourth set of acceptance criteria for the determination of dose variability. Rather, as an alternative to demonstrating compliance with 2.9.40 with a traditional sample size n = 30, compliance with the UDU test could be demonstrated by compliance with the criteria of 2.9.47

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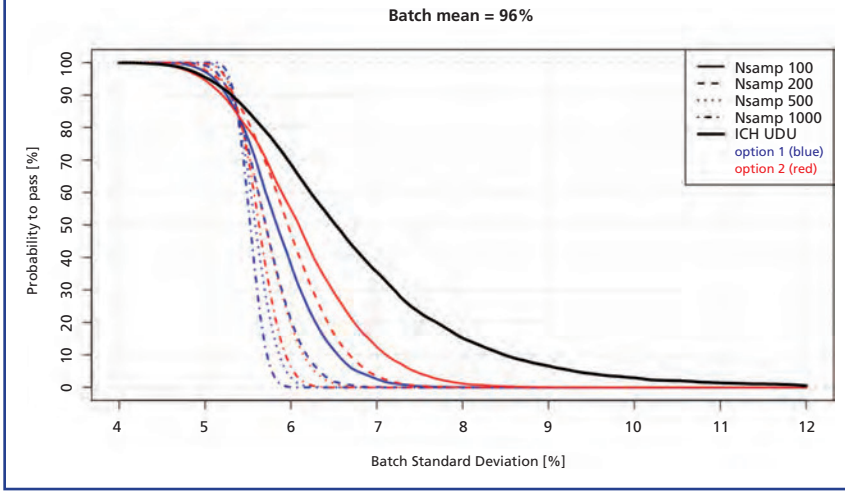
Table I: Draft proposal (*Pharmeuropa* 23.2): Number of largely deviating units allowed for a selection of sample sizes.

n (exact)	< 479	≥ 479	≥ 763	≥ 1903	≥ 4754	≥ 9888
n (rounded)	< 500	≥ 500	≥ 1000	≥ 2000	≥ 5000	≥ 10000
c2	0	1	2	6	16	34

Table II: Adopted test (*Ph.Eur.* supplement 7.7): Number of largely deviating units allowed for a selection of sample sizes.

n	< 176	≥ 176	≥ 280	≥ 490	≥ 908	≥ 1956	≥ 4995	≥ 9919
c2	0	1	2	4	8	18	47	94

Figure 3: OC curves for normal distributed batches with an off-target mean.



with a large sample (sample size ranging from n = 100 to n = 10,000). Chapter 2.9.47 should always be applied in conjunction with chapter 2.9.40, where the relevant parameters (e.g., acceptance value, reference value) are defined and explained. In fact, 2.9.47 is meaningless without a reference to 2.9.40. There is no formal link between 2.9.47 and the older dose variability tests described in 2.9.5 and 2.9.6.

General Chapter 2.9.47 presents two alternative sets of acceptance criteria: one parametric and one nonparametric test. It is the user's choice which of the two sets of criteria to apply. For a given sample, the two sets may not give the same result, due to their fundamental difference (parametric versus nonparametric). However, both alternatives are considered equivalent in the demonstration of compliance with 2.9.40. The nonparametric test criteria for largely deviating units (L2/c2-criteria) are identical in the two alternatives.

There is no regulatory expectation that 2.9.47 should be used by a marketing authorization (MA) applicant or a MA holder, in the determination of compliance with 2.9.40. There is also no regulatory expectation that any of the two alternative sets of test criteria should be favoured over the other. The new chapter does not represent a new requirement. It is the user's decision to demonstrate compliance with 2.9.40 by any of the criteria described in the new 2.9.47.

However, it is not acceptable that a batch failing the criteria of 2.9.47 is retested by the traditional criteria of 2.9.40, with the intention to achieve a more fortunate result. It is also not acceptable to retest a batch using the other alternative set of criteria in 2.9.47 if a batch has produced an unsatisfactory result with any of the two alternatives.

"The general acceptance criteria of the new chapter are too wide." The feedback from both industry and regulators was harmonized in that both parties argued that the new proposed acceptance criteria of 2.9.47 were too wide. From Monte–Carlo simulations, it was evident that for certain batch distributions, with unusually high standard deviation, a large sample fulfilling the acceptance criteria of 2.9.47 could easily fail the criteria of 2.9.40 when evaluated on a subset of the sample (n = 30). This concern is illustrated in **Figure 1**, where the red oval represents batch characteristics where there is a larger probability to pass the test criteria for large samples, than the UDU criteria for a small sample. For the batches with a standard deviation between 6 and 8.8 %, the probability to pass the previously proposed version of the 2.9.47 test is greater than the probability to pass the harmonized UDU test.

Consequently, the revised criteria of the adopted 2.9.47 are such that a very small range of batch characteristics gives a greater possibility to pass the new criteria, than the 2.9.40 criteria for n = 30. These batches already have a high probability (> 90 %) to pass the UDU test (indicated by the red oval in **Figure 2**):

"The specific acceptance criteria for largely deviating units in the large samples are too strict." In the original proposal for large sample test criteria, the first largely deviating unit (LDU) was allowed at sample size n = 500 (see **Table I**). A batch that complies with these acceptance criteria for LDU when evaluated on a large sample would have a 90% probability to pass the zero-tolerance criterion for LDU when evaluated on a small sample n = 30 (9).

In practice, current technology typically returns sample sizes of a few hundred, so that if the first largely deviating unit is allowed at n = 500, it was argued by several stakeholders that such acceptance criteria would not fully resolve the main concern—

the 2.9.40 zero-tolerance criteria for a largely deviating unit.

On the other hand, a batch that complies with the adopted acceptance criteria for LDU when evaluated on a large sample would have a 75% probability to pass the zero-tolerance criterion for LDU when evaluated on a small sample n = 30 (9). An extract of the revised acceptance criteria that are now integrated in the adopted chapter 2.9.47 is presented in **Table II**:

"Editorial issues." In the adopted *Ph. Eur.* text, the introduction to the general chapter has been rewritten to further clarify the relationship between the two alternative tests of 2.9.47 and the existing 2.9.40 (as discussed above). The tables of acceptance criteria (k, c1, c2 versus sample size n) have been expanded, and there has been no rounding of the sample sizes performed where a certain set of acceptance criteria apply.

The criteria for a "medium-sized" batch sizes (30 < n < 100) have been removed, as these were found to be less relevant for the problem statement (demonstration of UDU using large sample sizes).

Demonstration of the performance of the adopted 2.9.47 test. In the following, a series of operations characteristic (OC) curves are presented to demonstrate the performance of the new test, compared with the performance of the harmonised UDU test (Note: in the figures, Alternative 1 and 2 are denoted as "Option 1 and 2"; reference is also made to **Figure 2**).

Figure 3 represents the same situation as shown in **Figure 2,** except that the simulated batches has an off-target mean at 96 %. The batches are normal distributed around the off-target mean.

In **Figure 4**, the probability to pass the criteria of Alternative 1 for long-tailed and bimodal batches, respectively, is compared with the OC curve for normal distributed batches (n = 1000). The long-tailed distribution could typically appear in a batch where there is an inadequate blending process, or where demixing occurs. The bimodal distribution could typically appear where several independent pieces of equipment are involved in a crucial stage of the process, and one of the pieces is faulty. Examples include a rotary tablet press and single-dose preparations (e.g., powders) that are filled by several independent filling stations. Obviously, the long-tailed and the bimodal batches always have a smaller probability to pass the test than the normal distributed batches, provided that overall standard deviation is the same. The UDU test is also sensitive to the distribution of the batch, but there is a wide range of standard deviations where the UDU test is indecisive or in some cases even less discriminating for non-uniformly distributed batches. The new alternative tests are more precise as they evaluate a larger sample.

In **Figure 5**, the same simulated batches have been evaluated by the non-parametric test criteria of Alternative 2. Comparing Figures 4 and 5, it is evident that the two alternatives are very similar in their evaluation of the tested batches,

Figure 4: 2.9.47 Alternative 1: OC curves (sample size n = 1,000) for long-tailed and bimodal distributions, as compared to normal distributions with the same standard deviation. The results are compared with the UDU test (dotted curves). An illustration of the batch distributions is presented in Figure 5 below.

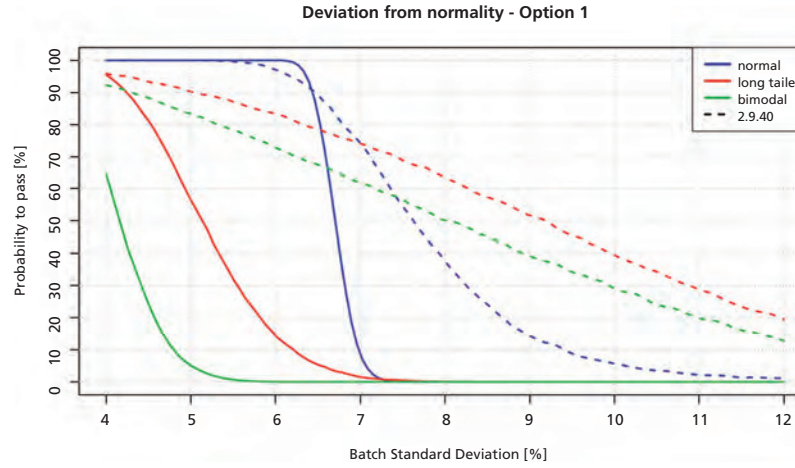


Figure 5: OC curves (sample size n = 1,000) for long-tailed and bimodal distributions, as compared to normal distributions with the same standard deviation. 2.9.47 Alternative 2.

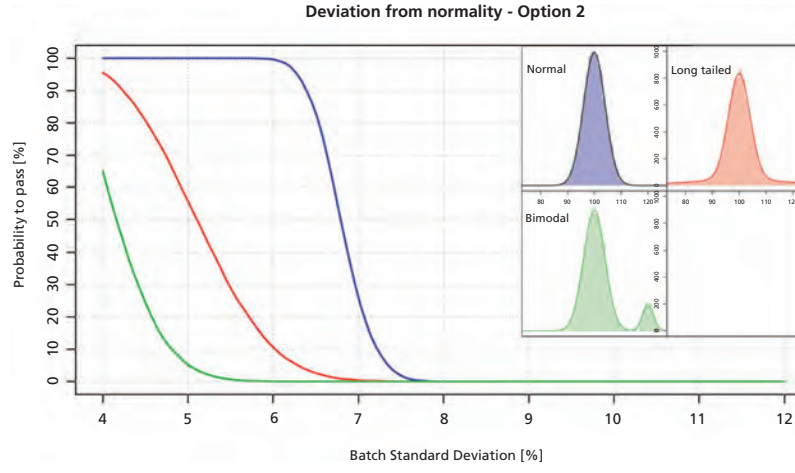
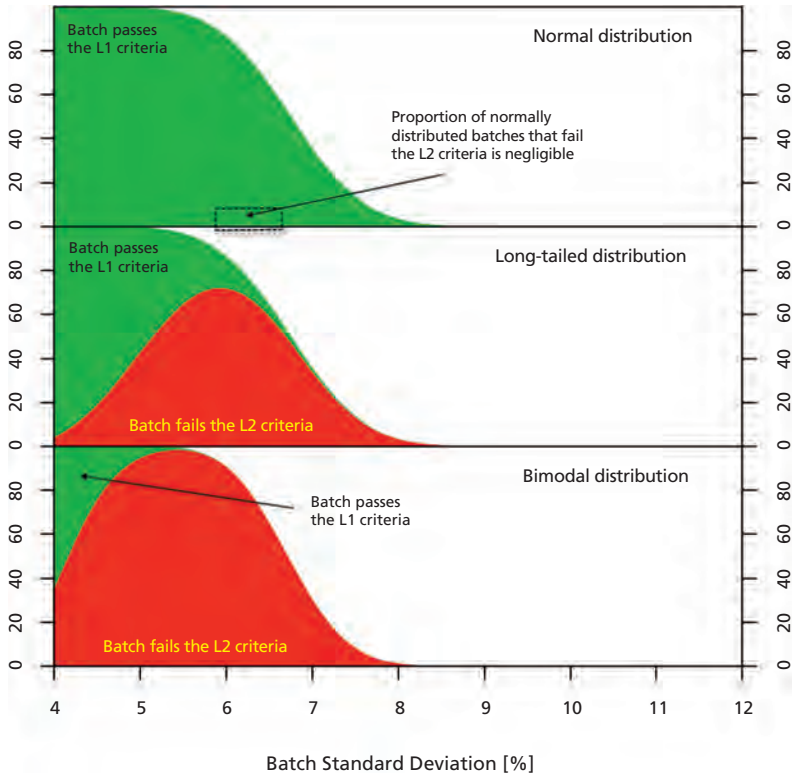


Figure 6: Illustration of the relative importance of the L1 and the L2 criteria in the evaluation of acceptable dose uniformity according to 2.9.47 (n =500). Green + red area: Probability to pass the L1 criteria. Red area: Probability that a batch that passes the L1 criteria, fails the L2 criteria. Green area: the probability to pass the 2.9.47 test.



in particular for the long-tailed and the bimodal batches. When looking at **Figure 6**, it is evident that any differences in evaluation based on the general L1 criteria would be compensated for by the L2 criterion, which is identical in the two alternatives.

Figure 6 illustrates whether the different simulated batches are rejected based on the general L1 criteria (AV/ c1), or based on the additional L2 criteria for largely deviating units (c2). The green + red area represents the probability that the batch passes the L1 criteria, and the red area alone represents the probability that a batch that passes the L1 criteria but fails the L2 criteria. Consequently, the green area alone is equivalent to the area under the curve in **Figure 4**, which represents the probability to pass the 2.9.47 test. It is apparent that the L2 criterion is important to disclose bimodal- and long-tailed distributions, as well as other deviations from normality. For the normal distributed batches, the L2 criterion hardly contributes to the evaluation at all. However, when evaluating the dose uniformity of a batch, and in particular by a third party, it is not practical, nor necessary to make any assumption as to the distribution of the batch or the sample.

Conclusion

The recently adopted *Ph.Eur.* General Chapter 2.9.47 should resolve the problems that have been addressed regarding the applicability of the harmonized UDU test (Chapter 2.9.40) when applied to large sample sizes. With the new test criteria, more information from the large sample is taken into account in the evaluation of dose uniformity than is available in a subset of the sample (n = 30). Thus, manufacturing processes where a large sample size is available are more precisely evaluated.

The new test does not represent new regulatory expectations. Chapter 2.9.40 represents the requirements for acceptable dose uniformity, and 2.9.47 is just an alternative means to demonstrate compliance with the 2.9.40 criteria.

The proposed test criteria are at least equally stringent as the requirements of *Ph.Eur.* 2.9.40, and more discriminating due to the larger sample size. Although the new test originally has been motivated by PAT applications, it is applicable also to traditional sampling and analysis.

Acknowledgments

The initial draft and adopted chapter were elaborated by the members of the *Ph.Eur.* PAT Working Party (Chair: Prof. G. Ragnarsson, Medical Products Agency, Sweden). We also acknowledge many helpful proposals and comments from experts from industry, industry associations, and regulatory authorities that participated in an expert hearing on Sept. 29, 2010, and contributed through the public comment process.

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Supplier Qualification

A Comparison of Comprehensive Third-Party Excipient GMP Audit Programs

Darcy Ewalt, Tracy L. Cooper, Frithjof Holtz, and Irwin Silverstein

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This paper provides a comparison of three comprehensive programs—Rx–360, EXCiPACT, and IPEA—available to pharmaceutical manufacturers for the purpose of auditing excipient suppliers and ensuring drug efficacy and patient safety.

