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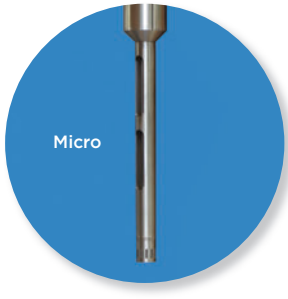

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Continued on page 8

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Continued from page 6

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Image Repair Must Get to the Root Cause

Rita Peters

Climbing out of a reputation hole starts with adopting a quality culture.

A recent Gallup poll concluded "Americans are more than twice as likely to rate the pharmaceutical industry negatively as positively."

In an August 2019 Gallup assessment of perceptions of US business industry sectors, 1525 adults ranked pharma last among 25 industries; 58% of the respondents gave a negative rating and only 27% gave pharma a positive rating. This grading—pharma's lowest net rating ever in nearly 20 years of the survey—ranks it behind often-criticized business segments such as airlines, banks, oil and gas, the legal field, healthcare, and advertising and public relations. Even the federal government was viewed more positively than drug manufacturers (1).

Other studies ranked pharma in a similarly negative light. In a 2018–2019 global study conducted by PatientView, only 41% of patients rated the pharma industry's corporate reputation as "excellent" or "good," down slightly from the previous study. Pricing appears to be a major factor in the perceptions that patients form about drug companies. Only 9% of the respondents rated pharma's fair pricing policies as excellent or good (2).

When looking at individual companies, reputation does not fare much better. Only four pharma companies are listed in the top 100 of the Reputation Institute's Global RepTrak 100, which was compiled from a survey of more than 165,000 individuals. Johnson & Johnson was the highest ranked pharma company, placing at number 82 (3).

While some executives may take the path of satisfying shareholders over patients, positive reputations can be crucial for securing investments and partnerships and sustaining innovation. Press releases, lobbying, or social responsibility mission statements can whitewash over some public perception problems. Resolving core issues—such as quality problems and drug shortages—requires investigations of the root cause of the problem and permanent fixes.

As confidence in drug companies falters, the industry also becomes less attractive to skilled researchers, who may turn to more respected fields of science and innovation. Patients who lose faith in pharma's ability to provide quality medicines at affordable prices may look elsewhere, turning to online or overseas pharmacies that sell products of questionable quality.

Problems with mainstream, regulated drugs can also undermine patient trust in the pharma industry. Consider the recent discovery of nitrosamines in a third classification of drugs (4) and the suspected manipulation of product testing data used in the development of a gene therapy's manufacturing process (5).

Drug development and manufacturing professionals do not have the authority to influence drug pricing or other business decisions. They can, however, make a difference in the quality of drugs produced.

A quality culture should be adopted throughout an organization, said Patrizia Cavazzoni, deputy director of operations at FDA's Center for Drug Evaluation and Research, at the September 2019 PDA/FDA Joint Regulatory Conference. Executive management is ultimately responsible for assuring reliable manufacturing operations and high-quality standards, Cavazzoni said, noting that warning letters are directed to the top company executive to emphasis the importance of quality throughout the organization (6).

Organizations should design quality into all systems, invest in manufacturing technologies, guard against decay in operational effectiveness, and ensure suppliers are aligned with your quality practices, she recommended.

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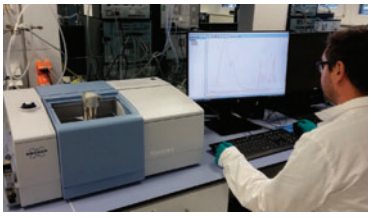

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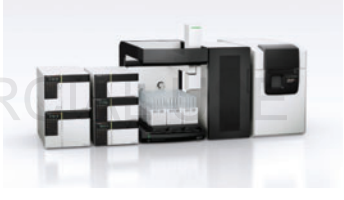

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Data Integrity Violations Draw Strong FDA Rebukes

Jill Wechsler

Falsified documents and manipulated test results prompt warnings and investigations.

Because federal investigators cannot inspect every drug test site or production facility, FDA relies on manufacturers to submit complete and accurate information in all submissions and market applications, especially for innovative cell and gene therapies. Evidence that Novartis submitted manipulated data from certain preclinical tests related to its production process for breakthrough therapy Zolgensma recently produced a strong, public warning from FDA, with implications that the agency may pursue civil or criminal charges. Congressional leaders also blasted Novartis and demanded a full accounting of its actions (1).

Another strongly worded warning letter from FDA to Chinese over-the-counter drug manufacturer, Ningbo Huize Commodity Co., similarly cited egregious data integrity lapses (2). In a statement issued on Aug. 20, 2019, FDA said it was banning the import of all the company's products following a plant inspection where local staffers provided FDA investigators with documents that were clearly falsified, including cleaning validation reports and batch production and control records for multiple drugs (3).

In highlighting this enforcement action, FDA Acting Commissioner Ned Sharpless stated that efforts to "prevent, uncover, and combat data integrity lapses" is a continuing commitment of the agency and involves increased global inspections, updated guidance, and additional staff training. FDA published final guidance in December 2018 for ensuring data integrity in compliance with current good manufacturing practices (CGMPs) (4), which emphasizes the importance of company top management establishing a "quality culture" that acknowledges the importance and value of data integrity in all aspects of drug development and production.

FDA aims to provide clear warnings to manufacturers that data manipulation is a serious offense.

Data integrity issues involving manufacturing activities are cited regularly in warning letters related to manufacturing facility inspections at home and abroad. A letter dated July 9, 2019 warned Indoco Remedies Ltd. of Mumbai, India of GMP and data integrity violations at a facility in Goa (5). It cited problems with batch production and control records for products intended for the US market. And a June 13, 2019 warning letter to Akorn Inc. raised concerns about the firm's failure to ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of its products (6). FDA cites a previous warning letter regarding inadequate quality controls at another Akorn production site and demands prompt correction of all cited violations or risk legal action and delays in product approvals.

Accurate data critical

In the Novartis case, Peter Marks, director of the Center for Biologics Evaluation and Research (CBER), sharply rebuked the company, emphasizing the importance of FDA having confidence in all tests and data provided by sponsors, particularly to support the rapid development and accelerated approval of innovative therapies. The submission of "truthful, complete, and accurate data" is critical for FDA to be able to protect the public health, and the law requires it, Marks asserted in a statement on Aug. 6, 2019 (7).

FDA's pronouncements aim to provide clear warnings to manufacturers that data manipulation is a serious offense, and that data quality is critical for product approval and continued marketing. Marks said that Zolgensma would remain on the market, as the faulty information involved early animal studies related to developing the production process for Zolgensma and did not compromise product safety. But he acknowledged that if the agency had been aware of the data manipulation by Novartis' AveXis unit, it probably would have delayed approval of the lifesaving $2-million drug.

Although Novartis claimed that it quickly investigated allegations of data

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manipulation when the issues first surfaced internally, the timing and disclosure of these problems raise questions. The company evidently knew of the data errors as early as March 2019 but did not launch a formal investigation until May and did not reveal its concerns until June. And that was after the May 24, 2019 approval of Zolgensma, based on limited, but convincing evidence that it dramatically improved the health of infants suffering from the most severe form of the neurodegenerative disease spinal muscular atrophy.

FDA compliance officers continue to investigate whether Novartis and AveXis staffers intentionally hid evidence of data manipulation until after approval. According to press reports, FDA inspectors raised questions about a mouse essay at an inspection of a Novartis manufacturing facility in Illinois earlier this year, but company staff said they had been corrected. However, FDA's follow-up inspection in July 2019 of AveXis' San Diego control test lab found evidence that management failed to thoroughly review unexplained discrepancies in potency assays, had incomplete records, and failed to follow quality control and test procedures (8).

Novartis dismissed the AveXis scientists linked to the data manipulation, but FDA holds corporate management responsible for ensuring adherence to rules at all levels. Although only a small portion of product test data in the market application appears to be manipulated, FDA says that a thorough assessment of all information will determine if further warnings or limits are warranted for this new therapy that has limited patient experience.

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The Demands of the Perfect Dose

Felicity Thomas

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As the development pipeline becomes more saturated with complex molecules and patient experience becomes more important, developers are looking to outsourcing partners to provide more specialized expertise and solutions.

Oral-solid dosage forms remain the most common drug formulation used within the pharmaceutical industry and, according to market research (1), should continue to experience market growth in the near future. However, a range of factors, such as an amassing focus on biologics, higher proportion of poorly soluble molecules in the development pipeline, and regulatory development pathways, are potentially set to shift the balance and raise the profile of newer, innovative dosage forms, increasing the requirement for expert skills.

"Pharma's development pipeline is being filled with more sophisticated, harder to make compounds that require complex delivery strategies to administer doses correctly," notes Louis Weber, managing director, Bora Pharmaceuticals. "Demand for specialist expertise has soared, and drug developers are increasingly seeking outsourced solutions to commercialize products."

Overcoming bioavailability issues

A major challenge currently impacting drug development is overcoming bioavailability issues, which is becoming more difficult as a result of the increasing number of complex and poorly soluble molecules entering the development pipeline. "Around 40% of all new chemical entities (NCEs) have low water solubility, meaning a strategy for improving poor bioavailability becomes mandatory," emphasizes Manuel Leal, business development director, Idifarma.

"The 'put it in a tablet' dosage form approach that may have worked in the past is no longer effective as molecules require more complex and advanced drug delivery technologies that address insoluble compounds," explains Robert Lee, president, Particle Sciences. "There are a range of technologies to increase bioavailability but for them to be viable, expertise and experience on how to apply them is required so formulations stand a better chance of being effective."

Using solvents, such as isopropyl alcohol, ethanol, and acetone, is a practical way in which developers can improve solubility of most drug substances, notes Weber. "In addition, solvent methods for dispersing drug substances can also be useful to

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deal with poorly soluble compounds prevalent in today's therapeutic compounds," he says.

For Leal, there is a need for innovative processes to advance the galenic formulation of finished products as the discovery of new drugs that improve existing therapies has slowed. "Using innovative technologies helps improve the therapeutic arsenal and reduces the reliance on finding new active molecules for the industry," he says. Constant adoption of a variety of strategies that enable enhancement of a drug's absorption is vital for formulation scientists, in Leal's opinion.

Adoption of an orthogonal approach and being open to a variety of methods, particularly during early development was also advised by Lee. "Good development practice starts with the client providing a clear target product profile (TPP), which describes an idealized drug product image, including route of administration, dose, form factor, pH, particle size distribution, and so on," he continues. "Once there is an understanding of the TPP and the physicochemical characteristics of the active, it is possible to assemble potential drug delivery technologies that may achieve the TPP."

"The key to success," stresses Jeremy Drummond, senior vice-president business development, MedPharm, "is to use a holistic approach considering the overall requirements of any formulation; from the properties of the API (the only ingredient that cannot theoretically be left out) to the end-use market, patient requirement, and target indication."

Advantages of the accelerated pathway

Speeding up the development pathway has obvious benefits for drug developers. Not only can these accelerated routes help shorten the development timeline but can also offer significant cost reductions.

Using the US FDA's 505(b)(2) pathway as an example, Lee highlights that innovative drug dosage forms are being realized thanks to the opportunities afforded by the accelerated development route. "A key advantage of the pathway is the 505(b)(2) sponsor can use clinical data produced by other companies to seek FDA approval without performing all the work required with a traditional new drug application," he says. "This pathway is being used to improve existing drug products with new dosage forms, indications, dosing regimens, and new routes of administration."

In agreement, Weber adds that through accelerated pathways, such as 505(b)(2), developers are managing to breathe new life into existing products in an economical way. "According to FDA, the pathway allows drug developers a faster route to improve existing drugs, including new dosage forms that are faster acting or that combine two active ingredients in a new way," he comments. "This includes creating new administration routes that enhance therapeutic performance or dose adherence."

On a global scale, other regulatory bodies also offer accelerated route options, for example in Europe the European Medicines Agency (EMA) allows developers to submit applications via the hybrid procedure, which is considered to be roughly equivalent to 505(b)(2). "The appeal of accelerated pathways is leading drug innovators to rethink existing market medicines and reformulate them in ways that place a greater emphasis on patient centricity," confirms Lee. "This is leading to innovations such as long-acting injectables that require a lower dosing regimen than before or improving the bioavailability of a drug so that it can be delivered via an alternative, more convenient route of administration."

Focusing on the patient

"The patient or consumer must always be at the forefront of any development strategy," stresses Drummond. "It should always be remembered that it is not a drug (i.e., an API) that you give to a patient, but a drug product. For a formulation to achieve a positive clinical outcome and be a commercial success for the developer, the patient must be happy to use it."

In fact, a patient-centric approach to dosage form can be particularly vital when considering specific patient populations. "Traditional dosage forms, particularly tablets, may not always be taken by a patient as prescribed, which can lead to a negative therapeutic outcome and render a course of treatment much less effective," says Lee. "Pediatric and geriatric patient populations are particularly averse to swallowing large tablets and in these cases powders or liquids formation can provide a much more convenient method of administering a therapeutic."

Another way of improving the patient experience and ultimately medication adherence in pediatric patients is through the use of modified-release formulations as they have a narrow therapeutic index and can support dose compliance strategies, confirms Weber. "Most patient groups respond well to taking medications that require fewer doses to be effective (and for longer periods) and reduced side effects from dose fluctuation for example," he notes. "In addition, fixed-dose combination products with multiple APIs and different modified-release profiles can deliver more therapeutic value and better outcomes for both pediatric and geriatric patients."