Darcy Ewalt is director of divisional GMP auditing at Merck Sharp & Dohme, Corp. (Merck is a member of Rx–360). **Tracy L. Cooper**, Johnson & Johnson, AD, Consumer Regulatory Compliance (J&J is a member of Rx–360). **Frithjof Holtz** is quality and regulatory management head of MM-QS Advocacy (EXCiPACT) at Merck Millipore. **Irwin Silverstein** is vice-president and chief operating officer of International Pharmaceutical Excipients Auditing, Inc.

Ingredient adulteration has been a growing concern for regulators. In June 2009, FDA sponsored a conference on economically motivated adulteration. In October 2009, the results of a study conducted on imported povidone analogs showed there was substandard excipient offered for sale (1). After confirmation, FDA issued an import alert for povidone analogs from an overseas manufacturer (2). Since then, FDA inspections of pharmaceutical manufacturers have added emphasis on supplier qualification. FDA announced at the FDA/Xavier University Global Outsourcing Conference in 2010 that site inspection of component suppliers will become a future requirement (3). Similar expectations are developing in Europe. The Falsified Medicines Directive (FMD) 2011/62/EU requires the holder of the manufacturing authorization to ensure that appropriate GMP is applied to the manufacture of ingredients (4). Although the FDA and EMA requirements for site audits have not yet been mandated for excipients, the excipient industry must be prepared to receive increasing numbers of audits.

Excipient manufacturers often host 10 or more audits performed by their direct customers per year, which is a small fraction of their many direct and indirect pharmaceutical customers. These audits do not include potential audits by excipient users that purchase material through distributers. The excipient manufacturer usually has no knowledge of the identity of those customers. Thus, it becomes impractical both physically and economically to host an audit from all direct and indirect pharmaceutical customers. Regulators worldwide recognize this conundrum and now allow the pharmaceutical company to rely on third-party audits and certification. As stated by FDA, an important consideration for acceptance is proper qualification of the third-party audit or certification provider. This article provides an overview and comparison of a third-party audit, Rx–360, and excipient GMP certification programs EXCiPACT and IPEA.

Rx–360

The Rx–360 International Pharmaceutical Supply Chain Consortium is a nonprofit international industry organization established in 2009. The mission of this organization is to develop and implement enhanced global quality systems and processes that will help ensure product quality and authenticity throughout supply chains. Members of Rx–360 include pharmaceutical companies and sup-

pliers, working in partnership to achieve the mission of Rx–360. Pharmaceutical associations and industry groups, auditing firms, and regulatory agencies are updated on the status of the audit programs and other initiatives of the consortium. In support of the mission, the consortium developed a Joint Audit Program and a Shared Audit Program, both of which aim to provide knowledge on the quality and authenticity of supplies and their suppliers.

Joint audit program. Pharmaceutical companies that are Rx-360 members (sponsors) can confidentially submit a request to the Rx-360 secretariat to have an audit performed by an Rx-360-qualified third-party audit firm, at a supplier site. Currently, Rx-360 supports audits of API, excipient, raw material, basic chemicals, and packaging suppliers, with potentially more categories to be added into the program (e.g., laboratories). As part of the audit request, the number of additional sponsors required for the audit to progress is stipulated. This can result in a single sponsor or multiple sponsors per audit, depending on the sponsor's needs. The sponsor's confidentiality is sustained throughout the entire audit process. A supplier that is targeted for an audit through Rx-360 must also agree to the third-party audit.

The program benefits both pharmaceutical companies and suppliers. For pharmaceutical companies, the cost of the audit is shared by the number of sponsors, which has the potential to significantly reduce the cost per audit. Additionally, Rx-360 provides a supplemental means to complete routine audits required by regulators worldwide. Suppliers benefit by having a potential reduction in time and resources spent hosting and responding to numerous audits, especially in cases where multiple sponsors are interested in auditing the same supplier.

Auditors from select qualified third-party auditing firms perform each audit. Each auditor must have the education, experience, and accreditation to be eligible to perform an audit. The experience required is specific to the type of audit being performed, whether API, excipient, raw material, or packaging material. Auditors use audit guides during the audit, which have been developed by Rx-360 and agreed to by the pharmaceutical company members. These guides ensure consistency of the audits performed and are based on industry standards such as ICH Q7, *Good Manufacturing Practice for Active Pharmaceutical Ingredients* for APIs and EXCiPACT GMP or GDP standards (see below) for excipients.

Each sponsor reviews the draft audit reports to ensure clarity of the report, completeness of the audit, and validity of observations. Following sponsor review, the audit report is returned to the auditor to address any questions and any needed revisions for clarity, before the report is issued to the supplier. Responses to any observations are provided to the auditor for review and concurrence. If a sponsor determines that a specific audit observation requires additional follow-up due to its company procedures, or if the response is not adequate per sponsor standards, the sponsor has the responsibility to negotiate further with the supplier.

If a pharmaceutical company is not an initial sponsor for an audit, the company may purchase the given audit report following approval of the report and permission from the supplier. Rx-360 non-member companies can also purchase audit reports, again pursuant to supplier agreement.

Shared audit program. Rx-360 member pharmaceutical companies, with agreement from the supplier, can elect to submit an audit report performed by the pharmaceutical company (rather than through an Rx-360 third-party audit), into the shared audit program. Information is redacted to protect any confidential information from both the pharmaceutical company and supplier perspective. These audit reports can be purchased by another Rx-360 member company, pursuant to supplier agreement, as a means of obtaining additional information about a supplier. This can be quite useful for companies evaluating a new supplier. Suppliers benefit by gaining visibility to a large number of potential customers, and a potential reduction in pre-audit paperwork as well as audit frequency or time spent on a single audit.

For both Rx-360 audit programs discussed, confidentiality is strictly maintained to ensure that only the appropriate information is visible to a sponsor or supplier.

EXCiPACT

EXCiPACT is a voluntary international scheme to provide independent third-party certification of manufacturers, suppliers, and distributors of pharmaceutical excipients worldwide. It aims to ensure patient safety, through supplier quality, while minimizing the overall costs for assessing the excipient supply chain. In early 2009, the European Fine Chemicals Group (EFCG), the International Pharmaceutical Excipients Council (IPEC) Europe, IPEC Americas, the European Association of Chemical Distributors (FECC), and the Pharmaceutical Quality Group (PQG) (UK) formed a project consortium to jointly develop a set of cGMP and current good documentation practice (cGDP) standards for pharmaceutical excipients. Launched as a project of the IPEC Federation, the EXCiPACT Association will become a stand alone not-for-profit organization based in Brussels once commercial activities fully commence.

The EXCiPACT standard is based on the Quality Management System ISO 9001:2008 and provides two annexes to ISO 9001:2008, which cover GMP and GDP requirements for excipients. Excipient manufacturers would be assessed to ISO 9001:2008 and the EXCiPACT GMP annex together, whereas distributors would utilize ISO 9001:2008 and the EXCiPACT GDP Annex. The remaining sections of EXCiPACT cover the requirements for third-party audit organizations, firstly for auditor competency and secondly for quality system requirements for these organizations. The former is based on ISO 19011:2002, Guidelines for Quality and/or Environmental Management System Auditing, whereas the latter is based on ISO/IEC17021:2006, Conformity Assessment—Requirements for Bodies Providing Audit and Certification of Management Systems.

Because the EXCiPACT Association has no auditors, the qualification of EXCiPACT auditors authorized to perform the certification audits is one of the program's most important elements. The EXCiPACT Scheme has two grades of certification: EXCiPACT Auditor and the EXCiPACT Audit Team Leader. These are equivalent to International Register of Certificated Auditors (IRCA) Quality Management Systems (QMS) 2008 certification grades. To be eligible for EXCiPACT Scheme cer-

tification, applicants must meet the requirements stated in the EXCiPACT Auditor Competency annex to ISO 19011. Being certified as an IRCA QMS 2008 Auditor or Audit Team Leader meets the basic auditing requirements; however, additional knowledge of excipient manufacturing, GMP, and GDP EXCiPACT Scheme auditing competencies are also required. Both grades require successful demonstration of the application of the fundamental competencies to excipient supplier audits against the EXCiPACT GMP and GDP standards. Demonstration of the additional requirement for at least five years of the IRCA general work experience to be in the pharmaceutical or excipient supplier industry for GMP auditors or three years for GDP auditors for all auditors is also required. If auditors wish to perform GMP and GDP audits then the additional requirement is five years.

For both grades, the successful completion of an EXCiPACT Association approved pharmaceutical excipient supplier auditing course is a prerequisite. This training should be completed within the three-year period immediately prior to application to undertake EXCiPACT certification. Training completed prior to this period may be accepted if evidence is provided of recent, relevant work experience, and currency of their auditing skills, as laid down in IRCA 602. The list of the qualified third-party auditors is published online at www.excipact.org.

The excipient supplier is the sponsor of the EXCiPACT certification audit. The supplier selects from qualified third-party auditing companies listed on the website. The excipient supplier pays for the audit (approximately US$12,500 [10,000 EUR] for the certification audit and approximately US$6500 [5000 EUR] for the annual surveillance audit) and the certification fee (US$7000 [5500 EUR]).

EXCiPACT Certification is expected to take an additional one to three days depending on the size and complexity of the site when done simultaneously with an ISO 9001:2008 audit. The excipient supplier can choose between a GMP, GDP, or combined audit depending on the activities performed with the scope of the EXCiPACT Certification similar to the ISO 9001:2008 audit. The excipient supplier selects the third-party auditing company, the scope, and the date of the EXCiPACT certification. Surveillance audits are performed every year and a recertification audit every three years.

The audit report is reviewed and approved by the Certification Body so that a decision on certification is made. The EXCiPACT Association acts as arbitrator in the case of disputes between the third-party audit organization and excipient suppliers. The auditee and the Certification Body agree to disclose the audit report and associated corrective action and preventive action (CAPA) plan to parties approved by the auditee. The auditee can share the audit report with any of its customers. The excipient user can verify audit report and certificate with the Certification Body.

IPEA

International Pharmaceutical Excipients Auditing (IPEA) was organized in 2001 as a subsidiary of the IPEC-Americas, as a consequence of the poisoning in Haiti that resulted from contaminated Glycerin *USP*. The objective of IPEA is to reduce the cost of supplier audits through a shared audit program, which can facilitate broader site audit of excipient suppliers for supplier qualification.

Shared audit program. The basic audit is a one-day audit at the excipient manufacturer for a single monographed excipient plus additional time for each additional monographed excipient. The sponsor pays for the audit with the price beginning at US$5500. However for each audit report sold, the sponsor receives a credit of US$500 to be used for the purchase of other services from IPEA. The excipient manufacturer reviews the report for factual accuracy and may append a corrective action plan. Pharmaceutical purchasers of the report remain confidential. To date, The IPEA shared audit program has gained limited acceptance.

ANSI Accredited Certification Program. In 2008, FDA asked IPEA to become accredited by the American National Standards Institute (ANSI) as a conformity body for the operation of an excipient GMP certification program. This accreditation was achieved in April 2010. IPEA certifies conformance to the IPEC–PQG Excipient GMPs, but will soon use the new ANSI Standard NSF/IPEC 363, which is designed for audit assessments. Certification requires a minimum of four man-days at the site with additional time allotted for multiple excipients or processes and off-site operations, including subcontracting. Annual surveillance audits are conducted for one-half the time of the certification audit.

Draft audit reports are reviewed by IPEA for completeness, clarity, the appropriate rating of findings, and to ensure the terminology will be understood by the pharmaceutical reader. The draft is then sent to the excipient manufacturer to review for factual accuracy and so a corrective action plan can be prepared. The draft report and corrective action plan are then submitted to the Certification Board.

The Board is comprised of four members with extensive experience in the excipient or pharmaceutical industry including responsibility for supplier qualification. During a teleconference, the Certification Board reviews the report and corrective action plan and interviews the audit team. If the consensus of the Board is that the site is in substantial conformance to excipient GMPs, the site is recommended for certification.

Certification is founded on the audit and audit report. Auditors must demonstrate extensive prior experience in the performance of GMP audits of component suppliers with an emphasis on excipients. Candidate auditors receive one to three days of training in the certification program, excipient auditing, and conformance expectations. Successful candidates are assigned an excipient audit witnessed by an IPEA executive. The auditor is deemed qualified upon demonstration of appropriate audit skills, rating of observations, and audit report preparation. Qualified auditors are subcontractors who execute an agreement with IPEA that requires their compliance with IPEA standard operating procedures (SOPs) including conflict of interest and maintenance of client confidentiality.

Qualified IPEA auditors conduct certification audits as a member of an audit team. Periodic performance reviews are conducted by an IPEA executive based upon review of their audit reports, participation in Certification Board meetings, and/or witnessing an audit plus their continuing improvement activities.

Certification is paid for by the excipient manufacturer and begins at US$20,000. Annual surveillance audit, priced at 50% of certification, is conducted at the site such that every two years the site has been audited for an equivalent number of days as during the certification audit. To facilitate acceptance of IPEA certification, the audit report is offered to pharmaceutical companies at a nominal cost of $500-750. The majority of the proceeds from sale of audit reports are credited to the excipient manufacturer to defray their surveillance fee.

Conclusion

It is apparent that many generic manufacturers and smaller pharmaceutical companies use means other than physical audit to qualify their suppliers. An ANSI accredited certification program, therefore, is particularly useful because the program has been qualified by ANSI and can be so recognized by government agencies. An ANSI accredited certification program, furthermore, allows pharmaceutical companies to use certification in lieu of site audit for supplier qualification.

Assuring the safety of the drug supply has modified the development of each of these programs. FDA has explicitly stated at meetings and presentations that shared-audit and third-party audit programs are acceptable as part of a supplier qualification program (5). Continuing reports of economically motivated adulteration reminds the industry that each site supplying excipients must be physically audited to ensure conformance to GMP requirements. Supply chain security must begin with a site audit.

Participation by an excipient supplier in any one program can provide adequate assurance of the conformance of the excipient to GMP because the basis of the audit is the well accepted IPEC-PQG GMP *Guide for Pharmaceutical Excipients*. As described herein, the Rx–360, EXCiPACT, and IPEA programs each exercise great care in the selection, training, and qualification of their auditors. FDA has informally stated that these schemes meet regulatory expectations because they have addressed the issue of auditor competency as a core part of the audit process. Thus the schemes can provide the excipient user with a high degree of assurance that excipient from suppliers that have participated in a program meet cGMP expectations and will continue to do so. The cost barrier for this assurance can be greatly reduced by these programs.

These schemes, therefore, can help to ensure patient safety when the drugs that patients consume have been formulated with excipient components supplied by manufacturers whose facilities have been audited.

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Nano-syringes for delivering combination-drug therapies

Researchers at the Methodist Neurological Institute and Rice University recently reported on their work in developing a hydrophilic carbon clusters (HCCs) antibody drug-enhancement system (HADES), a methodology for cell-specific drug delivery (1). The researchers manufactured antigen-targeted, drug-delivering nanovectors by combining specific antibodies with drug-loaded poly(ethylene glycol)–HCCs (PEG–HCCs) (1). In the HADES, the drug and antibody component can be varied for selective killing of a range of cultured human primary glioblastoma multiforme (GMB). The researchers used three different chemotherapeutics and three different antibodies without the need for covalent bonding to the nanovector (1).