Adherence issues are also found within patient groups suffering from chronic conditions, specifies Leal. "One answer for chronic disease therapies is to improve the solubility and bioavailability to allow for oral administration, which can improve comfort for the patients and allow them to take the drugs at home," he adds. "A further way of supporting patient-centric approaches to drug dosage forms is through taste masking. Overcoming this issue can also directly impact the comfort of the patient taking the product and improve therapeutic compliance."

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According to Weber, patient-centric principles are being applied in a variety of ways in pharmaceutical development. "Genetic profiling and advanced analytical techniques for example are assisting the personalized/precision medicine approach by providing deep insight into different patient populations and the pharmacokinetic and pharmacodynamic effects of drugs," he says. "Therefore, patients can be more selective in their choice of pharmaceutical products, taking into consideration their efficacy in certain subsets of the populations."

Gaining unique access through outsourcing

As a result of cost-efficiency and patient compliance being major considerations for primary healthcare providers and payors, solid-dosage forms are still a preferred option for many pharmaceutical products, Leal specifies. "Demand for contract manufacturing of solid forms is, therefore, still strong," he says. "However, there have been vast therapeutic improvements witnessed in smaller patient populations with unmet medical needs, such as in the field of oncology."

Oncology treatments tend to require smaller manufacturing volumes and require a higher degree of expertise, such as containment capabilities and agile manufacturing methods, Leal continues. "For traditional contract development and manufacturing organizations (CDMOs), who manage large volumes, these specialist products are very complicated to handle," he emphasizes. "Hence, made-to-measure services can be better provided by smaller independent CDMOs."

In agreement, Lee adds that working with an outsourcing partner for formulation and development can be particularly relevant for non-conventional dose forms. "Dosage forms, such as nasal and ophthalmic, as well as implantable devices and depots, can have additional complexity and regulatory issues for developers to consider," he notes. "Through an outsourcing partner, developers can access expertise and technologies that they do not possess in-house."

A further benefit for Lee is that an outsourcing partner can also provide an extension to a developer's available resources. "If there is a backlog or lack of available resources with the client, they can use an outsourcing partner as an extension of their internal development teams," he says.

Flexibility and being able to adapt to any changes that may occur during formulation development is critical to drug development success, stresses Weber. "By partnering with organizations that have experience in commercialization and technical expertise in complex dosage forms such as modified release or fixed-dose combinations, companies will be able to overcome project challenges in an agile and efficient way," he confirms.

"Specialism is key in the pharma industry. If our clients were to make the investment into their own manufacturing facilities, they would have to dedicate huge amounts of resource and capital," states Leal. "Outsourcing gives a drug developer access to unique skills and support within the supply chain, which means other benefits such an increased speed to market and reduced cost in the long run can be achieved."

Areas of growth

In Lee's opinion, routes of drug administration that have been previously overlooked, such as nasal dosage forms, will experience growth in the near future. "Nasal delivery can offer an ideal route and increased bioavailability for several drug types, particularly those indicated to treat the central nervous system," he explains. "This route of administration may also be suitable for non-conventional APIs, such as biologics."

For Leal, the increasing prevalence of high-potency ingredients being developed is leading to more growth in demand for outsourcing partners that can effectively manage the associated containment issues. "High potency facilities are capital intensive and containment requirements are stringent," he says. "Therefore, it will be more economical and practical for pharmaceutical companies to work alongside outsourcing partners to develop and manufacture their products in a more efficient manner."

A further trend that Leal believes will be important in the near future is that of value-added medicines that are based on well-known molecules with new applications, indications, finished-dosage forms, or strengths. "These drugs are an improvement on the traditional generics, which means more cost, but they remain more economical to develop than medicines based on new chemical entities," he adds.

Currently, there is a trend happening in the industry to use artificial intelligence to mine for APIs to hit relevant newly discovered biochemical pathways, according to Drummond. "A major trend going forward will be the alignment of formulation with information technology and any relevant devices with a focus on making it simple and easy, and even attractive, for the patient to be compliant," he comments.

Ultimately, however, keeping the patient in mind when looking at drug development is and will remain to be of critical importance, emphasizes Lee. "If a patient does not like the dosage form then they are unlikely to take the drug, leading to negative therapeutic outcomes," he concludes. "Dosage forms should appeal, not repel, the target audience."

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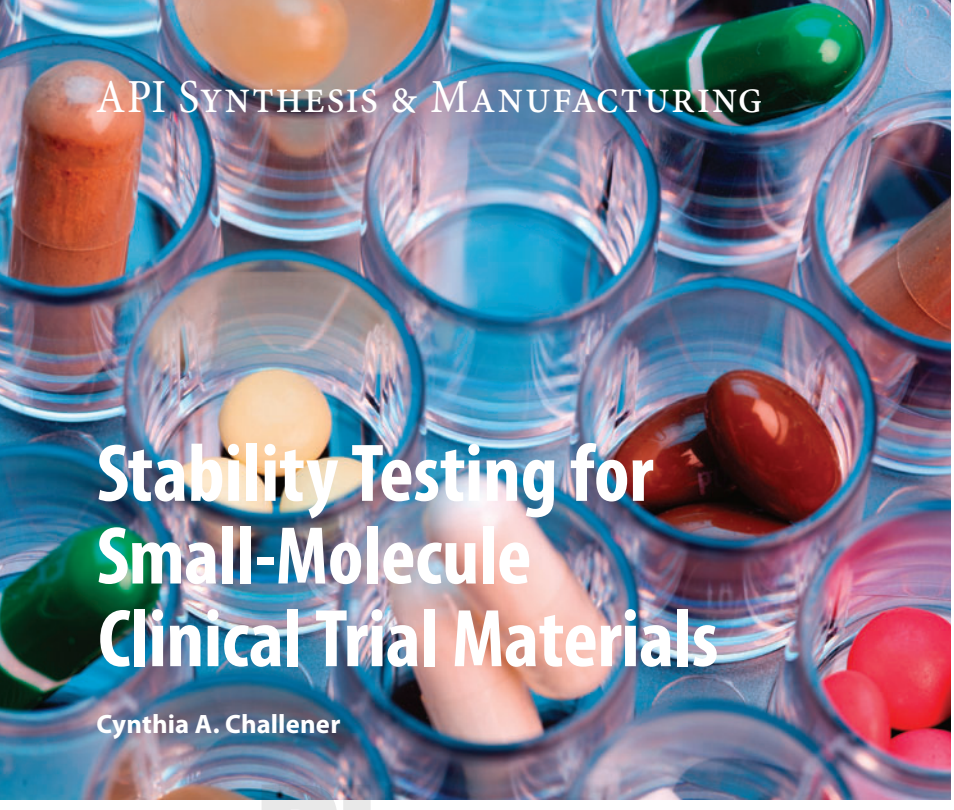

Stability Testing for Small-Molecule Clinical Trial Materials

Cynthia A. Challener

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Limited guidance and numerous challenges create confusion about the scope and timing of stability testing for drugs in development.

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The stability of clinical trial materials, regardless of the trial phase, must be understood to ensure patient safety. Stability can be affected by the nature of the API, the production process, the choice of excipients, the container and container closure system, and other factors. Stability testing is therefore essential for demonstrating that the formulations administered to patients in any clinical trial will remain unchanged throughout the duration of the trial. The type and length of stability tests typically depend on the phase of development and the nature of the clinical trial (e.g., use of placebo or comparator drug).

Fragmented regulatory guidance

Various guidance documents from FDA and the European Medicines Agency (EMA) have been published regarding stability testing of clinical trials materials (CTMs). The language regarding duration of testing in these documents tends to be vague, however. For Phase I trials, FDA recommends monitoring of the stability and quality of the drug during the clinical trial (1). Similarly, EMA recommends an ongoing stability program be performed with accelerated and long-term storage studies initiated prior to the study (2).

For Phase II and III trials, FDA expects submission of a description of the stability performance and also suggests the development of stability-indicating analytical procedures that will detect significant changes in the quality of the drug product (3). The agency also encourages the completion of stress studies at Phase II, while in Phase III studies these stability studies should be extended to provide marketing application stability data.

While the International Council for Harmonization (ICH) guidelines on stability testing (4) specifically indicate that formal stability protocols do not apply to CTMs and such protocols are not required for clinical stability studies or submission as part of clinical authorization applications, it is highly recommended that companies do conduct stability studies by means of established procedures.

Duration confusion

For CTMs, at a minimum, real-time data must be collected for a sufficient period to demonstrate shelf life for the product in use, as well as cover the duration for any intended clinical trial, according to Alyn McNaughton, technical director at Lonza Pharma & Biotech. The essential purpose of these stability studies, adds Geoff Carr, director of analytical development for Patheon Pharma Services by Thermo Fisher Scientific, is to ensure that CTMs will remain satisfactory over the period that they are intended to be administered to subjects enrolled in the clinical study, which is often dependent on the clinical trial phase.

The duration of a clinical phase will vary depending upon the number of subjects required to complete the study, the therapeutic indication and the data read out period, according to Teresa Iley, director of pharmaceutical development and manufacture for Intertek Pharmaceutical Services. It also tends to get longer as the project progresses, which impacts the required length of the stability study, adds McNaughton.

"As stability testing is commonly on the critical path for any product development, due to the need for real-time data, most stability studies are extended beyond the required time period to gain more knowledge about the product's robustness and potential maximum shelf life. This approach allows an understanding of product supply needs for future clinical evaluation; for example, if additional manufacturing may be required during a clinical study to supplement product supply for batches that will expire during the clinical study, or if the product's shelf life is not long enough for future trials or even for a viable commercial product," McNaughton says.

Iley also notes that shelf-life justification can be supplemented by data generated from technical batches manufactured in support of clinical trial applications, but it is typically recommended that the actual batches used to supply the trial are also assessed concurrently with the trial itself.

Initially a CTM is put on stability at both the long-term or storage temperature and under accelerated con-

Cynthia A. Challener is a contributing editor to *Pharmaceutical Technology*.

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ditions. If the material is stable under both, the shelf life can be extrapolated up to twice the period covered by the long-term data (5), according to Judy Carmody, founder and principal consultant of Carmody Quality Solutions. "For Phase I trials, for instance, there may be one pull point at three months, which would allow an extrapolated shelf life of six months," she explains.

CTMs for Phase II or III studies are likely to be much closer to the product intended for commercialization, adds Carr. "These trials are usually larger, longer duration, multicenter, and often in multiple countries, so longer-term stability studies (e.g., two years or more) are likely to be more appropriate," he says. In addition, Carr notes that because the formulations are likely to be closer to the intended commercial products, data from these studies may be used as supportive in new drug applications.

The use of accelerated data to justify shelf life longer than real-time data can be a source of confusion, according to McNaughton. "Accelerated data collection provides a means of predicting the shelf life beyond the actual age of the product. However, interpreting any changes in the product impurity profile, relative to the toxicology-based safety information, can prove challenging in situations where the product does demonstrate some instability. It is also critical to ensure that real-time data, when it does catch up to the age of the product at the end of the study, remain in specification," he explains.

Impacts on trial design

The vague guidance regarding stability testing for CTMs can have a number of impacts, including on study designs. For instance, because many companies base their studies on ICH guidelines, especially Q1A(R2) (6), and then make modifications to make protocols more suitable for CTMs, there is often considerable variation in how different companies conduct their studies, according to Carr.

In addition, because it is important to ensure that batches in clinical studies always have the data available to demonstrate they remain in specification during the duration of the trial, it is necessary to continuously update the shelf life as soon as data are available and before the previous shelf life expires, McNaughton stresses. That can be challenging during early-phase studies, but simpler for later-phase trials because more time is available for completing stability studies.

On the other hand, if changes in the chemical or physical stability of a drug product are identified in stability studies, clinical programs may need to be suspended until new batches can be supplied, according to Iley. She notes that data provided from technical batches can be a good indicator of how clinical batches will perform and could save precious time when planning for contingencies.

The need to re-supply batches may also arise due to factors such as subject recruitment delays or dropouts, changes to dosing regimens, the introduction of new active, excipient, or packaging materials or revision to manufacturing processes. "Using a risk-based approach, it may be possible to undertake bridging studies to justify these changes, but it may also require performance of new or extended analytical studies. Any of these factors can impact the trial design and supporting stability program," Iley says.

The design of bridging studies will depend on the changes that created the need to perform them, according to Carmody. They typically involve the use of the established analytical methods, with comparison of results to previous data to confirm agreement.

Potential timeline extensions

Any issues identified related to the chemical or physical stability of the drug product could cause a delay to the entire clinical development program. "A well-designed stability study, initiated early in the program, will facilitate detection of these issues and lessen any impact they may otherwise cause if not understood and resolved quickly," asserts Iley.

The key challenge is the fact that as candidates progress through the development cycle, typically changes are made to the formulation, manufacturing process, analytical methodology, container closure system (CCS), or other aspects. Any such change requires generation of new stability data, according to Carmody. "The new material must also be demonstrated to be stable for the duration of the clinical trial. Any additional time for manufacturing the new CTM further adds to the potential for delays due to the need for additional stability studies," she says.

A development program would, however, take decades if each of these studies were run sequentially to completion, according to McNaughton. "It is necessary to take risks based on limited data from partial studies, which must be done while ensuring that product used in trials remains covered by a stability study that demonstrates it remains within specification," he says.

This necessary approach results in a balancing act of timing and risk with respect to determination of the best time to conduct these studies, and sometimes, when shelf life is limited or not yet known, ensuring a contingency to remanufacture to keep a clinical trial supplied is required. "Careful extrapolation of data obtained from samples stored at accelerated conditions can help predict when additional batches may be required to support clinical studies and therefore allow planning with some level of confidence when manufacturing slots will be required," Iley adds.