HCCs are nanovectors with protective antioxidant properties, capable of transporting and delivering drugs and bioactive molecules, explained an Apr. 16, 2012, Methodist Hospital System press release. To bring the drug carriers close enough to the cancer cells and successfully deliver the chemotherapy combination, three different antibodies were combined with the HCC to allow the nanoparticle to stick to the cell membrane. The drugs stayed inside the HCC until it attached to the cell membrane. Once binding occurred, the drugs were released into the lipid environment in the membrane. The chemical properties of the chemotherapy drugs inside the HCC are such that they prefer to accumulate in areas with high concentrations of lipids and avoid areas with high water content, such as the extracellular space, according to the release. The researchers used a 20-nm syringe to deliver the drug.

"Without our nano-delivery system, we know that current drug delivery would be highly toxic to patients if we tried to deliver all three of these drugs at once," said David Baskin, MD, neurosurgeon at the Methodist Neurological Institute, in the press release. "But delivered in combination using these nano-syringes, our research demonstrated extreme lethality, with at least a threefold increase in the number of dead cancer cells following treatment. The nano-syringes selectively deliver these drugs only to cancer cells and appear not to be toxic to normal neurons and other noncancerous brain cells."

The researchers noted that the carrier system is an advance over previous nanotube-based systems, which were shown to be toxic. "Some of the chemotherapy agents used in this research traditionally perform poorly with GBMs," said Martyn Sharpe, scientist with the Methodist Neurological Institute 's Department of Neurosurgery, in the release. "Now that we've shown a successful kill rate of these cells *in vivo*, we're looking at treating human tumors that will be grown in immune-compromised mice models."

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JONATHAN EVANS/PHOTODISC/GETTY IMAGES

Sizing the Market for Contract Manufacturing

Jim Miller

Measuring the size of the market for contract-manufacturing services requires a careful hand.

How big is the market for contract-manufacturing services? PharmSource gets that question more than any other. Published estimates of market size vary widely and often seem to be exaggerated or inflated.

Measuring the market

Determining the size of the contract-manufacturing market is a methodological challenge. The biggest obstacle is the fact that most CMOs are either privately owned and do not report their financial results or are part of larger corporations that usually do not break out their CMO revenues in their financial reports. Although good research can overcome some of these problems, determining market size ends up requiring some amount of "guesstimation."

Another methodological problem is defining what is included as "contract manufacturing." Many published reports are unclear about what they are measuring, which can lead to widely divergent market-size estimates. Understanding a given market size estimate requires that the reader and user fully appreciate what is being measured. Some of the dimensions that must be considered are discussed below:

• *Which products are included in the market?* The definition can include prescription products, over-the-counter (OTC), and nutritional products. Although prescription and OTC products are both governed by drug GMPs, nutritional products often are not, so the market dynamics and participants tend to be different, albeit with some overlap.

The contract-dose manufacturing market in 2011 was $13.7 billion.

• *Is the product being manufactured proprietary to the client or is it generic?* Some estimates of the contract-manufacturing market appear to include generic APIs, which are really commodities that can be bought by any company looking to manufacture a generic or OTC drug. There also are generic or OTC drug products that the manufacturer licenses to a customer to be packaged under the customer's name, the so-called "private label" business. By contrast, pure contract manufacturing involves a CMO manufacturing an API or drug product using the client's proprietary process or proprietary formulation.

• *What regulatory standards must be met?* Many manufacturers in emerging markets offer contract manufacturing, but they do not operate under North American, Western European, or Japanese regulatory standards. These companies are competing in a different market and under a different set of terms than manufacturers that meet higher regulatory requirements.

Given the potentially broad dimensions of the CMO industry, users of market-size data must be clear about the applicability of the data they are using. PharmSource recently published its own estimate of the size of the dose CMO market, *Dose CMOs by the Numbers—2012 Edition*. We measured the market for contract manufacturing of a client's formulation under FDA, Western European, or Japanese GMP standards and built our estimate based on extensive research of company revenues and revenue modeling.

We (PharmSource) arrived at a contract-dose manufacturing market size of $13.7 billion in 2011. That was up 7% from 2010, but that growth rate includes revenue from facilities that became contract-manufacturing sites during the year after they were acquired by CMOs from biopharmaceutical/pharmaceutical companies. The organic growth rate (i.e., the growth of revenues at facilities that were in CMO networks in 2010) was 6%. We estimate that overall, dose CMOs accounted for 22% of the biopharmaceutical/pharmaceutical industry's dose-related cost-of-goods in 2011.

Of course, size and growth are not the only dimensions that matter for the health of the industry. Contract-dose manufacturing suffers from overcapacity, especially for solid-dose forms, and the intense competition to sell capacity means that only a minority of dose CMOs make reasonable profits. Further, global biopharmaceutical/pharmaceutical companies continue to show a strong preference for building captive manufacturing, shutting CMOs out from some of the most attractive segments of the market.

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Getting paid

A recent analysis of working capital management practices ofbiopharmaceutical/pharmaceutical companies has some mixed implications for the contract-services industry. The report from financial services giant Citi claims that the global biopharmaceutical/pharmaceutical companies could release $33 billion in cash by managing their working capital better. Working capital is the difference between current assets (which include accounts receivable and inventories) and current liabilities (which include accounts payable and short-term debt). Companies use cash when they build up inventories and receivables and pay their bills; they increase their cash when they run down their inventories, slow payments to suppliers, or collect receivables more aggressively.

Companies could free up that cash by reducing inventories and taking longer to pay their bills, according to the Citi report. The additional cash resources could be used for licensing and acquisition deals or could be returned to shareholders as dividends and stock buybacks.

Having to wait longer for their money is not something that CMOs and CROs want to hear. Service providers are already getting squeezed on prices and profit margins, and a slowdown in payments will eat further into their profits by forcing them to borrow more against their lines of credit or to forego discounts they might get from paying their own suppliers. In the worst cases, CROs and CMOs could be forced to delay hiring or purchasing materials and equipment, which would hurt the quality and reliability of the services they provide.

On the other hand, helping their biopharmaceutical/pharmaceutical clients to reduce their inventories could be a big opportunity for CMOs. Managing inventories is about managing production schedules, cycle times, and supply chains. These are skill sets at which CMOs are supposed to excel because they are at the core of modern manufacturing practice. CMOs that are able to reduce schedule lock-in times from the traditional three months for dose forms and six to twelve months for APIs could increase their share of business from key customers and probably earn somewhat higher margins.

The working-capital challenge raised by the Citi report is further proof that success for CMOs will go beyond traditional measures of quality and cost of goods. **PT**

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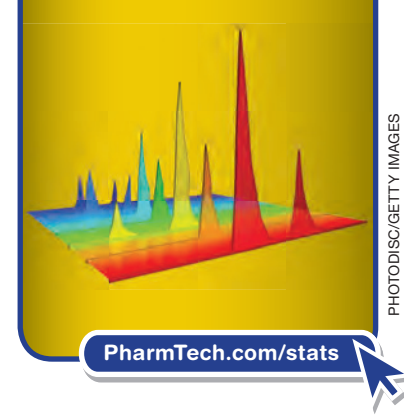

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Determining Potency of Preclinical Dose Formulations

Ashley Sanchez, Melissa Whitsel, and Amy Smith

Multiple factors arising during sample preparation can affect potency measurements.

Potency is a required measurement to determine the amount of active ingredient contained in a preclinical dose formulation. Assessing potency ensures that the test system receives the appropriate amount of active ingredient based on predetermined specifications. Potency determinations are made using a validated analytical method.

Preclinical dose formulation potency

Assessing the potency of preclinical dose formulation is completed by sampling the prepared formulation and assaying using a validated analytical method. Each dosing concentration is sampled and assayed; typically, assays are completed in duplicate. The observed concentration is compared to the theoretical amount and a percent of the theoretical concentration is determined. Typical acceptance criteria are listed in **Table I**.

In the event that a dose formulation does not meet the predetermined acceptance criteria, the result must be investigated for laboratory error. If an analytical error cannot be discovered, the effect on the study must be determined.

Each dosage concentration, including control samples, should be assessed for the first and last test batches of *in vivo* studies, at a minimum. Theoretical concentrations considering displacement factor and density will aid in achieving the targeted concentration, but measuring the actual result of a formulation will detect the true potency level of the drug in vehicle. Conversely, achieving the correct potency level is not always a simple addition of active ingredient to vehicle. The use of laboratory equipment, filtration, compound characteristics, storage, and chemical instability, including weighing and mixing procedures, are factors that can affect potency.

Table I: Typical acceptance criteria for different formulation types.

Formulation type	% of Theoretical
Solutions	100 ± 10%
Suspensions	100 ± 15%
Feeds/Solid matrices	100 ± 20%

Table II: Low recovery observed in a high-range quality control sample preparation.

Concentration (mg/mL)	Average % recovery	% RSD
15.0	67.7	3.403

Mixing

Proper and appropriate mixing of a compound is essential to ensure adequate potency and homogeneity of the ingredient in the formulation. However, assumptions regarding solubility frequently exist when preparing a simple formulation. For example, a formulation prepared as a solution may appear soluble; however, results can dictate otherwise. Such an occurrence was observed in a high-range quality control sample preparation shown in **Table II**.

A laboratory investigation was conducted to identify an assignable cause for the low recoveries. A secondary dilution was prepared from the primary dilution as the method instructed. This time, however, recoveries were within specification of 100% ±10. Although the solution appeared to be a true solution, it was clear that the formulation presented problematic mixing and/or dissolution. Furthermore, in a consecutive run, precipitate was later observed in the primary dilution, indicating the potential problem was dissolution of the analyte in the primary dilution. The analytical method was updated to include in the processing procedure that adequate mixing must be performed after the primary dilution to assure complete dissolution, because particles of the analyte may be present. Thereafter, all samples passed the solution cri-

Ashley Sanchez is an ssociate scientist, **Melissa Whitsel** is analytical manager, and **Amy Smith** is director of Analytical Laboratory Operations, all at MPI Research, Mattawan, MI.

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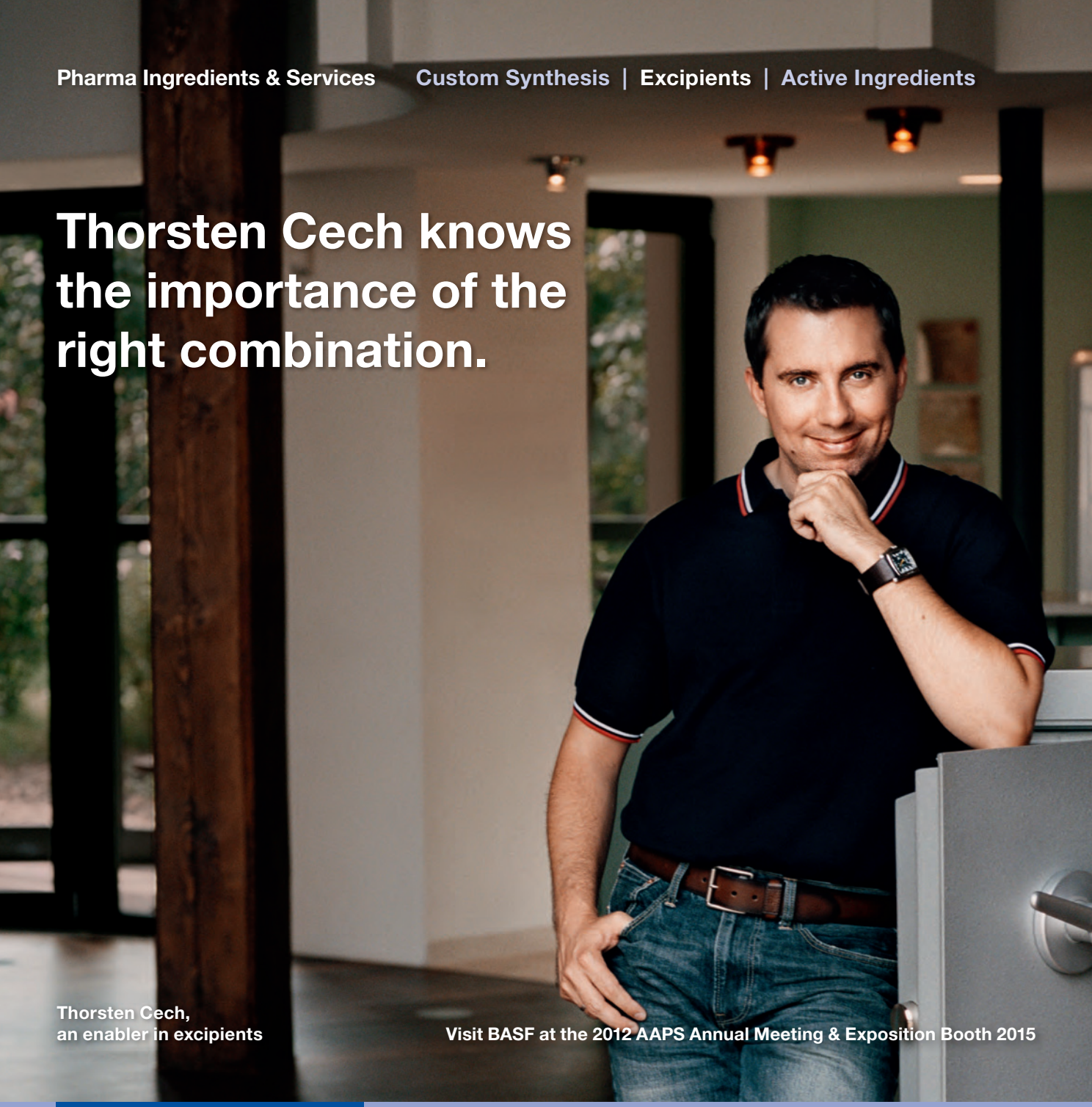

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terion. In this instance, the formulation itself achieved the targeted potency; the problem arose during sample processing for analysis. Though the test system did receive the correct dosage potency, it is necessary to have the analytical data to support this conclusion.

Equally important when carrying out many mixing procedures, especially sonication, is allowing the formulation to cool before performing any additional aliquots. Neglecting this in itself can cause low recoveries when diluting. Special mixing considerations are also necessary when working with analytes that are not small molecules. Cautious inversion can effectively mix large molecules and proteins, without potential destructive effects observed from vigorous mixing procedures.

Laboratory equipment

Another factor to consider in achieving accurate potency is the effect of laboratory glassware and/or equipment. Interactions may occur between the analyte and surface of the volumetric flask used. Such an observation was discovered in preparation of samples in plastic versus glass (see **Table III**).

Solutions were left in plastic for 30 minutes. As demonstrated, the analyte possessed a high affinity for plastic. Furthermore, an assessment made using a glass serological pipette yielded higher recoveries, as compared with using a positive displacement pipette containing a plastic tip.

Filtration

Filtration is an effective method for removing impurities from a solution; however, if the correct pore size and/or media are not used, the analyte may be removed along with the impurities. An experiment was conducted on a clear, colorless solution. The solution was filtered through a 0.22 µm polyvinylidene fluoride (PVDF) syringe filter, and analyzed prefiltration and postfiltration. At low and high levels, the prefiltered solution had an average percent recovery of 97.1% and 97.7%, respectively. Postfiltered samples had 0% recovery at both low and high concentrations because the analyte was removed by the filter.

Table III: Recovery when sample was prepared in plastic versus glass.

Concentration (µM)	Storage	Average % recovery
0.8	Glass	84.1
0.8	Plastic	12.7

Compound characteristics

If potency issues exist after assessing most potential mixing complications, it is important to refer back to the compound characteristics. If a compound is micronized, problematic weighing may exist because of the static, cohesiveness, and/or lightness of the material. Alternatively, the material may be highly hygroscopic and require the use of a desiccant in storage. When weighing a hygroscopic material, it is essential to consider the amount of water being absorbed, as this can cause uncertainty during the weighing process. It is also significant to account for a correction factor in consideration of salt factors and purity. This is important when considering manufactured lots used for *in vivo* studies that do not undergo purification processes that are performed for clinical trials.