There are also often increasing types of stability tests that need to be conducted as candidates move through later clinical trials. For instance, Carmody notes that diluents added to a powder to create a solution for infusion must be subjected to stability studies if the diluent manufacturer cannot provide relevant data. The in-use stability of the solution formed with the diluent must also be demonstrated. This information will impact the product handling protocol for the trial. "In-use studies should therefore be executed during early stages because the results directly impact and inform formulation and process development activities," Carmody says.

API availability is an important factor as well because synthetic route and process development typically proceed in parallel with clinical programs, according to Carr. "Supplies are often

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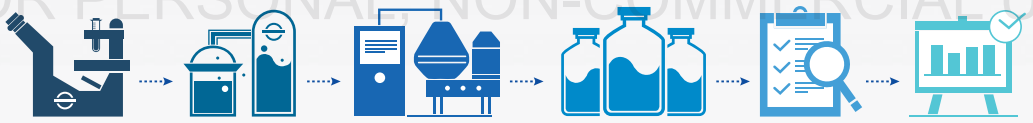

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limited around Phase I as synthetic route and scale-up activities have not yet progressed. Limiting stability study duration is important for avoiding wastage of valuable API," he observes. API availability generally increases as candidates move to Phases II and III, so longer-term stability studies can be more readily supported. In addition, Carr comments that long-term data are more useful at this point because the nature of the API and dosage form is likely to be more representative of future commercial batches.

Complications can also arise in early-phase studies if the product is not tested promptly. In some cases, artificial failures can occur due to product being older than it should when tested, according to McNaughton.

Method development/validation challenges

Often during early-phase studies, knowledge of both products and methods are limited, according to McNaughton. "When unknown degradation occurs, or a method does not behave as anticipated due to an unforeseen change, this can lead to pressure on the project. There exists a need to explain the change and justify it as safe for ongoing work or understand quickly that it is a change that does have an impact on product safety," he notes.

Establishing methods at the start of the process and how the method lifecycle progresses (e.g., identification of new impurities, formulation changes) can require careful assessment and may identify gaps in planned studies or potentially initiate new studies, Iley says.

What is important, adds Carr, is the strategy for method development/validation. Because CTMs are considered GMP even at Phase I, at least some validation of analytical procedures is required. Many companies adopt an approach of "phase-appropriate validation" or "qualification" using methods that have only been partially validated. "The objective is to be economic with the resources applied to validation without compromising patient safety," he states.

Quality-by-design approaches to analytical method development/validation conflict with this strategy, however. Even so, Carr remarks that analytical development can only proceed to a certain extent until the full details of product strength and formulation are known.

He suggests that, given the likelihood of limited knowledge regarding potential degradation products and how to set limits for them, the best approach is to use "alert limits" rather than pass/fail limits or "report results" with no defined limits. "Alert limits may be set applying ICH Q3B(R2) principles (5); an advantage of this approach is that if an alert limit is exceeded, an investigation can be conducted but confirmation of the result does not necessarily require a batch to be rejected, as would be the case with an out-of-specification result," he explains.

The issue of validation is perhaps one of the most confusing aspects of conducting stability studies, according to Carmody. It is a Catch-22; stability studies and stability-indicating studies (forced degradation of the CTM) should be validated, but validation is typically not completed until Phase III.

"What should be done," Carmody says, "is to understand the target product profile, mechanism of action, and other important characteristics (e.g., solubility, chromophoric, etc.) to identify the most appropriate analytical methods to choose from." The best methods can then be chosen for identification, potency, purity, and impurity analyses and the relevant parameters validated according to regulatory authority expectations. For any deviations, good scientific rational must be documented.

"Even for Phase I CTMs, analytical methods can be developed with the intended use and validation parameters in mind. As important, stability-indicating studies and appropriate methods must be developed to ensure that the possible degradation products for the CTM can be detected," Carmody states.

Comprehensive approach and logical strategy beneficial

A carefully designed study that stratifies the storage conditions, specific tests, and material batches is required to avoid the often-nebulous growth of a stability program while still generating pivotal development data, according to Iley. "Ensuring strong, validated methods are in place and planning for potential trial extensions in the stability program design with the inclusion of optional time points and sufficient spare samples to support them is essential," she adds.

The more knowledge of the product and methods that is generated in advance, the more a study can be derisked, agrees McNaughton. "It is important to ensure sufficient windows for testing are left, before the data are critically required, to allow for investigational work to take place at every time point in the early stages of a product. For this investigational work, there also needs to be sufficient product added to the study to facilitate investigations to examine what may or may not be a critical change," he adds.

Other factors to consider include stability testing of placebos and comparator products, climate zones the product may be exposed to, using batches of drug product manufactured to established procedures, and prioritizing patient safety while collecting reliable clinical data.

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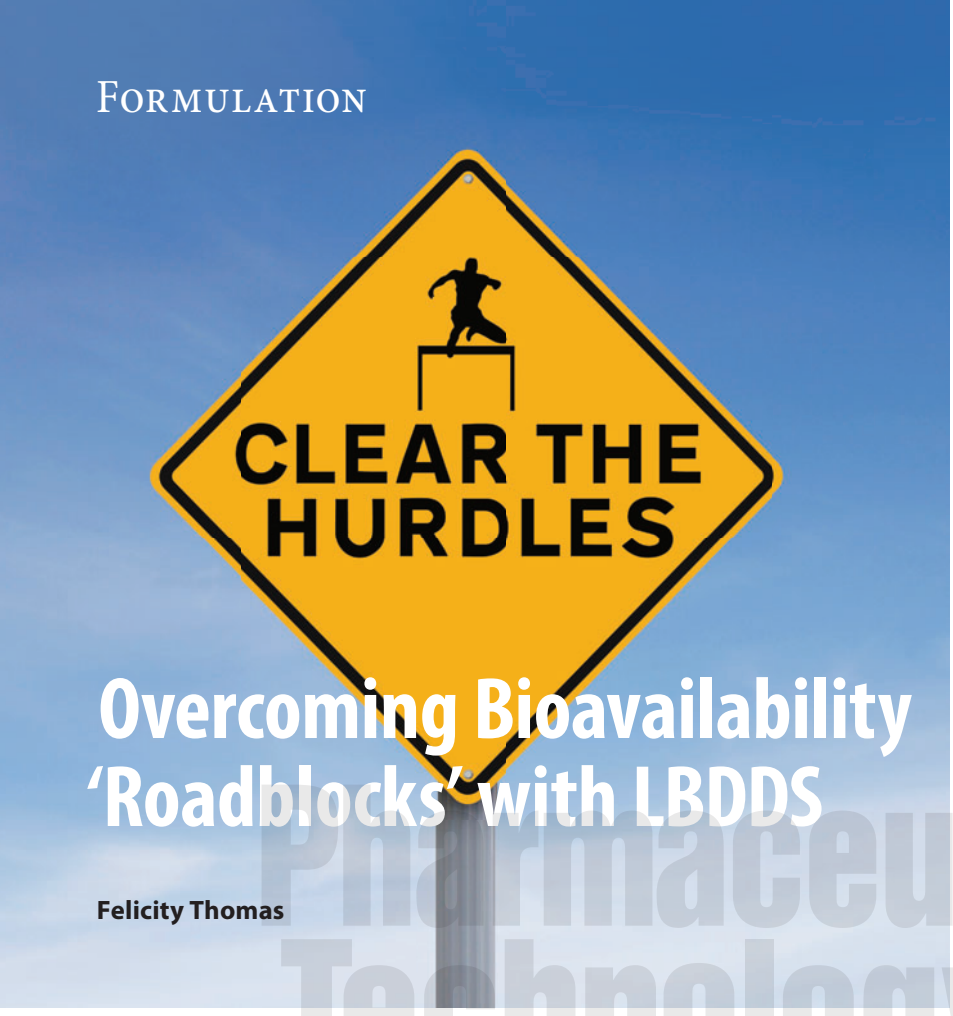

Overcoming Bioavailability 'Roadblocks' with LBDDS

Felicity Thomas

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Lipid-based formulations provide a versatile solution to bioavailability issues, but a multidisciplinary approach is needed to overcome limitations with poorly soluble compounds.

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Lipid-based approaches to drug delivery have been extensively researched and have gained importance within the bio/pharma industry for their ability to enhance bioavailability of drug products. This capability to enhance bioavailability is becoming ever more desired in recent times due to the fact that increasing numbers of molecules entering the drug development pipeline are poorly soluble.

"As of late, more than 70% of new chemical entity (NCE) molecules are poorly soluble, with moderate lipophilicity (LogP >2)," says Ravinder Kodipyaka, head, formulation R&D, Custom Pharma Services, Dr Reddy's. "As a result, industry is witnessing opportunities in novel drug discovery for the formulation of new NCEs in lipid-based drug delivery systems (LBDDS) so that bioavailability is improved."

A tremendous solution

"Lipid-based formulations offer a tremendous solution for molecules exhibiting poor solubility and bioavailability," Kodipyaka continues. "These formulations provide excellent solubilization capacity; improve permeation; overcome transporter, enzyme-based inhibitions; and support lymphatic transport, thereby overcoming major roadblocks for achieving optimum bioavailability."

Using lipids to enhance oral bioavailability is a popular choice, adds Michiel Van Speybroeck, head of formulation, Ardena. "When an API is dissolved in a lipid formulation and subsequently administered, the API is presented to the gastrointestinal (GI) fluids in a predissolved form, which avoids slow dissolution from the crystalline form," he notes. "The great advantage that lipids and lipophilic excipients offer over water-miscible solvents is that they are less likely to lose solvent capacity on dilution with the GI fluids. On contact with water, lipophilic excipients phase-separate and form a coarse or finely dispersed emulsion in which the API is sequestered. This protects the API from precipitation in the aqueous phase."

Furthermore, Vincent Plassat, lead product development scientist, Catalent, emphasizes that by delivering drugs in a solubilized form, dose-uniformity can be improved, minimizing patient-to-patient variability. "There is a lot of precedent for the use of lipid-based drug delivery systems as a result of their value to drug developers and ultimately to patients. LBDDS are extremely versatile because there are many excipients and combinations of excipients that can be used in their development," he explains.

Along with improved dose uniformity, LBDDS are also capable of mitigating food effects (1), Plassat confirms. "For very lipophilic drugs with a LogP value greater than five, formulation of long chain fatty acids can improve lymphatic uptake and bypass the liver. In addition, lipid-based formulations can maintain their solubility throughout the entire journey of the API through the GI tract, allowing higher absorption," he says. "This is unlike non-lipid-based formulations, which exhibit supersaturation, decreased solubility, and lower absorption."

Administration of lipid-based formulations is possible across several routes—oral, injectable, and topical—and depending on the lipophilic nature of a drug, it is possible to determine the optimal lipid delivery

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system using the Lipid-Formulation Classification System (2), explains Kodipyaka. Employing a suitable lipid excipient component can also aid in modulation of drug release. "The greater the hydrophobicity of the lipid excipient the slower the drug release due to reduced water penetration," he adds.

Being able to control drug release is important so that rapid, high drug plasma level peaks are avoided, which can cause unwanted side effects in patients, notes Ellie Au, product development scientist, Catalent. "A slower release may also protect the drug from degradation in the stomach and facilitate release of the drug throughout the GI tract to improve absorption. Self-emulsifying lipid formulations typically have faster drug release than those lipid formulations that require digestion. The use of waxes, which are solid at room temperature, creates a matrix for modified release. The drug is therefore released with a controlled kinetic as the matrix slowly erodes," she says.

"Drug release can be further modulated by incorporating pore formers, hydrophilic polymers, and surfactants in the composition or by virtue of a process that creates a more porous structure," Kodipyaka comments. "Drug release is the important determinant to ensure maximum bioavailability at the site of action. Thus, lipid formulations could be tailored to achieve desired drug-release kinetics by careful selection of lipid excipients."

With versatility comes challenges

Lipid-based formulations offer versatility and compatibility in terms of generally recognized safety, route of administration, and capability to overcome bioavailability issues. However, with this versatility, some challenges with LBDDS arise, such as stability issues and drug loading, reveals Karunakar Sukuru, vice-president, Product Development (US & EU) Softgel & Oral Technologies, Catalent.

Drug loading, for example, can be quite low in LBDDS as a result of the improved solubility offered. "Nevertheless, drug loading is a challenge faced by many other bioavailability enhancing technologies," Sukuru adds.

For Kodipyaka, a common challenge associated with lipid-formulations is ingredient stability issues, particularly when using liquid formulations rather than solid forms, and drug precipitation during storage or contact with *in-vivo* GI fluids. "After administration, dilution and digestion effects will lead to a reduction in the solvent capacity of the lipid formulation. As a result, the API that was initially in solution may precipitate, and this may reduce the bioavailability-enhancing potential of the formulation," agrees Speybroeck. "While lipid formulations are generally less susceptible to these effects than those based on water-miscible solvents, some precipitation may still occur. The magnitude of this effect can be assessed using *in-vitro* techniques that consider the effect of formulation digestion."

Therefore, appropriate design of LBDDS is necessary to ensure that drug precipitation upon exposure to GI fluids is indeed avoided, Sukuru confirms. "Understanding the mechanism and predicting *in-vivo* performance of LBDDS has gained a lot of attention recently," he says. "Many lipid excipients are naturally derived and contain multiple lipids (e.g., mixtures of mono-, di-, and triglycerides). There may be issues as ratios of lipid components change from batch-to-batch. Because of these variables, it is recommended that drug developers work with experts who have extensive experience and knowledge of the development of LBDDS."

Another challenge experienced with lipid-based formulations is that of Ostwald ripening, which is where small particles dissolve and then redeposit onto larger particles due to surface energy instability. "Ostwald ripening is a major challenge for lipid-based formulations, particularly for injectable products," says Kodipyaka. "There are a limited number of approved, safe emulsifiers commercially available that can stabilize the emulsion system; hence, it would be very challenging to develop emulsion systems with the desired target product profile."