Failure to achieve accurate potency levels is affected by many factors including weighing and mixing procedures, use of laboratory equipment, filtration, and even compound characteristics and storage.

Storage

A final factor in achieving correct potency is a consideration of storage and stability of the formulated compound. It is necessary to have data to support conditions and duration of storage. Degradation of a compound can be seen at different temperature conditions (e.g., ambient, refrigerated, frozen or ultra-frozen). Yellow light versus ambient light may also affect potency if the formulated test article requires protection from light. Analysis of potency of a formulated drug in specified storage conditions, extending longer than the dose formulation, should be performed before dosing. Covering the time window from preparation to dosing ensures that the proper potency of drug is delivered to the test system.

Conclusion

Potency of a dose formulation is an essential and crucial component in ensuring that the test system receives the appropriate amount of active ingredient based on predetermined specifications. If the correct potency is not achieved, the toxicological effects of the drug may not be observed. Failure to achieve accurate potency levels may be affected by many factors including weighing and mixing procedures, use of laboratory equipment, filtration, and even compound characteristics and storage. When these problems occur, it is important to isolate and investigate each variable to identify the root cause.

References

Code of Federal Regulations Title 21, Food and Drugs (Govenment Printing Office, Washington DC), Part 58.

M. Whitmire et al., *The AAPS Journal,* **12** (4), 628–634 (2010). **PT**

API Development: Risk Evaluation and Control of Genotoxic Impurities

LIVE WEBCAST: Thursday, November 8, 2012 at 10:00am EST

Register free at www.pharmtech.com/genotoxic

EVENT OVERVIEW:

Developing a successful synthesis and manufacturing process for a small-molecule active pharmaceutical ingredient (API) requires not only approaches to optimize product yield, purity, and process conditions, but also a full understanding of the regulatory issues to ensure product quality. When developing synthetic routes to APIs, the stages at which impurity generation occurs must be elucidated to identify and determine impurities, including genotoxic impurities, in order in control their formation during a synthesis. This 60-minute webcast will offer insight from leading industry experts on current regulatory guidelines, including an analysis of FDA's recently issued guidance in June 2012 on genotoxic impurities, and the analytical and chemical approaches used to control and mitigate the risk of genotoxic impurities in small-molecule API development.

Who Should Attend:

- CMC (chemistry, manufacturing and controls) professionals in small, mid-sized and large pharmaceutical companies
- Managers, directors, and heads of regulatory affairs and quality control/quality assurance functions
- Process chemists responsible for developing and manufacturing key starting materials and active pharmaceutical ingredients (APIs).
- Project managers responsible for clinical-stage compounds (small molecules)
- CMC and regulatory consultants

The webcast will offer insight on

- Regulatory guidelines regarding genotoxic Impurities
- Analytical and chemical approaches
- Risks of genotoxic impurities in small- molecule API development

PRESENTERS:

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Senior Vice-President of R&D
Neuland Laboratories Limited

Christopher M Cimarusti, PhD
Non-Executive Director
Neuland Laboratories Limited

Edward Delaney, PhD
President
Reaction Science Consulting

Bo Shen, PhD
Principal Scientist, Amgen,
Chair of the AAPS Pharmaceutical Trace Impurities Focus Group

MODERATOR:

Patricia Van Arnum
Executive Editor
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For questions, contact Kristen Farrell at kfarrell@advanstar.com

Xcelience Opens Clinical-Supplies Facility in Tampa

Xcelience opened its new 24,000-ft^2 facility in Tampa, Florida, on Sept. 14, 2012. The building will be used for primary and secondary packaging, labeling, distribution, and warehouse services. This is the company's second facility in the Tampa Bay area, and the company says it will be audited and approved for domestic as well as European clinical trials.

Catalent, Otsuka Form Supply Pact

Catalent Pharma Solutions has begun its supply to Otsuka Pharmaceutical of Abilify (orally disintegrating tablets), which utilize Catalent's Zydis fast-dissolve drug-delivery technology.

AMRI Adds to Management Team

Albany Molecular Research Inc. (AMRI) has appointed Daniel Conlon as senior director of business development. AMRI has also named Michael Nolan vice-president, chief financial officer, and treasurer, succeeding Mark Frost, effective Sept. 17, 2012.

Cambridge Major Labs Expands API Manufacturing Facility

Cambridge Major Laboratories (CML) is planning a significant expansion of its large-scale API manufacturing facility in Germantown, Wisconsin. The expansion comes three years after commissioning the new site. The expansion will include additional reactor capacity as well as isolation equipment. Alongside capacity additions, CML has made additional investments in engineering controls to ensure the sustainability of the business.

Brookfield Unveils Sample Testing Lab in UK

Brookfield Viscometers has completed its new sample testing laboratory at its offices in Harlow, Essex, United Kingdom. According to Brookfield, the facility has been developed in response to increasing customer demand for material comprehensive rheological analysis and method development for viscosity testing.

The new laboratory features a range of analytical equipment, including: a CT3 Texture Analyzer, a Powder Flow Tester, and R/S Rheometers.

CMIC Increases Capacity at its New Jersey Site

CMIC CMO USA has added three new development suites at its FDA-registered site in Cranbury, New Jersey. Gary Wada, executive vice-president and general manager said, "The increased capacity will allow us to initiate development projects quickly and reduce the time for our clients to initiate clinical trials and file for regulatory approval."

The company also appointed Jeffrey Dopf as director of business development. Dopf served most recently as a business development manager with Glatt Pharmaceutical Services, and previously was with Patheon.

Q&A with

James Ingebrand, *Vice President and General Manager of 3M Drug Delivery Systems Division*

PharmTech:
How has the increase in biopharmaceutical development influenced innovation in drug delivery? On an industry level, what are some key developments and targets for delivering biologic-based drugs?

Ingebrand:
It has to be acknowledged that the challenge of delivering biologic-based drugs has been an important driver of innovation in the drug delivery technology industry. Unfortunately, many of these technologies have failed to deliver on their initial promise. We have all seen the bold claims for the oral delivery of proteins and peptides. Inhaled insulin and the like burst on to the scene, and then faded into obscurity. This was not for lack of effort so, clearly, the technical and market challenges are great.

The fact that the industry, including 3M Drug Delivery Systems, continues to innovate in this arena speaks to the great need to offer a real alternative to injections and provide options for improved pharmacokinetic profiles and dose-sparing possibilities. At 3M Drug Delivery Systems, we believe our Microstructured Transdermal System (MTS) is a practical solution for addressing many of these issues. Our initial clinical success is turning concept into reality and generating considerable interest for a range of therapeutic areas, ranging from rheumatoid arthritis to vaccines.

PharmTech:
How do you think personalized medicine will influence drug-delivery technology and methods of delivery?

Ingebrand:
I think we will continue to see personalized medicine expand in scope. We see this manifested in a number of ways, including the launch of companion diagnostic tests as part of new drug introductions. Peering deeper into the crystal ball, I think the most interesting future developments for the drug delivery industry will be around "smart dosing" and therapeutic feedback loops. I can imagine a time when one's Smartphone, loaded with the latest apps, will monitor key physiological parameters and then either recommend or actually control the delivery of a therapeutic agent.

3M Drug Delivery Systems' hollow microneedle arrays (hMTS), for example, can provide a platform that could well enable that sort of next-generation technology.

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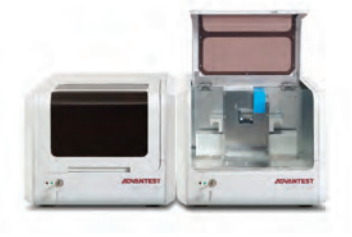

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Advantest's new TAS7500 THz bench-top spectroscopy and imaging systems for the pharmaceutical R&D market use proprietary terahertz wave technology to acquire characteristic spectra based on crystalline structure and 3D images yielding tablet coating thickness and uniformity and the non-destructive detection of cracks and voids in the tablet core. The terahertz spectra are used to measure solid phase transitions and crystalline/amorphous composition while the imaging experiments provide information on the strength properties of coatings and multilayer interfaces in tablets. The system offers lower cost and higher efficiency in development, lab research and product manufacturing.

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AAPS booth 1939

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AsahiKASEI

Description

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- Celphere MCC spherical cores – a superior alternative to sugar spheres for higher production rates, lower agglomeration, better dissolution control, and all-around more robust formulations.

AAPS booth 4830

Biddle Sawyer Corporation

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Description

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AAPS booth 3731

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AAPS Booth #3112

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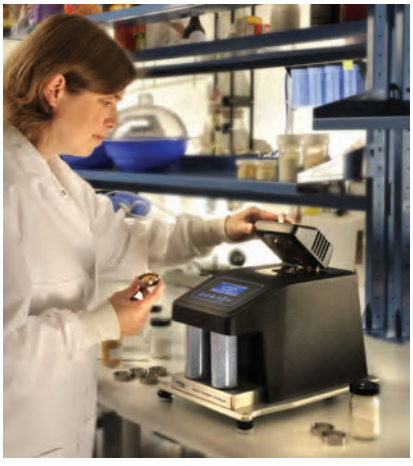

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Our Focus - Your Success
Topical product development has been Dow Pharmaceutical Sciences' successful focus for more than 34 years. Dow helps clients with early feasibility studies through proof of concept in man and on to NDA. Over one 30% of all topical prescription dermatological products approved by FDA 2005-2011 were developed by Dow.

Dow provides a full range of product development services for pharmaceutical and biotechnology clients in the dermatologic, ophthalmic, women's' health, topical pain, and topical anti-infectives arenas. Services include formulation development, in vitro tissue penetration studies, analytical services, regulatory strategy and submissions, and GMP clinical manufacturing and labeling.

AAPS Booth #4700

DPT Laboratories

318 McCullough
San Antonio, TX 78215
tel. 210.476.8100
fax 210.227.5279
www.DPTLabs.com

DPT®
A DFB COMPANY

Description
DPT is a contract development and manufacturing organization (CDMO) specializing in sterile and non-sterile semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the source for semi-solid and liquids — from concept to commercialization and beyond.

Drug development services range from pre-formulation, formulation and biopharmaceutical development, analytical development and validation, through process development.

Production capabilities include five cGMP facilities, clinical trial materials, full scale commercial production, controlled substance registration Class II – IV and complete supply chain management.

Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging.

AAPS booth 4224

Dr. Reddy's Laboratories Inc.

200 Somerset Corporate Blvd.
Bridgewater, NJ 08807
tel. 908.203.4932
fax 908.203.4914
cps@drreddys.com
www.drreddys-cps.com

Description
Dr. Reddy's Custom Pharmaceutical Services (CPS) offers a variety of programs specifically geared to solve your development or commercial needs. We can help you extend your product life cycle by leveraging generic assets, by utilizing effective chiral chemistry solutions for asymmetric problems, by providing the right facilities and technologies for high potent, steroidal or prostaglandin products, or by utilizing the variety of formulation technology platforms that we have at our disposal for difficult and sophisticated formulation needs. With our vast experience in custom solutions, we have the technical and industry experiences required to provide the right solution services for you.

DSM

45 Waterview Blvd.
Parsippany, NJ 07054
tel. 973.257.8011
fax 973.257.8024
info.dsmpharma@dsm.com
www.dsm.com

Description
DSM is an outsourcing manufacturing partner committed to meeting market demand globally with quality, regulatory excellence and innovations for sustainability. DSM offers preclinical/R&D through Phase I, II and III to commercial scale production for active pharmaceutical ingredients, biologics (mammalian cell cultures), microbial fermentation, anti-infectives and, sterile and solid dosage manufacturing.

AAPS booth 1411

Fette Compacting America

400 Forge Way
Rockaway, NJ 07866
tel. 973.586.8722
fax 973.586.0450
www.fetteamerica.com
sales@fetteamerica.com

Description
Fette Compacting America, North America's leader in precision tablet press technology, is a subsidiary of German manufacturer Fette GmbH. Fette Compacting America offers customers in the United States, Canada, and Puerto Rico a variety of services, including new and used machine sales, technical assistance, machine installations, training and seminars, validation, maintenance, spare parts, and tooling.

Products
Fette Compacting America's groundbreaking FE Series of tablet presses delivers unprecedented levels of productivity, flexibility, and availability. Details include:

- Easily-detachable, FDA-certified high-performance polymer
- 360° access includes unique filling system for simple, safe feeding
- Innovative filling system for easy, reliable feeding and increased product output
- Fast format and product changeover
- Maximum yields, minimum product loss, and easy changeover

FMC Corporation
FMC BioPolymer

1735 Market Street
Philadelphia, PA 19103
tel: 1.215.299.6534
fax: 1.215.299.6669
eMail: **pharm_info@fmc.com**
url: **www.fmcbiopolymer.com**

Description:

FMC BioPolymer is the market leader for microcrystalline cellulose, alginates and carrageenan. We offer a range of products that deliver consistent performance and reliable functionality:

Avicel® binders
Ac-Di-Sol® super-disintegrants
Alubra® lubricants
Aquacoat® coatings
Protanal® alginates
SeaGel® carrageenan

AAPS 2012:

Avicel® **MCC** is 50 years young! We invite you to come celebrate the past 50 years of successful formulations, and look ahead to new opportunities with:

Aquacoat® **ARC** ***[NEW]***,
SeaGel® capsule technologies, and
QbD Express™

AAPS Booth 2019

FOSS NIRSystems, Inc.

7703 Montpelier Road
Laurel, MD 20723
tel. 301.680.9600 / 800.343.2036
fax 301.236.0134
info@foss-nirsystems.com
www.foss-nirsystems.com

FOSS NIRSystems

ProFoss

Description

FOSS NIRSystems is the world's leading supplier of laboratory, at-line, and process Near-Infrared (NIR) solutions for use in the pharmaceutical, chemical, petrochemical, and related industries. We have more than 45 years of industry experience and over 18,000 successful installations worldwide. We are committed to providing the most accurate and precise rapid test and measurement products to meet our customer's needs.

Products and services

We provide laboratory, at-line, and process NIR solutions for many applications, including:

- Raw material inspection
- Inspection of solids, powders, and liquids
- Content uniformity of solid dosage forms
- Blending, mixing, granulation and drying processes
- Reaction monitoring
- Endpoint determination.

Please contact us regarding your specific application!

AAPS Annual Meeting booth 4604

EAS booth 201/203

GlobePharma, Inc

2B & C Janine Place
New Brunswick, NJ 08901
tel. 732.296.9700
fax 732.296.9898
Sanni@globepharma.com
www.globepharma.com

GlobePharma

Description

GlobePharma's vision is to provide solutions for some of the problems in the pharmaceutical industry and excellent customer support. GlobePharma was established in 1993 with the introduction of unit-dose powder samplers.

Our Products:

GlobePharma has introduced & patented several products. Our products are used by pharmaceutical companies worldwide. These include a variety of unit-dose and bulk samplers for powders, liquids and and semi-solids, remote swabbing and microbiological sampling tools, cleaning validation coupons, POWDEREX™ apparatus, accelerated powder segregation tester, R&D and pilot scale blenders with interchangeable V-shells, Bins and Double-cones with high-speed intensifier-bars, SimpleBlend™—new stand-alone blenders, new patent-pending attachment, SIFT-N-BLEND™, cGMP butterfly valves, manual tablet compaction machine, table-top rotary tablet presses, tablet press instrumentation, high shear granulator, tablet de-duster, capsule polisher, empty capsule eliminator, cone-mill, and a line of refurbished equipment. Visit our FaceBook page and website!