"Finally, while the excipients used to construct lipid formulations are usually quite inert, many of these contain impurities, such as peroxides, aldehydes, or formic acid, that may trigger degradation pathways that are not seen when the same API is formulated in a solid formulation," specifies Speybroeck.

Available techniques and their limitations

Assessing the precipitation risk of lipid-based formulations as a result of dilution and digestion is possible using *in-vitro* experiments. These tests are more complex than standard dissolution tests but are capable of providing a more reliable indicator of lipid formulation performance, notes Speybroeck.

"*In-vitro* lipolysis experiments have been the traditional experiment to study a LBDDS mechanism and correlate it with *in-vivo* performance," confirms Au. "Newer approaches, such as kinetic solubility measurements, are gaining interest to correlate with *in-vivo* behavior of LBDDS."

Sukuru adds that a main limitation of current techniques that are aimed at overcoming challenges associated with lipid-based formulations is that all the work is undertaken in a closed system, whereas the human body is dynamic and always in motion. "A variety of new techniques and tools are available to quickly evaluate lipid-based formulations. One such tool is fiber optic dissolution testing, which allows for monitoring of dissolution profiles in real-time in a variety of biorelevant media and makes it easier to compare the performance of the formulation without the need for complex and lengthy analytical

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methods. It is also easier to asses any impact of the media modification," he says. "With such advances in analytical instrumentation, product development can be expedited and made more robust through the generation of data and providing the opportunity to challenge different parameters of the formulation earlier in development."

There is also the emergence of technologies in the field to enhance API loading of lipid-based formulations, adds Speybroeck. "Some researchers have reported on the use of supersaturated lipid formulations (3), whereby the API loading is increased by subjecting the lipid formulation to a heat-cool cycle," he states. "This way, the concentration of API in the formulation is increased beyond its equilibrium solubility, which may lead to several-fold increases in API loading. This technique may be a viable option to reduce administration volume in preclinical and early clinical development. However, the utility for commercial products is more limited given the risk of API precipitation during storage, as the API is present at concentrations above its equilibrium solubility in the formulation."

Regarding ingredients, Speybroeck notes that lipophilic salts are developing within the industry. "While traditional pharmaceutical salt forms are usually developed using small, hydrophilic counterions in an attempt to increase aqueous solubility, lipophilic salts are constructed with large, lipophilic counterions," he says. "These salts may exhibit greatly depressed melting temperatures relative to the free form of the API and therefore also exhibit much higher solubility in lipophilic vehicles."

In terms of unsaturated lipid components, which are prone to lipid peroxidation, formulators can employ saturated medium chain triglycerides along with appropriate antioxidants, explains Kodipyaka. "Excipient compatibility and stress stability studies during early stage development help formulators choose the right excipients according to the degradation pathway of the drug," he says. "Decreased mobility by making semi-solid formulations also can help to physically and chemically stabilize the formulation."

Additionally, alternative ingredients for capsules are coming to the fore, such as the use of hydroxypropyl methylcellulose (HPMC) or polyvinyl alcohol, instead of traditional gelatin-based capsules. "These ingredients are chemically and thermally stable and are less prone to humidity compared to gelatin-based capsules," Kodipyaka confirms. "Furthermore, with the invention of liquid encapsulated micro-spray sealing technology, problems that were common with the conventional banding approach have been resolved."

Size matters

As molecules entering the drug development pipeline are increasing in size and becoming more lipophilic and chemically diverse, solubility challenges are also rising and can lead to a higher level of drug susceptibility to food effects, notes Au. "The broad range of lipid excipients available offer many options to customize formulations to meet the specific needs of the molecule," she says. "Investing time and effort early in the development of a LBDDS can result in significant savings in time and overall development costs, and often with a better outcome."

With an expanding proportion of drugs gaining fast-track designation, particularly for those therapies aimed at unmet medical needs, the benefits of LBDDS, which were primarily used to introduce life-saving drugs such as HIV proteases and anti-cancer treatments, are apparent, notes Plassat. "For example, within the industry, there has been a growing interest in peptides and other macromolecules due to their high specificity and potency," he states. "The molecules are usually more sensitive to degradation, and lipid-based formulations can provide them with a better environment for long-term stability, and/or protect them from degradation in the GI tract."

Yet, developing a lipid-based formulation essentially remains an empirical endeavor, notes Speybroeck. "Given the plethora of lipids and lipophilic excipients available, initiating a lipid formulation development may seem like a daunting task," he adds. "However, great progress is being made in *in-silico* (computer-assisted) prediction of solubility. Adoption of such techniques may dramatically reduce the initial development effort."

Thanks to these formulation design advancements in addition to new technologies that can enhance API loading and an improved understanding of how lipid-based formulations perform *in-vivo*, Speybroeck anticipates an enhanced adoption of the lipid approach in the future. "I believe we will witness a steady increase in the use of lipid formulations in clinical and commercial drug products going forward," he says.

Taking a lipid-based approach for the formulation and delivery of new molecules with large molecular weights and high lipophilicity has shown great promise, stresses Kodipyaka. "However, technology development and implementation in the area of lipid drug delivery needs to be expedited to catch up with the discovery pace," he summarizes. "A multidisciplinary approach is required to overcome limitations pertaining to development of lipid formulations for poorly soluble molecules. Knowledge of lipid chemistry, predictive *in-silico* models, nanotechnology, and bio-pharmaceutics coupled with advanced characterization techniques would be helpful in resolving complex issues moving forward."

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Optimizing Manufacturing Based on the Storage Stability of Pegylated Products

Chintan Patel, Sanjay Bandyopadhyay, and Gayatri Patel

Research into peginterferon alfa-2b's degradation pathways suggest that drug substance be immediately and continuously converted to drug product when the material is in liquid form.

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Depending on the polyethylene glycol reagent and chemistry used to manufacture them, pegylated products may exhibit different degradation patterns under different storage conditions. To ensure product quality, it is essential to prevent degradation, which can occur when temperatures exceed optimal levels during manufacturing, storage, and shipping. To get a better understanding of degradation patterns, research was done to evaluate the stability of pegylated products under various storage conditions.

This article discusses work that was done to examine the effect of repeated freezing and thawing cycles on the stability of peginterferon alfa-2b, and to study its storage stability in frozen as well as liquid form. It also discusses how results might pertain to various other pegylated products. Size-exclusion chromatography, circular dichroism, and fluorescent spectroscopy were all used to evaluate stability under different conditions. Results suggest that storage in liquid form can lead to degradation at temperatures between +2 °C and +8 °C.