AAPS booth 3827

Hamilton Company

4970 Energy Way
Reno, NV 89502
Tel: (800) 648-5950
Fax: (775) 858-3024
roboticsales@hamiltoncompany.com
www.hamiltonrobotics.com

Description
Hamilton Company is a global enterprise with manufacturing facilities in Reno, Nevada and Bonaduz, Switzerland. We are the worldwide leader in the design and manufacture of manual, semi-automated and robotic products for precision fluid measuring. For over 50 years, Hamilton has been satisfying customer needs by combining quality materials with skilled workmanship, ensuring the highest level of performance of every precision fluid measuring device we manufacture. Hamilton Robotics is dedicated to the design and manufacture of automated liquid handling workstations. Key to our products is our air displacement pipetting and monitoring technology as well as the software controlling our systems.

AAPS booth 3725

Hospira One 2 One™

275 North Field Drive
D-0988, Bldg. H-1
Lake Forest, IL 60045
tel. US: 1.224.212.2267
tel. Europe: +44 (0) 1926 835 554
fax US: 1.224.212.3210
one2one@hospira.com
www.one2onecmo.com

Parenteral Contract Manufacturing Service of Hospira

Description
Hospira's One 2 One™ business is a world leader in the custom development and manufacture of injectable products packaged in vials, prefilled syringes, cartridges, and flexible containers. Hospira has extensive experience with injectable drug commercialization, and One 2 One™ has over 20 years of contract manufacturing experience serving bio/pharmaceutical companies.

Product/service information
- Sterile filling and lyophilization facilities in the US, Italy, Australia and India.
- Manufactured over 25 large molecules, 10 cytotoxic products and 10 beta-lactam products.
- Extensive product development experience with complex formulations.
- Practical knowledge of 70 markets, including expert regulatory filing strategies for the Americas, Europe, and Asia Pacific.

International Centre for Diffraction Data

12 Campus Boulevard
Newtown Square, PA 19073 USA
Phone: 610.325.9814
Fax: 610.325.9823
Email: marketing@icdd.com
Website: www.icdd.com

Description
ICDD, a not-for-profit corporation, is dedicated to the collecting, editing, and publishing of the Powder Diffraction File (PDF). Our mission is to be the world center for quality diffraction and related data to meet the needs of the technical community.

ICDD's PDF-4/Organics 2013 database featuring 471,257 entries is designed for rapid materials identification. Its design allows for easy interface with diffractometers and data analysis systems of leading software developers and manufacturers of X-ray equipment. The database is useful for scientists working in consumer products, catalysis, forensic science, analytical labs, drug discovery, and production.

AAPS booth 2613

Jubilant HollisterStier

Contract Manufacturing & Services Division
U.S.A. – Canada – India
3525 N. Regal St.
Spokane, WA, U.S.A. 99207
tel. 800.655.5329
info@jublHS.com
jublHS.com

Description

Jubilant HollisterStier Contract Manufacturing is an integrated contract manufacturer, able to manufacture sterile injectable, solid and semi solid dosage forms. Our facilities across North America and India provide specialized manufacturing services for the pharmaceutical and biopharmaceutical industries. We provide a full-range of support and services to streamline the manufacturing process.

- Sterile Injectable Fill/Finish (clinical to commercial)
- Lyophilization (clinical to commercial)
- Sterile Ophthalmics & Otics
- Non-Sterile Topicals & Liquids
- Solid Dosage
- Multiple Formats (vials, ampoules, tablets, capsules, bottles, tubes, jars, applicators)

Jubilant HollisterStier is registered with such Regulatory authorities as the FDA (CDER, CBER) EMA, ANVISA, PMDA, and Health Canada.

Eurofins Lancaster Laboratories

2425 New Holland Pike
Lancaster, PA 17601
717-656-2300
www.LancasterLabsPharm.com
pha@lancasterlabs.com

Description

With a proven track record of providing quality scientific solutions for the largest pharmaceutical and biopharmaceutical companies in the world, Eurofins Lancaster Laboratories is a global leader in bio/pharmaceutical laboratory services providing innovative and timely scientific solutions to streamline the drug development process.

With facilities in Lancaster, PA, Portage, MI and Dungarvan, County Waterford, Ireland, and a global capacity of over 300,000 square feet, Lancaster Laboratories has the capabilities to meet your global regulatory requirements. All of our facilities offer cGMP-compliant laboratory services and operate under the same strict quality control program and utilize the same LIMS system.

Our clients can choose from five service models, including our award-winning Professional Scientific Staffing℠ (PSS) and our Full Time Equivalent (FTE) model, to determine the most efficient and cost-effective service solution for their project. We also provide 24-hour data access via our innovative and secure online tool at LabAccess.com℠.

AAPS Booth #3030

Meissner Filtration Products

4181 Calle Tesoro
Camarillo, CA 93012
tel. 805.388.9911
fax. 805.388.5948
info@meissner.com
www.meissner.com

Description

Meissner is your source for innovative microfiltration and single-use systems. We are a technology centric company that leverages our R&D efforts to offer our clients products that deliver advanced processing and fluid handling solutions for the pharmaceutical and biopharmaceutical industries.

Our One-Touch® single-use product portfolio demonstrates our commitment to manufacture innovative products. We introduced the industry's first slip agent-free PE biocontainers, TepoFlex®, thus reducing its extractables profile, and giving the biocontainer its remarkable visual clarity. We also introduced the industry's only multilayer PVDF biocontainer, FluoroFlex®, thus expanding the application of single-use systems beyond the limits of existing PE biocontainers, and into areas such as API storage.

Metrics, Inc.

1240 Sugg Parkway
Greenville, NC 27834
tel. 252.752.3800
fax 252.758.8522
www.MetricsInc.com

Description

Metrics Inc. is one of the most respected contract pharmaceutical development and manufacturing companies in the United States. Metrics is a full-service provider of quality pharmaceutical formulation development; First Time In Man formulations; CTM for Phase I, II and III trials; commercial manufacturing; and analytical method development and validation services. Metrics has particular expertise in FTIM and Phase I, II, and III CTM manufacturing.

Globally, Metrics provides a broad spectrum of CMC services to support IND, NDA and ANDA submissions to regulatory agencies. Metrics' specialty services include:

- Potent and Cytotoxic
- Formulation
- Manufacturing
- Analytical
- Stability Storage
- Microbiology

MG America

31 Kulick Rd.
Fairfield, NJ 07004
tel. 973.808.8185
fax 973.808.8421
sales@mgamerica.com
www.mgamerica.com

MG AMERICA
A partnership for success

Description

MG America is a recognized leader in the supply of processing and packaging machinery to the pharmaceutical, nutritional, cosmetic, food, and general packaging industries in the United States, Canada, and Puerto Rico. MG America offers equipment designed for flexibility, compact operation, ease of use and maximum reliability.

Products and services

- **Packaging Machinery** including case packers, cartoners, thermoforming machines, blister packaging machines, aseptic filling lines, powder microdosing, washing machines, palletizers, inspection systems, and syringe assembly machines.

- **Capsule Filling Machinery** to handle R&D, scale-up, intermittent and continuous motion. Speeds range from 6000 to 200,000 capsules per hour. Dosage forms include powders, pellets (beads), tablets, and liquids.

Micron Technologies

333 Phoenixville Pike
Malvern, PA 19355
tel. 610.251.7400
fax 610.251.7499
info@microntech.com
www.microntech.com

Micron Technologies

Description

Micron Technologies provides contract particle size reduction and analytical services for the pharmaceutical industry. We offer micronization, mechanical milling and classification, for enhancing bioavailability, improving content uniformity, and refining the delivery of inhalation pharmaceutical products.

Products and services

Micron is capable of micronizing R&D to bulk production scale quantities, as well as highly potent compounds and controlled substances. Our contract analytical laboratory provides material characterization, release testing, stability testing, method development and method validation. Our facilites in the US and UK are FDA inspected, we operate according to cGMP regulations, and we are committed to being the industry's "Provider of Choice."

AAPS booth 1216

Mikart, Inc.

1750 Chattahoochee Ave.
Atlanta, GA 30318
tel. 404.351.4510
fax 404.350.0432
sales@mikart.com
www.mikart.com

Description

Since 1975, Mikart has been a recognized leader in providing contract manufacturing, product development, and packaging services to the pharmaceutical industry. The company specializes in solid dose and liquid oral dose products.

Mikart offers more than 37 years of experience and knowledge to take products from formulation development through full-scale commercial production.

Products and services

- Formulation development
- Analytical methods development
- Methods and process validation
- Stability testing
- Clinical supplies packaging
- Immediate- and controlled-release tablet manufacturing
- Capsule manufacturing
- Oral liquid manufacturing
- Schedule II–V controlled drug manufacturing
- Film coating
- Solid dose and liquid bottle packaging
- Laminated foil pouch packaging
- Blister packaging
- Regulatory services

AAPS booth 4233

Natoli Engineering Company, Inc.

28 Research Park Circle
St. Charles, MO 63304
tel. 636 926 8900
fax 636 926 8910
info@natoli.com
www.natoli.com

Description

With nearly 40 years of service in the tablet compression industry, Natoli Engineering Company, Inc. provides customers with quality products and expert insight.

Products and Services

- Tablet Compression Tooling
- Tablet Presses, Refurbishing and Repair
- Tableting Accessories Catalog
- Tablet Press Replacement Parts and Turrets
- Tool Management Software
- Laser Vision Punch Inspection System
- Tooling and Tablet Design
- Technical Training
- Laboratory Services
- Technical Support and Troubleshooting
- Expedited Global Delivery

Patheon™
Performance the World Over

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Durham, NC 27703-8580 USA
P: +1 866 Patheon (+1 866 728 4366)
or +1 919 226 3200
Fax: +1 919 474 2269

E-mail: DoingBusiness@Patheon.com
Website: www.patheon.com

Patheon Inc. (TSX: PTI) is a leading global provider of contract development and manufacturing services to the global pharmaceutical industry. The company offers a wide range of services from developing drug candidates at the pre-formulation stage through the launch, commercialization and production of approved drugs. Patheon has established its position as a market leader by leveraging scale, global reach, specialized capabilities, broad service offerings, scientific expertise and a track record of product quality and regulatory compliance to provide cost-effective solutions to its customers. Patheon serves approximately 300 of the world's leading pharmaceutical and biotechnology companies.

AAPS Booth # 2219

PerkinElmer, Inc.
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Waltham, MA 02451 USA
P: (800) 762-4000 or
(+1) 203-925-4602
onesource@perkinelmer.com
www.perkinelmer.com/onesource

PerkinElmer®
For the Better

As the one of the most experienced, most complete provider of laboratory services worldwide, OneSource® Laboratory Services is uniquely positioned to offer a more valuable, customizable and profitable partnership to help laboratories control costs and improve scientific productivity.

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- And much more

AAPS booth 4000

Pfizer CentreSource

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Kalamazoo, MI 49001
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fax 269.833.3604
Europe/Middle East/Africa:
tel. +32.2.714.6502
fax +32.2.749.5509
Asia/Pacific:
tel. +65.6419.0248
fax +65.6419-0022
www.pfizercentresource.com

Description

Pfizer CentreSource offers worldwide expertise and capacity in fine chemicals and finished dosage form manufacturing. A recognized industry leader in steroid synthesis and production, we also provide advanced facilities that meet or exceed GMP standards for contract manufacturing sterile dosage forms (including high potency) as well as product development, process development, and advanced manufacturing for high potency drug product.

Services

The company supplies high quality and high value APIs and intermediates from its chemical synthesis, custom fermentation, and bioprocessing capabilities. PCS also provides high quality solutions in aseptic filling and a suite of highly potent drug product development, manufacturing, and packaging services.

Pharmaceutical Technology

485 Route One South
Bldg F, First Floor
Iselin, NJ 08830
www.PharmTech.com

Description

For 35 years, *Pharmaceutical Technology* has published authoritative, reliable, and timely information on every aspect of applied pharmaceutical science and biotechnology. More than 38,000 professionals rely on *Pharmaceutical Technology* to stay ahead of the curve in manufacturing equipment and processes, formulation and drug delivery, active pharmaceutical ingredients and excipients, software and automation, validation and compliance, packaging and labeling, outsourcing issues, and a host of related topics.

The industry's premier editorial staff delivers unequaled double-blind, peer-reviewed research, authoritative technical articles, independent news reports, and in-depth analyses.

Opportunity

Through regular and special issues, electronic publications, and custom publishing services, *Pharmaceutical Technology* reaches the readers who make pharmaceutical manufacturing run. For information on advertising and special projects, please contact Publisher Mike Tracey (732.346.3027 or mtracey@advanstar.com). To make an editorial contribution, please contact Editorial Director Angie Drakulich (732.346.3038 or adrakulich@advanstar.com).

AAPS booth 5011

Powdersize, Inc.

20 Pacific Dr.
Quakertown, PA 18951
tel. 215.536.5605
fax 215.536.6630
thigley@powdersize.com
www.powdersize.com

Description

As a leader in custom powder sizing, Powdersize has optimized its tolling services for improved yield, grinding performance and process robustness. By combining expertise in both equipment design and nearly two decades of toll manufacturing, Powdersize delivers unique solutions to the challenges of poor precision during feeding, product "blowback" and system loss associated with large surface areas, especially for small batch sizes necessary for early stage R&D studies or clinical evaluation. Capabilities of reducing product exposure down to 10 ng/m^3 via containment approaches has also been added to address the challenges associated with handling cytotoxic and/or highly sensitizing APIs.

Powdersize, Inc.

PYRAMID Laboratories, Inc.

3598 Cadillac Ave.
Costa Mesa, CA 92626
tel. 714.435.9800
fax 714.435.9585
info@pyramidlabs.com
pyramidlabs.com

PYRAMID Laboratories, Inc.

Description

PYRAMID Laboratories, Inc. is located in Southern California, United States. Our facilities are housed in three buildings covering more than 70,000 ft^2. The combination of our manufacturing facilities and state-of-the-art laboratory allows PYRAMID to offer the pharmaceutical and biotech industry both analytical and manufacturing support capabilities.

Products and services

PYRAMID provides contract Aseptic Manufacturing and Analytical Services for Sterile Injectable Drugs. PYRAMID provides expertise in formulation and process development and aseptic filling for vials and syringes, as well as lyophilization applications for clinical and commercial products. PYRAMID has established a reputation of exceptional performance, integrity, and quality.

AAPS booth 1230

Qualicaps, Inc.

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Whitsett, NC 27377
tel. 800.CAPSULE
fax 336.449.3333
info@qualicaps.com
www.qualicaps.com

Description

Qualicaps is an international manufacturer of empty pharmaceutical capsules and pharmaceutical processing equipment. With more than 100 years of experience, Qualicaps is a leader in innovation in both gelatin and Quali-V® (hypromellose) capsules, and offers a proprietary product line of pharmaceutical equipment, including lab scale capsule filling and sealing machinery.

Products and services

Qualicaps is committed to supplying and servicing the industry with a variety of solutions for capsules, equipment and related technology. We offer high-quality gelatin capsules for pharmaceutical applications and Quali-V® is the leading HPMC pharmaceutical capsule. Qualicaps offers a complete line of processing equipment, including capsule filling, band-sealing and inspection equipment.

AAPS booth 4227

ROQUETTE America, Inc.

2211 Innovation Drive
Geneva, IL 60134
(630)463-9430 Main
(630)232-2157 Fax
www.roquette.com

ROQUETTE is a global solution provider, enabling functional pharmaceutical excipients and pyrogen-free actives for outstanding formulations. Our long-standing expertise assures worldwide, consistent availability of innovative technologies and highest quality, multi-compendial, nonGMO excipients like native, pregelatinized starches, cyclodextrins, mannitol, xylitol, sorbitol, maltitol, maltodextrins, proteins, soluble fiber, and specialized film-coating excipients.

ROQUETTE America, Inc.

"Offering the Best of Nature"

AAPS Booth 4024

Sartorius Stedim North America, Inc.

5 Orville Dr.
Bohemia, NY 11716
tel. 800.368.7178
fax 631.254.4253
patricia.stancati@sartorius.us
www.sartorius.us

Description

Sartorius Stedim Biotech is a leading provider of cutting-edge equipment and services for the development, quality assurance, and production processes of the biopharmaceutical industry. The company's integrated solutions covering fermentation, filtration, purification, fluid management, and laboratory technologies enable the biopharmaceutical industry around the world to develop and produce drugs safely, timely, and economically.

Sartorius Stedim Biotech, a leading supplier of equipment and services for the biopharmaceutical industry, offers bioreactors, fermenters, crossflow, integrity-test equipment, housings, single-use fluid handing, and mixing technology. Consumables include crossflow cassettes, membrane adsorbers, depth filters, sterilizing and prefilter cartridges and capsules, mycoplasma, and viral filtration. Comprehensive validation and training services support the company's products.

schenckAccuRate

Schenck AccuRate
746 E. Milwaukee St.
Whitewater, WI 53190
Phone: 262-473-2441
Fax: 262-473-4384
Email: mktg@sarinc.com
Web site: www.accuratefeeders.com

By working closely with its customers, Schenck AccuRate has excelled at designing weighing and feeding systems for pharmaceutical processes worldwide. Whether it is sanitary level screw or disc feeders, vibratory feeders, weighbelt feeders or bulk bag discharging systems Schenck AccuRate has the right bulk solids handling solution for tablet coating, multi-ingredient batching, intermediate bulk packaging, and jet milling.

With operations in over 75 countries, 125 years of bulk solids weighing and feeding experience, global service and support, Schenck AccuRate is prepared to meet your pharmaceutical processing equipment needs.

Sensient® Pharmaceutical Coating Systems

2515 N. Jefferson Ave.
St. Louis, MO 63106
tel. 800.325.8110
info@sensientpharma.com
www.sensientpharma.com

Description

Sensient Pharmaceutical Coating Systems is a global leader in the development and manufacture of superior coating systems and brand-defining color solutions for the pharmaceutical and nutraceutical markets. Servicing leading pharmaceutical companies from 35 locations globally, Sensient's comprehensive range of versatile and novel coating systems offers the visual and functional attributes necessary for brand definition, product identification, and trademark protection.

Products and Services

Sensient partners with customers globally and regionally to create market-defining opportunities and advanced product solutions. Combining sophisticated technologies with our unique color expertise, we work with you to develop safe, high-performance coating systems with the visual, application, and production-efficiency benefits to better define and protect brands.

AAPS booth #3815

Sheffield Bio-Science

A Kerry Group Business

158 State Highway 320
Norwich, NY 13815
tel. 800.833.8308
fax 607.334.5022
Melanie.Cacciottolo@kerry.com
www.SheffieldBioScience.com

Description

Sheffield Bio-Science continues a reputation of excellence in providing pharmaceutical grade lactose, tabletting systems, and film coatings for drug delivery systems. As part of Kerry Group, Sheffield Bio-Science has a history of leadership in providing the highest quality excipients that exceed customer expectations every day.

These include superior products such as:

SheffCoat coating systems: One step, ready-to-use coating systems to match existing coating and color, while offering a full spectrum of best-in-class, cost effective solutions.

LubriTose™ is a co-processed, direct compression, complete excipient system for high-speed tabletting operations that eliminates blending issues associated with lubricants such as magnesium stearate.

Shimadzu Scientific Instruments

7102 Riverwood Drive
Columbia, MD 21046
Phone: 800-477-1227
Fax: 410-381-1222
webmaster@shimadzu.com
www.ssi.shimadzu.com

Description

Shimadzu is a world leader in the analytical instruments industry. Our instruments are used throughout the pharmaceutical pipeline, from proteomics and metabolomics research and drug discovery/development to QA/QC and manufacturing, providing a total solution to researchers working within the pharmaceutical industry.

Products

- HPLC/UHPLC
- LC/MS/MS
- UV-Vis
- FTIR
- GC
- GC/MS/MS
- AA/ICP
- TOC
- MALDI
- Balances
- Particle Size Analyzers
- Thermal Analyzers

AAPS Booth 4304

Spectrum Chemical Mfg., Corp.

769 Jersey Ave.
New Brunswick, NJ 08901
tel. 800.772.8786
marketing@spectrumchemical.com
SpectrumChemical.com

Description

Spectrum Chemicals Mfg. Corp. manufactures and distributes fine chemicals and laboratory products. Our chemical offerings include >1,200 USP/NF/FCC grade chemicals, excipients, controlled substances, active pharmaceutical ingredients including items for obesity and Alzheimer's research (2013-2015 Spectrum USP Chemical Catalog) and >22,000 organic chemicals for research (2013-2015 Spectrum TCI Organic Chemical Catalog). Our entire chemical offering (>35,000 items) is available in research, scale-up and production sizes. Spectrum's ISO 9001:2008-certified facilities are FDA registered and operate under current Good Manufacturing Practices. Spectrum also distributes nearly 150,000 supply and equipment items from over 200 manufacturers such as Mettler-Toledo, Corning, Thermo Scientific and PerkinElmer.

Suheung Capsule

16610 Marquardt Ave.
Cerritos, CA 90703
tel. 562.926.5685
fax 562.926.4272
sales@suheung-america.com
www.suheung.com

Description

Suheung Capsule's founding in 1973 has solely focused on manufacturing the highest quality capsules. Through our research and development, and technical investments Suheung is the world's leading manufacturer of hard capsules. Suheung's dedication to quality is seen in each and every element, and every process of capsule production.

Products

Suheung's EMBO CAPS® Capsules come in the following size's #00EL, #00, #0EL, #0, #1, #2EL, #2, #3, #4. The capsules are made of gelatin (bovine, porcine & fish) or Hypromellose material. Patented Locking Mechanism/ variety of colors, print options/Kosher and Halal certified/DMF No. 1521.

AAPS booth 4145

Suzhou Pharma Services

9 Polito Ave, Suite 900
Lyndhurst, NJ 07071
tel. 732.317.0620
info@suzhoupharma.com
www.suzhoupharma.com

Description

Suzhou Pharma Services is a US based contract development and manufacturing organization specializing in solid oral dosages with an FDA approved and Chinese SFDA licensed cGMP Finished Dose manufacturing facility located in Suzhou, China. We offer a unique combination of Western pharmaceutical expertise, service and quality standards with **attractive Chinese cost advantages**. We have an experienced project management team in place to support our customer base in the US and locally in China. Whether you are seeking formulation development or commercial manufacturing services for the US and global markets or a partner for the growing Chinese market, be sure to make Suzhou Pharma Services part of your next outsourcing solution.

AAPS Booth # 1506/1606

UPM Pharmaceuticals, Inc.

6200 Seaforth St.
Baltimore, MD 21224
tel. 410.843.3700
info@upm-inc.com
www.upm-inc.com

Description

UPM Pharmaceutical is a Baltimore-based, independent provider of contract drug development, cGMP manufacturing and analytical testing services. We specialize in oral routes of administration with a focus on solid dosage forms. With our commitment to efficiency, timeliness and flexibility, we deliver industry-savvy, customer-focused services.

Analytical Services

- HPLC / UPLC Based
- Dissolution Testing
- Full ICH Stability Testing

Formulation Development

- Complex Formulations
- Low Solubility Solutions
- Bevi-Batch™

Clinical Manufacturing

- cGMP Manufacturing
- Phase I - III
- Direct API Fill into Capsules

Commercial Manufacturing

- FDA Inspected
- Solid Oral Dosage Forms
- DEA Controlled Substances

AAPS booth 2816

Veltek Associates, Inc.

15 Lee Blvd.
Malvern, PA 19355
tel. 888.478.3745
fax 610.644.8335
vai@sterile.com
www.sterile.com

VELTEK ASSOCIATES, INC.

Description

Veltek Associates Inc. plays an innovative role to the pharmaceutical, biotechnology and medical device industries by developing products and services to improve operations and reduced costs associated with contamination.

We focus on identification and control of contamination in classified areas. We produce a complete range of sterile pharmaceutical grade disinfectants, sporicides, lubricants, and buffer solutions; hand sanitizer and hands-free dispensers; Environmental Monitoring Systems; In-line and Cage cleaners; and Core2Clean Spray/Mop/Fog Systems.

VAI Labs provides microbiological testing ranging from the identification of microorganisms to antimicrobial effectiveness studies to prove the effectiveness of selected disinfectants.

Aseptic Processing Inc. provides detailed consulting services.

Vindon Scientific (USA) Inc.

300 Town Park Drive
Building 1, Suite 130
Kennesaw, GA 30144
Tel: +1 770 988 3095
Fax: +1 770 988 3094
Email: sales@vindonscientific.com
Website: www.vindonscientific.com

Description:
Vindon Scientific (USA) provide outsourced storage to clients in our stability storage suite in Atlanta, encompassing walk in rooms and chambers, a complete range of World Climatic ICH conditions as well as unique conditions.

In addition Vindon Scientific manufacture and distribute stability storage walk in rooms, reach in rooms and chambers for the pharmaceutical and chemical industry.

Products & Services:

- Contract Storage to cGMP standards, ISO 9001, 24/7/365 support.
- Walk in rooms and cabinets for the stability storage of products within the pharmaceutical and chemical industry.
- Validation services (IQ, OQ, PQ, CQ): Utilize Eurotherm datalogger system.
- Laboratory grade freezers/refrigerators and Photostability cabinets

Vindon Scientific has manufactured stability chambers for over 40 years and has provided validation and contract storage services for the past 20 years.

AAPS Booth 1024

Watson-Marlow Pumps Group

37 Upton Technology Park
Wilmington, MA 01887
tel. 800.282.8823
fax 978.658.0041
support@wmpg.us
www.wmpg.com

Description

Products from the Watson-Marlow Pumps Group Biopharmaceutical Division provide many benefits including filling validation, sterile processes, traceability, superior flow rates and metering accuracy, scalable solutions, and reliable dispensing performance.

Watson-Marlow peristaltic pumps totally contain fluid to be pumped, ensuring isolation from any source of contamination. Flexicon aseptic filling systems provide solutions from laboratory bench to fully automatic aseptic filling, plugging, and capping systems. The Watson-Marlow range of Biopharmaceutical-grade tubing for peristaltic dispensing delivers consistent, accurate, and long-term performance. In our state-of-the-art cleanrooms, we manufacture Pumpsil, a premium quality platinum cured silicone tube; Bioprene, a unique Thermoplastic Elastomer (TPE); and PureWeld XL, a high-quality weldable TPE tube used in the biotechnology and pharmaceutical industries.

Wellspring Pharmaceutical

400 Iroquois Shore Rd.
Oakville, ON Canada L6H 1M5
tel. 866.337.4500
fax 905.337.7239
info@wellspringcmo.com
www.wellspringcmo.com

Description

WellSpring Pharmaceutical is a flexible and responsive CMO offering full-service clinical and commercial manufacturing, packaging and analytical services from a single cGMP facility. Our global experience and superior customer care will ensure your aggressive timelines are met. Over our 10 year history we've developed solid foundations with small biotech to multinational pharmaceutical organizations.

Technical Services

Our highly skilled technical professionals will assist you with every facet of your product needs, including:

Manufacturing & Packaging
- Tablets
- Capsules
- Over-encapsulation / Blinding
- Creams, lotions, ointments & gels
- Non-sterile liquids
- Controlled substances
- Scale-up to commercial size batches
- Process & packaging validations

Quality Services
- Full service QA & QC Laboratory
- Method development & transfer
- ICH compliant stability testing
- Microbial testing & Validation

Xcellerex

170 Locke Drive,
Marlborough, MA 01752
tel. 508.480.9235
fax 508.480.9238
Webinquiry@xcellerex.com
www.gelifesciences.com/xcellerex

Description

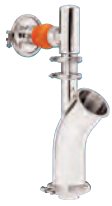
Xcellerex, a GE Healthcare company, is transforming biopharmaceutical manufacturing with its FlexFactory biomanufacturing platform. Based in Marlborough, Massachusetts, Xcellerex was founded in 2002.

FlexFactory is a fully modularized and integrated biomanufacturing platform. It enables the deployment of new production facilities for vaccines, biotherapeutics, biosimilars, monoclonals in as little as 9 months—versus 3 to 5 years for present technology—at half the total cost of traditional stainless steel plants.

FlexFactory is designed for quick start-up and easy expansion at a fraction of standard costs.

Now, companies can advance new drugs from research and development to commercial manufacturing. The system provides easy scale up to bioreactors as large as 2,000 liters—with full downstream purification through final bulk product—all on the same integrated, single-use flow path.

MANUFACTURING EQUIPMENT & SUPPLIES



Gravimetric feeder

The PureFeed DP-4 is a gravimetric feeder that meters dry pharmaceutical, nutraceutical, and cosmetic powders at feed rates as low as 20 g/h. A speed-controlled, inert ceramic-feed disc is positioned at the base of an electropolished stainless-steel material storage chamber to precisely rotate and discharge tiny amounts of material continuously over a 20- to 2000-g feed-rate range. **Schenck AccuRate,** *Whitewater, WI • www.accuratefeeders.com • tel. 262.473.2441*

Storage containers

Meissner's QuaDrum storage containers are available in 50-, 100-, and 200-L volumes to support its One-Touch single-use biocontainer assembly portfolios. The polyethylene storage containers are chemically resistant and easy to clean, and are available with slotted or solid lid options to offer varying levels of accessibility. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Powder-flow tester

Brookfield's Powder Flow Tester (PFT) is designed to deliver quick and easy analysis of powder-flow behavior in industrial-processing equipment. The PFT minimizes process downtime for manufacturers and processors of powder-based materials. The unit performs quality-control checks on incoming materials and quickly characterizes new formulations for flowability. **Brookfield Engineering Laboratories,** *Middleboro, MA • www.brookfieldengineering.com • tel. 800.628.8139*

MANUFACTURING EQUIPMENT & SUPPLIES

Portable tanks and mixers

Ross's portable tanks and mixers include: batch high-shear mixers on mobile lifts, inline high-shear mixers on mobile carts, powder injection systems, laboratory multishaft and planetary mixers on mobile benches or wheels, static mixer skid systems, ASME-code process vessels, custom sanitary tanks, specialty reactors, and other products. **Ross, Charles & Son Company,** *Hauppauge, NY • www.mixers.com • tel. 800.243.ROSS*

Supervisory bioprocess control

Sartorius's BioPAT MFCS/win enables users to mirror each step of bioprocess applications by selection of customized recipes that comply with the ANSI/ISA-88.01 standard for computerized batch control. The device features fully or semiautomatic operations, and contains state- or time-dependent transitions that enable organized and structured batch processing as well as flexible manufacturing. **Sartorius Stedim North America,** *Bohemia, NY • www.sartorius.com • tel. 631.254.4249*

Peristaltic filling system

Flexicon's FF15 vial filling system uses new Flexicon AsepticSU single-use fluid-path technology to simplify validation and deliver effortless changeover for a variety of fills. The FF15 can accurately fill vials from 0.1 to 100 mL at a rate of up to 2000 fills per hour. The unit features a depth of only 19.7 in., and is, thus, compact enough to fit in the tight space of a biosafety cabinet. **Watson-Marlow Tubing,** *Wilmington, MA • www.wmtubing.com • tel. 800.282.8823*

MANUFACTURING EQUIPMENT & SUPPLIES

Tablet-compression accessories catalog

Natoli's new tablet-compression accessories catalog allows the functionality to browse products and quickly request quotes online. The catalog offers customers the capability to flip through the pages of the digital catalog, click items to add to a virtual "Quote Cart" feature, and checkout upon completion. Visit natoli.com/catalog.html. **Natoli Engineering Company,** *St. Charles, MO • www.natoli.com • tel. 636.926.8900*

Small-flow element filters

Meissner's Small Flow Element filters can be specified with a variety of adapters for installation into new housings or retrofit applications. The filters are available in lengths of 2.5 or 5 in., and adapter selection includes an industry standard 116, 222, and 226 O-rings. A specialized SK adapter version is also available for Meissner SKR filter housings. **Meissner Filtration Products,** *Camarillo, CA • www.meissner.com • tel. 805.388.9911*

Fluid-bed dryer bags

Kavon provides custom replacement fluid-bed dryer bags for US and European equipment models. The bags are appropriate for wet granulation, dry filtration, and wet and dry coating applications. The company offers flexible 1–4-bag systems in various fabrics choices and also repairs bags.
Kavon Filter Products, *Wall Township, NJ • www.kavonfilter.com • tel. 732.938.3135*

MANUFACTURING EQUIPMENT & SUPPLIES

Product-development capsules

Qualicaps' Prism Capsules are empty two-piece capsules that include a range of colorants and two ink formulations that help expedite product-development timelines. The capsules are designed to assist companies in determining product trade dress in parallel with stability studies, and its colorants can be extracted when final trade dress is determined. **Qualicaps,** *Whitsett, NC • www.qualicaps.com • tel. 800.CAPSULE*

Nano-16 twin-screw extruder

A nano-16 twin-screw extruder with 16-mm outer diameter screws and a 1-mm flight depth was designed to evaluate extrusion with as little as a 20-g batch. Screws and barrels are segmented, and the extruder uses trilobal screw elements. A 1.2:1 outer diameter:inner diameter ratio results in a free volume of approximately 1 cm^3/diameter. **Leistritz,** *Somerville, NJ • www.leistritz-extrusion.com • tel. 908.685.2333*

Tablet-coating platform

The Accela-Cota FLEX 500 tablet-coating platform features seven exchangeable drums and provides a batch-size range of 50–920 L. Innovative gun positioning, a segmented exhaust plenum, and interchangeable mixing baffles configure the coater according to the requirements of the batch size and coating processes. **Thomas Engineering,** *Hoffman Estates, IL • www.thomaseng.com • tel. 800.634.9910*

MANUFACTURING EQUIPMENT & SUPPLIES

Industrial vacuum

The Model 860/02 industrial vacuum is designed to help eliminate drum handling and collect and discharge powders in a safe, dust-free way. The vacuum uses VAC-U-MAX's Air-Powered Vacuum cover with manual pulse-jet filter cleaning and nonstick filtration that captures 99.9% of particles as small as 0.5 μm. **VAC-U-MAX,** *Belleville, NJ • www.vac-u-max.com • tel. 973.759.4600*

OUTSOURCING & CONSULTING SERVICES

API manufacturing services

Lonza offers fully integrated end-to-end development and manufacturing for a wide range of technologies with Swiss quality performance and safety standards, strict containment and product segregation, and a focus on safe handling of compounds with low occupational exposure limits. **Lonza,** *Basel, Switzerland • www.lonza.com • tel. +41 61 316 81 11*

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Lyophilization

DSM offers a lyophilization system with the precision to serve demanding cycles. DSM's lyophilizers are equipped with LyoAdvantage software for cycle control, which provides the accuracy necessary for high-value products. The system enables scale-up from an 8-ft^2 unit that does not comply with good manufacturing practice to any commercial unit. **DSM Pharmaceuticals,** *Greenville, NC • www.dsmpharmaceuticals.com • tel. 252.707.4376*

OUTSOURCING & CONSULTING SERVICES

Contract services

Mikart has provided contract development, manufacturing, and packaging services to the pharmaceutical industry since 1975. The company's capabilities include formulation development; analytical services; solid- and liquid-dose manufacturing; packaging in bottles, blisters, and multilaminate pouches; project management; and regulatory services. **Mikart,** *Atlanta, GA • www.mikart.com • tel. 888.4 MIKART*

CAPSUGEL®

Dosage-form services

Capsugel specializes in dosage forms and solutions for the healthcare industry. Its portfolio of products and services include: two-piece hard gelatin, liquid-filled, and vegetarian capsules, R&D equipment, and liquid formulations as part of its Licaps drug-delivery system. Capsugel also provides support to customers from formulation to final production. **Capsugel,** *Greenwood, SC • www.capsugel.com • tel. 888.783.6361*

Bilcare Research

Packaging services

Bilcare Research is a packaging solutions provider that serves the global pharmaceutical and healthcare industries. The company manufactures pharmaceutical and medical blister films and foils, and supplies a range of thermoforming films, Alu-lid foils, and cold-form foils. **Bilcare Research,** *Delaware City, DE • www.bilcaresolutions.com • tel. 302.838.4000*

OUTSOURCING & CONSULTING SERVICES

Fill–finish services

CANGENE bioPharma is a leading provider of high quality fill–finish services in sterile liquids (e.g., vials and syringes) and lyophilized products. CANGENE bioPharma has an outstanding regulatory profile, including excellent regulatory compliance with US, EU, and Japanese regulations. The company has helped produce more than 20 commercial and 185 clinical products for customers. **CANGENE bioPharma,** *Baltimore, MD • www.cangenebiopharma.com • tel. 800.441.4225*

Contract analytical services

Chemic Laboratories is a full service cGMP/GLP contract analytical-chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: extractables and leachables analysis, method development and validation, quality control analysis, release testing, raw-materials analysis, compendial testing, bioanalysis, organic synthesis and formulation development, and ICH stability testing. **Chemic Laboratories,** *Canton, MA • www.chemiclabs.com • tel. 781.821.5600*

Contract manufacturing services

CMIC is a contract manufacturing organization partner for pharmaceutical development, analytical services, and commercial manufacturing of oral solid-dosage drugs. The company specializes in multiparticulate and modified release technologies. CMIC's FDA-registered site includes six suites for development or GMP clinical-trial manufacturing, and six suites for scale-up and GMP commercial manufacturing. **CMIC CMO USA,** *Cranbury, NJ • www.cmiccmousa.com • tel. 609.395.9700*

OUTSOURCING & CONSULTING SERVICES

Development and manufacturing services

UPM Pharmaceuticals provides contract drug development, cGMP manufacturing, and analytical testing services. The company specializes in the administration of solid oral-dosage forms. UPM's scientists have experience with product development challenges such as low-dose content uniformity, high-dose compressibility, and controlled drug-release rates. **UPM Pharmaceuticals,** *Baltimore, MD • www.upm-inc.com • tel. 410.843.3738*

Laboratory services

Eurofins Lancaster Laboratories works with clients in the bio/pharmaceutical industry to advance candidates from development through commercialization, ensuring regulatory compliance, cost effectiveness, and achievement of timelines. The company has facilities in Pennsylvania, Michigan, and Ireland, and offers five service models, including professional scientific staffing and full-time equivalent programs. **Eurofins Lancaster Laboratories,** *Lancaster, PA • www.lancasterlabspharm.com • tel. 717.656.2300*

Contract manufacturing services

Pharma Tech Industries (PTI) is a contract manufacturer and packager of powder products. The company's services include product development, manufacturing, molding, and packaging. PTI has two facilities—in Georgia and Missouri—with a combined area of 360,000 ft^2 that include nine International Organization for Standardization 8-clean-room design for prescription and new drug application products. **Pharma Tech Industries,** *Royston, GA • www.pharma-tech.com • tel. 706.246.3555*

OUTSOURCING & CONSULTING SERVICES

Biomanufacturing platform

FlexFactory is a fully modularized and integrated biomanufacturing platform. It enables the deployment of new production facilities for vaccines, biotherapeutics, monoclonals, and biosimilars in as little as 9 months. The suite is designed to enhance the efficiency of start-up and expansion costs and advance new drugs from R&D to commercial manufacturing. **Xcellerex,** *Marlborough, MA • www.gelifesciences/xcellerex • tel. 508.480.9235*

Development and manufacturing services

Cook Pharmica is an integrated contract development and manufacturing organization that provides the pharmaceutical and biopharmaceutical industry with drug-substance manufacturing from mammalian cell culture. The company's portfolio of services includes: analytical and formulation development, aseptic filling in vials and syringes, lyophilization, and secondary packaging. **Cook Pharmica,** *Bloomington, IN • www.cookpharmica.com • tel. 877.312.2665*

Outsourced services

Coating Place is a leader in services from Wurster fluid-bed formulation development to commercial manufacturing. The company performs bead layering, extrusion–spheronization, roller compaction, and capsule filling and tableting. Coating Place processes both solvent and aqueous formulations. Its facilities are registered with the US Food and Drug Administration. **Coating Place,** *Verona, WI • www.encap.com • tel. 608.845.9521*

OUTSOURCING & CONSULTING SERVICES

Size reduction

Micron Technologies provides contract particle-size reduction and analytical services for the pharmaceutical industry. The company offers micronization and mechanical milling in isolated processing suites. Its analytical laboratory provides material-characterization testing, including particle size and Karl Fischer moisture analysis. Additional services include method development and validation and release and stability testing. **Micron Technologies,** *Malvern, PA • www.microntech.com • tel. 610.251.7440*

Contract services

Patheon is a leading provider of contract development and manufacturing services to the global pharmaceutical industry. The company supplies products and services to approximately 300 of the world's leading pharmaceutical and biotechnical companies. Patheon's fully integrated worldwide network helps ensure that customer products can be launched anywhere in the world. **Patheon,** *Research Triangle Park, NC • www.patheon.com • tel. 905.821.4001*

Job-focused training

PDA's Training and Research Institute provides intensive, job-focused training that clients can apply immediately. The curriculum is designed to foster professional development in areas such as aseptic processing, biotechnology, environmental monitoring, filtration, microbiology, quality, regulatory affairs, training, and validation. Courses can be customized and provided at the client's location. **Parenteral Drug Association,** *Bethesda, MD • www.pda.org • tel. 301.656.5900*

OUTSOURCING & CONSULTING SERVICES

Parenteral Contract Manufacturing Service of Hospira

Contract-manufacturing services

Hospira's One 2 One business specializes in contract manufacturing of injectable products packaged in vials, prefilled syringes, cartridges, flexible containers, and ampoules. Additional offerings include product development and fill–finish of clinical trial materials, registration, and commercial batches. The company's range of capabilities spans biologics, potent drugs, vaccines, cytotoxics, controlled substances, and lyophilization. **Hospira One 2 One,** *Lake Forest, IL • www.one2onecmo.com • tel. 224.212.2267*

Contract services

Metrics is a respected contract pharmaceutical research, formulation, development, and manufacturing company. Offering first-in-man (FTIM) development and Phase I–III clinical-trial materials (CTM), Metrics has conducted more than 120 FTIM studies for various chemical entities in the past five years while producing more than 700 batches of CTM. **Metrics,** *Greenville, NC • www.metricsinc.com • tel. 252.752.3800*

Outsourced services

Pfizer CentreSource provides solutions for sterile manufacturing, high-containment manufacturing, and oral and solid dosage forms. Its capabilities draw upon Pfizer's global network of facilities, technologies, and expertise to fulfill a broad range of sourcing and outsourcing requirements, regardless of dosage form, batch size, or the complexity of the process. **Pfizer CentreSource (PCS),** *Kalamazoo, MI • www.pfizercentresource.com • tel. 269.833.5844*

OUTSOURCING & CONSULTING SERVICES

High-potency micronization

Powdersize has added the capability to micronize high-potency active pharmaceutical ingredients to containment levels of 10 ng/m³. The company's 2- and 4-in. jet mills can scale to a 10-in. jet mill. Gram and kilogram quantities as high as 100 kg thus can be micronized. **Powdersize,** *Quakertown, PA • www.powdersize.com • tel. 215.536.5605*

Development services

AAIPharma is a provider of services that encompass the entire pharmaceutical drug-development process from early development through commercialization. The company has more than 30 years of experience and specializes in analytical chemistry, formulation development, clinical packaging, oral drug delivery, and contract manufacturing. **AAIPharma,** *Wilmington, NC • www.aaipharma.com • tel. 800.575.4224*

CLEANROOM EQUIPMENT & SUPPLIES

Sterile wipes

Veltek offers sodium-hypochlorite and hydrogen-peroxide wipes that are Class 10 laundered, filtered at 0.2 µm, and formulated with *US Pharmacopeia* water-for-injection. The products have laser-cut edges and are guaranteed sterile with lot-specific documentation. **Veltek,** *Malvern, PA • www.sterile.com • tel. 610.644.8335*

PACKAGING EQUIPMENT & SUPPLIES

Transfer packaging for prefillable syringes

BD TSCF packaging ensures the secure transfer of sterile prefillable syringe components into the pharmaceutical filling environment. The packaging is compatible with IDC Biosafe doors for aseptic filling machines within isolator or barrier systems. This packaging is part of the BD SCF global offer, which features expertise in sterile processing of preservative-free drugs; secure, reliable, easy-to-use systems; and drug master files and technical dossiers. **BD Medical–Pharmaceutical Systems,** *Franklin Lakes, NJ • www.bdpharma.com • tel. 800.225.3310*

Packaging solution

The NextBottle package from Catalent and One World Design and Manufacturing Group is designed to improve patient compliance. The product's dial mechanism dispenses one pill at a time and automatically reminds patients of the last day that a pill was taken. **Catalent Pharma Solutions,** *Somerset, NJ • www.catalent.com • tel. 866.720.3148*

LABORATORY EQUIPMENT & SUPPLIES

Autosampler

Shimadzu's Nexera MP UHPLC features high-speed, low-carryover, enhanced precision, and high throughput capabilities. The SIL-30ACMP autosampler also contains a high-speed injection (7 seconds) and a near-zero carryover. In addition, a maximum of 2304 samples can be analyzed continuously, making it suited as a front end for all LCMS platforms. **Shimadzu Scientific Instruments,** *Columbia, MD • www.ssi.shimadzu.com • tel. 800.477.1227*

LABORATORY EQUIPMENT & SUPPLIES

Laboratory blenders

MaxiBlend and MiniBlend laboratory blenders are available in sizes from 0.5 to 16 qt. The units are made of 316-L stainless steel and supplied with V-shells, bins, or double cones. The units feature a tabletop design and include programmable logic controls and safety-interlocked guards. **GlobePharma,** *New Brunswick, NJ • www.globepharma.com • tel. 732.819.0381*

Spectroscopy and imaging systems

Advantest offers bench top spectroscopy and imaging systems for the pharmaceutical R&D market. The configurable and compact TAS7500 THz systems use proprietary terahertz wave technology to acquire characteristic spectra based on crystalline structure and 3-D images yielding tablet coating thickness and uniformity, and the nondestructive detection of cracks and voids in the tablet core. **Advantest,** *Princeton, NJ • www.advantest.com • tel. 609.799.0797*

Production-control analyzer

The FOSS NIRS DS2500 analyzer is designed for routine control of intake for optimal use of raw materials, production control for improved efficiency and economy, and final product monitoring on diverse control parameters. The analyzer features an optical performance across a wavelength of 400–2500 nm, and is suitable for networking using LAN (local) or WAN (internet). **FOSS NIRSystems,** *Laurel, MD • www.foss-nirsystems.com • tel. 301.680.9600*

LABORATORY EQUIPMENT & SUPPLIES

On-line TOC analysis

To help pharmaceutical companies improve quality and reduce costs, GE Analytical Instruments offers a science- and risk-based program for achieving real-time release of pharmaceutical water. The program streamlines a complex process and helps companies move total organic carbon testing from the laboratory to the production floor in approximately six months. **GE Analytical Instruments,** *Boulder, CO • www.geinstruments.com • tel. 800.255.6964*

Pharmaceutical processing sensor

Hamilton's Oxyferm FDA ARC sensor provides accurate electrochemical oxygen measurements in biotechnology and pharmaceutical fermentation processes. In addition, the company's Conducell PWSE ARC provides low conductivity measurements in pure and ultrapure water for injection and clean-in-place validation. The measurement range of the Conducell PWSE is 0.01 to 2000 µS/cm. **Hamilton Company,** *Reno, NV • www.hamiltoncompany.com • tel. 800.648.5950*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Inorganic salts

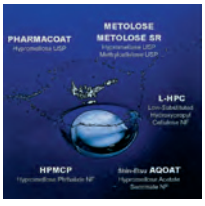
Jost Chemical manufactures over 350 high-purity inorganic salts. The company's FDA-registered site in St. Louis, Missouri, totals 190,000 ft^2 and operates under bulk pharmaceutical cGMPs. Jost is a global supplier of chemical salts that meet USP/EP/BP/JP/ACS and multicompendia requirements. Jost's products are BSE/TSE free and allergen free, and its selection of products includes carbonates, nitrates, phosphates, and sulfates. **Jost Chemical,** *St. Louis, MO • www.jostchemical.com • tel. 314.428.4300*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

ROQUETTE America, Inc.

API and excipients manufacturing

Roquette is a global manufacturer of pharmaceutical excipients and actives. The company offers a range of polyol excipients that is intended to combine chemical stability with good taste, sugar-free sweetness, and oral health benefits for a variety of pharmaceutical applications. Roquette's portfolio includes: Pearlitol (crystalline/granulated mannitol), Neosorb (sorbitol), SweetPearl (maltitol), Xylisorb (xylitol), and Lycasin (maltitol syrups). **Roquette America,** *Geneva, IL • www.roquette.com • tel. 630.463.9430*



Excipients

Biddle Sawyer's low-viscosity Pharmacoat grades are film formers and granulation binding aids. The company's Metolose and Metolose SR excipients are designed for thickening liquids and formulating sustained-release matrices. Biddle Sawyer also offers hydroxy propyl methyl cellulose phthalate and its Aqoat product for enteric coatings. **Biddle Sawyer,** *New York, NY • www.biddlesawyer.com • tel. 212.736.1580*

SENSIENT®

Pharmaceutical coating systems

Sensient Pharmaceutical Coating Systems specializes in high-quality coating systems, brand-defining color solutions, and enhanced product performance for the pharmaceutical and nutraceutical markets. The company provides complete coating and visual-enhancement solutions in addition to its personalized service.
Sensient Pharmaceutical Coating Systems, *St. Louis, MO • www.sensientpharma.com • tel. 800.325.8110*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

FERRO Pfanstiehl

Sugars

Ferro Pfanstiehl manufactures sucrose, trehalose, galactose, and maltose according to the standards of the International Conference on Harmonization to help ensure compliance to active-ingredient standards for injectable products. The company uses validated endotoxin-removal processes and conducts final-product testing to ensure high purity through very low endotoxin levels. **Ferro Pfanstiehl Laboratories,** *Waukegan, IL • www.pfanstiehl.com • tel. 800.383.0126*

Sheffield BIO•SCIENCE

Lactose

LubriTose is a self-lubricating lactose that offers excellent excipient performance without the need for magnesium stearate, thus eliminating overblending and production slowdowns. The product is intended to allow tablet manufacturers to run large batch sizes at high speeds for long periods of time and achieve reliable results. **Sheffield Bio-Science,** *Norwich, NY • www.SheffieldBioScience.com • tel. 800.833.8308*

Polyethylene glycol

Carbowax Sentry low-aldehyde polyethylene glycol (PEG) excipient grades 300, 400, and 600 are suited for gelatin capsules or liquid formulations in which aldehyde impurities decrease stability. Clear, viscous grades resist rancidity and microbial growth and carry a low specification limit for ethylene glycol, which helps high-dose products comply with *US Pharmacopeia* <467> standards. Dow also offers Carbowax Sentry PEG excipient grades 3350, 4000, and 8000 in hard, waxy form. **The Dow Chemical Company,** *Midland, MI • www.dow.com • tel. 800.447.4369*

CHEMICALS, RAW MATERIALS, INTERMEDIATES, & EXCIPIENTS

Microcrystalline cellulose

The Ceolus KG-1000 product is Asahi Kasei's most highly compactible microcrystalline cellulose (MCC). Only a small amount (as little as 5–10% in some cases) in a formula will provide the desired tablet hardness. The company also offers the Ceolus KG-802 and UF-711 ingredients, and additional highly compactible MCC grades with different properties to solve various tablet-hardness problems. **AsahiKASEI America,** *New York, NY • www.ceolus.com • tel. 212.371.9900*

INFORMATION TECHNOLOGY

Materials-identification database

ICDD's PDF-4/Organics 2012 database features 470,181 entries, and is designed for rapid materials identification. Its design allows for easy interface with diffractometers and data analysis systems of leading software developers and manufacturers of X-ray equipment. The database is useful for scientists working in consumer products, catalysis, forensic science, analytical labs, drug discovery, and production. **International Centre for Diffraction Data,** *Newtown Square, PA • www.icdd.com • tel. 610.325.9814*

Compliance software

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I certify that the statements made by me above are correct and complete.

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from FDA reviewers (1, 2). It is disturbing that an FDA contractor also apparently inadvertently made accessible over its website a significant amount of sensitive FDA documents (1, 2).

Companies spend huge amounts of money generating data to support the approval of pharmaceuticals, biologics, and medical devices. Companies expect that FDA will keep this information confidential and will not disclose it to competitors or to the public while the review process is ongoing. Disclosure of confidential information prior to a company receiving marketing approval or clearance can cause significant economic harm. Competitors can get advance notice of the products under review and adjust their marketing plans for competing products. Competitors may also use this information to further develop their own products.

FDA staff, outside contractors, special government employees, advisory committee members, and others who have access to company confidential, commercial, and trade-secret information must take their obligation to keep such information confidential seriously. FDA staff and others should not make the decision to disclose confidential information to the media just because they may disagree with or are challenging the scientific judgment of their superiors. FDA staff must follow the procedures established to present differing views of scientific data and the conclusions drawn with respect to safety and efficacy. If certain members of the FDA review staff disagree with the decision to approve or clear a product, they can document such objections in writing. If the review staff question the approval decision because they believe it was not supported by the clinical data, the public safety is at risk, the review process was compromised, or that there was corruption or incompetence uncovered during the review process, there are procedures that can be utilized to report such allegations. Staff can always raise concerns with internal management structure at FDA, Health and Human Services, the Office of Special Counsel, the President's staff, or through Congress. When raising the concerns up the chain of command, staff are well advised to present their allegations and documentation to support their assertions in an organized, responsible manner.

Maintaining confidentiality

As part of routine procedure, companies identify the parts of their submission (e.g., 510(k), PMA, NDA, and ANDA) that are considered confidential, commercial, trade secret information. Prior to approval or clearance, FDA is obligated to maintain that confidentiality. How should the agency ensure this confidentiality? It has been suggested by the attorney representing the whistle blowers that FDA have different computers and systems for maintaining confidential information that do not have, for example, Internet access. This is an expensive option; therefore, FDA staff should be trained and reminded on a periodic basis of their responsibility and obligation to maintain the confidentiality of submissions. If FDA staff members feel compelled to discuss concerns with the media, they can have these discussions without disclosing confidential information.

In closing, members of the FDA staff must understand and appreciate their obligation to maintain the confidentiality of submissions and not disclose confidential, commercial, trade secret information to the media. There must also be checks and balances on the review process. FDA staff should be aware of and follow procedures for raising scientific concerns that can impact the public health and safety. Ultimately, the public must continue to have confidence that FDA is making sound decisions on the approval and clearance of products.

References

1. S. Usdin, *BioCentury,* **20** (30), July 23, 2012.
2. E. Lichtblau and S. Shane, *New York Times*, July 14, 2012. **PT**

Ad Index

VIEWPOINT

FDA and the Importance of Confidentiality

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PharmTech.com/view

David L. Rosen

Do you have to worry about FDA releasing confidential data? Apparently so.

Recent news stories have reported that FDA scientists have been suspected of leaking confidential, commercial, and trade secret information to the media (1, 2). These scientists claim that faulty review procedures led to the clearance of medical devices that exposed patients to dangerous levels of radiation (1, 2). The scientists raised questions regarding the judgment and integrity of senior management officials in the Center for Devices and Radiological Health (CDRH). In investigating the suspected leaks, FDA monitored the emails of these scientists through the use of sophisticated software that captured the keystrokes, keywords, and phrases of numerous individuals (1, 2). During the course of this monitoring, it appears that FDA may have gone beyond the scope of the initial suspected leak of confidential information by looking at protected information such as individuals' password-protected private emails, communications to Congressional staff and the US Office of Special Counsel, attorney and client communications, workplace grievances, and items protected by whistleblower statutes.

A need for checks and balances

The Office of Special Counsel has found that the scientists' claims regarding the medical device review process were sufficiently valid to warrant a further investigation (1, 2). In taking a step back from the news stories, it can be agreed upon by those involved in the FDA review and approval processes that it is sound scientific and public policy to have checks and balances on the FDA review and approval process. FDA has internal procedures that permit and encourage the presentation and discussion of the interpretation of scientific data. Expressing the differing views of the product review team leads to a thorough evaluation and discussion of the data and, ultimately, to better decision-making on the review and approval process for FDA-regulated products.

Various positions regarding the interpretation of the data are discussed in a forum at FDA where the exchange of differing views on safety and efficacy data are presented to an experienced team of senior FDA staff. There is an opportunity for all team members involved to present their analysis and views on the risks verses benefits of products. Invariably, disagreements as whether the benefit of the product is acceptable in light of the risks may occur. In the end, FDA must make a decision as to the acceptability of the data and whether the application can be cleared or approved for marketing.

Ultimately, FDA senior management must weigh the scientific evidence and exercise their judgment and experience in making decisions on whether the data support the clearance or approval application. The American public puts its faith in processes and relies on the belief that FDA scientists and senior management review products and make decisions on the acceptability of the data. In my 30-plus years of experience in dealing with FDA-regulated products (including more than 14 years at FDA), I can personally attest to the fact that FDA staff take their responsibility for the review and approval of products seriously and work diligently to make decisions that are in the best interest of public health and safety.

The importance of confidentiality

In the recent situation reported in the media, the scientists questioned the approval of a premarket approval application supplement and clearance of certain 510(k) applications (1, 2). The scientists claimed that FDA senior managers in CDRH and the FDA Commissioner were corrupt and incompetent (1, 2). The scientists reportedly publicly disclosed company confidential, commercial, trade secret information to the media in airing their concerns regarding the decisions made to approve or clear certain medical devices for marketing (1, 2). It is surprising and disturbing that the FDA scientific reviewers leaked confidential commercial information to the press. FDA regulations are clear: if the existence of a premarket submission has not been publicly disclosed and the submitter requests that the intent to market a device remain confidential, provides a certification to the Commissioner requesting confidentiality, and complies with various provisions regarding the maintenance of such confidentiality, then FDA will not disclose the existence of a premarket notification. This relates to existence and the intent to market a medical device, which is evident by the submission of a 510(k) application. There are similar confidentiality provisions relating to investigational products, full and abbreviated new drug applications, biologic license applications, and premarket approval applications. The news media has reported not only the existence of the companies intent to market certain medical devices but appears to have received internal agency files, documents, and confidential commercial information

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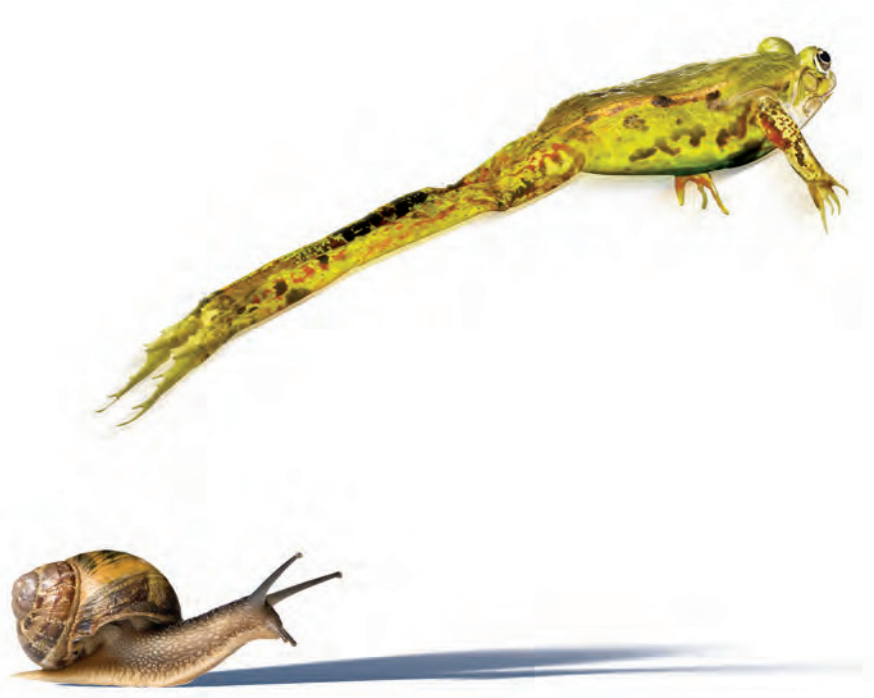

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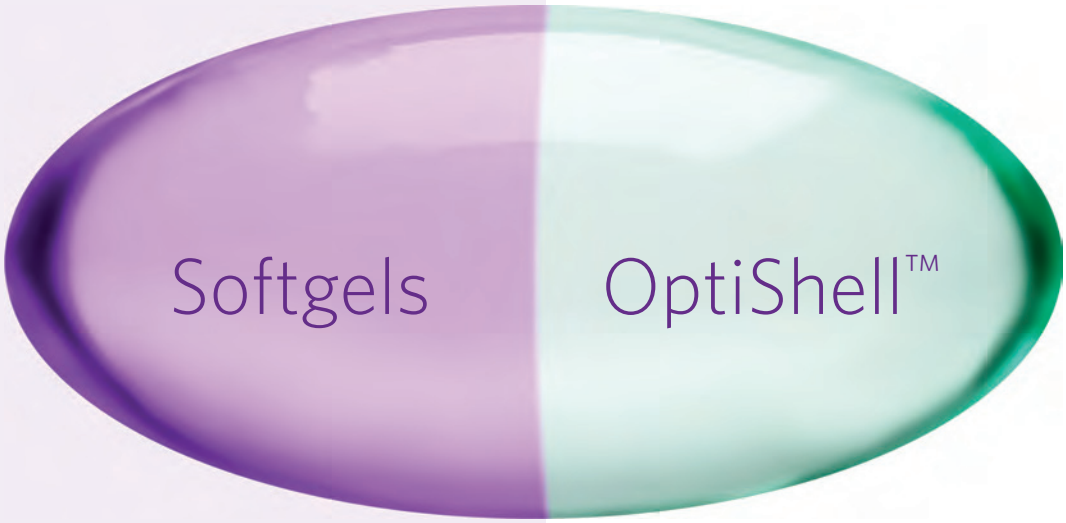

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