Interferons exhibit both antiviral and antineoplastic effects (1). Interferon alfa-2b (Intron A), interferon alfa-2a (Roferon-A), and interferon beta-1b (BETAFERON) are approved for various indications either alone or combined with other agents. Both alfa-2b and alfa-2a types have half-lives of less than 12 hours, necessitating multiple injections (at least three times per week) for the duration of treatment, which can range from three weeks to 24 months (2,3).

Longer-acting versions of both alfa 2b and alfa 2a have been developed to help offset this problem. Examples include peginterferon alfa-2b (Pegintron/ViraferonPeg) and peginterferon alfa-2a (Pegasys). Pegintron/ViraferonPeg has been approved as part of a combination regimen to treat chronic hepatitis C (CHC) in patients with compensated liver disease. Pegasys is indicated for CHC and chronic hepatitis B.

Most of the first generation of pegylated products (i.e., Adagen (Pegademase), Oncaspar (Pegaspargase), Pegintron (peginterferon alfa-2b) and Pegasys (peginterferon alfa-2b)

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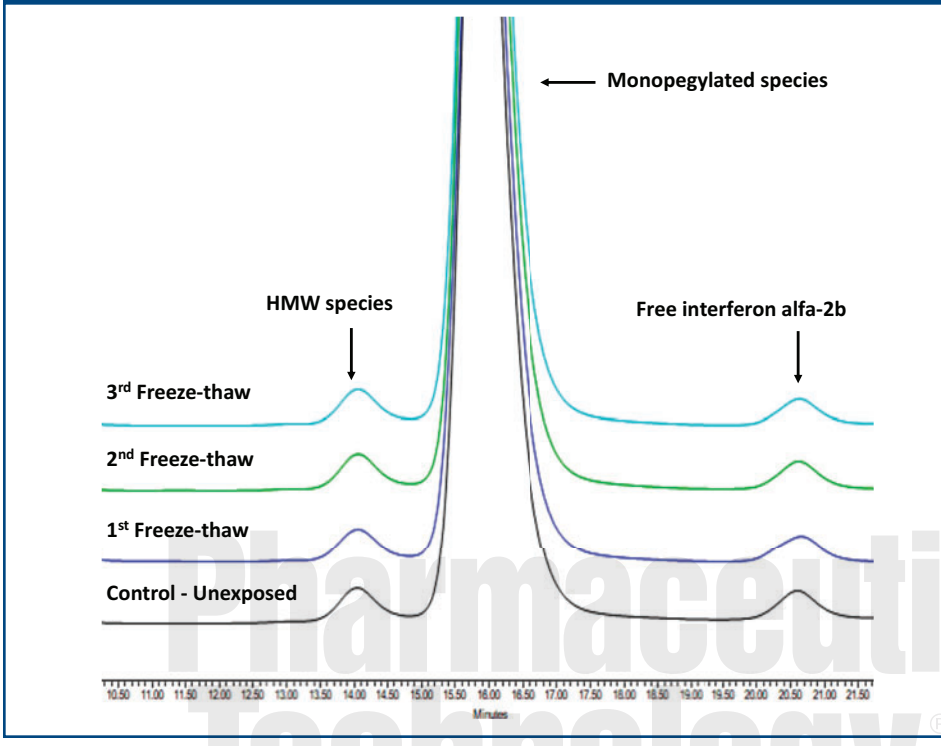
Figure 1: Overlaid HP-size exclusion chromatograms of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples.



were developed with commercially available acylating PEG reagents (4). Adagen and Oncaspar were prepared using monomethoxy PEG activated with succinimidyl succinate (mPEG-SS) (5). Pegintron is prepared by conjugating interferon alfa-2b with a single chain 12 kDa PEG activated with succinimidyl carbonate (mPEG-SC), while Pegasys is prepared by conjugating interferon alfa-2a with N-hydroxysuccinimide (NHS) activated 40 kDa branched PEG molecule (6,7). Pegintron is a mixture of biologically active mono-pegylated positional isomers so that most of the pegylation occurs at the Histidine 34 (His34) residue. Within this residue, a urethane-like bond that is formed by succinimidyl carbonate (SC) conjugation chemistry with the imidazole ring of His34 is hydrolytically labile. In contrast, however, Pegasys is produced utilizing N-Hydroxysuccinimide (NHS) chemistry through amide bond formation. These bonds are not susceptible to spontaneous hydrolysis (8).

For any pegylated interferon, changes in protein temperature stability have been found to depend on the coupling chemistry, degree of pegylation, number of protein subunits, and formulation involved. It is known, for example, that pegylation has no effect on the secondary or tertiary structure of interferon alfa-2b and interferon alfa-2a. Not only the conformational stability of the protein molecule but the stability of the PEG-protein conjugate is important if the drug is to exhibit the desired biological activity and bioavailability. For example, Oncaspar (Pegaspargase), which is produced by conjugating mPEG-succinimidyl succinate (SS) with L-asparaginase, has a short shelf-life when supplied as a liquid solution, where the enzyme activity of L-asparaginase increases upon depegylation (9). In addition, pegaspargase shows different degradation pathways when exposed to high temperature and freeze-thawing stress (10). Pegylated products produced using different PEG reagents and pegylation chemistries (i.e., pegylation with mPEG-SS vs. mPEG-SC) may follow different degradation pathways under different storage conditions. Product may be exposed to sudden temperature excursions during the manufacturing process, storage, and shipping, which can affect product stability. Stability of pegylated products should be evaluated under various storage conditions, considering the nature of the product. The authors researched the effect of repeated freezing and thawing on the stability of peginterferon alfa-2b, as well as the stability of frozen peginterferon alfa-2b and liquid material maintained between +2 °C and +8 °C. Research focused on identifying the degradation pattern of peginterferon alfa-2b under these storage conditions, and were discussed with respect to the stability of various pegylated products.

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Materials and methods

Preparation of peginterferon alfa-2b. Interferon alfa-2b was produced in-house using recombinant DNA technology and pegylated using activated polyethylene glycol with a particle diameter of 12 kDa. Peginterferon alfa-2b was produced by pegylating interferon alfa-2b with 12-kDa monomethoxy polyethylene glycol succinimidyl carbonate (mPEG-SC), to the innovator product, PEGINTRON. PEG conjugation was carried out through integration of a carbamate (urethane) linkage, between N-atoms of the imidazole side-chain of His34 or the μ-NH2 group of N-terminal Cysteine residue, or the ε-NH2 group of Lysine side-chains of interferon alfa-2b and a 12-kDa mPEG-SC molecule.

Pegylation was carried out at pH 6.5 in the presence of a molar-excess amount of mPEG-SC over the protein amount. After pegylation, multiple-column chromatography (using GE's Amersham Biosciences' AKTA) was used to purify the peginterferon alfa-2b, mainly in monopegylated form.

After chromatography, peginterferon alfa-2b was brought into 10 mM sodium succinate buffer using succinic acid and sodium hydroxide (Merck) and maintained at a pH of 6.8. A 0.2-μm sterile filter (Sartopore 2, Sartorius Stedim Biotech GmbH) was then used to filter the protein solution.

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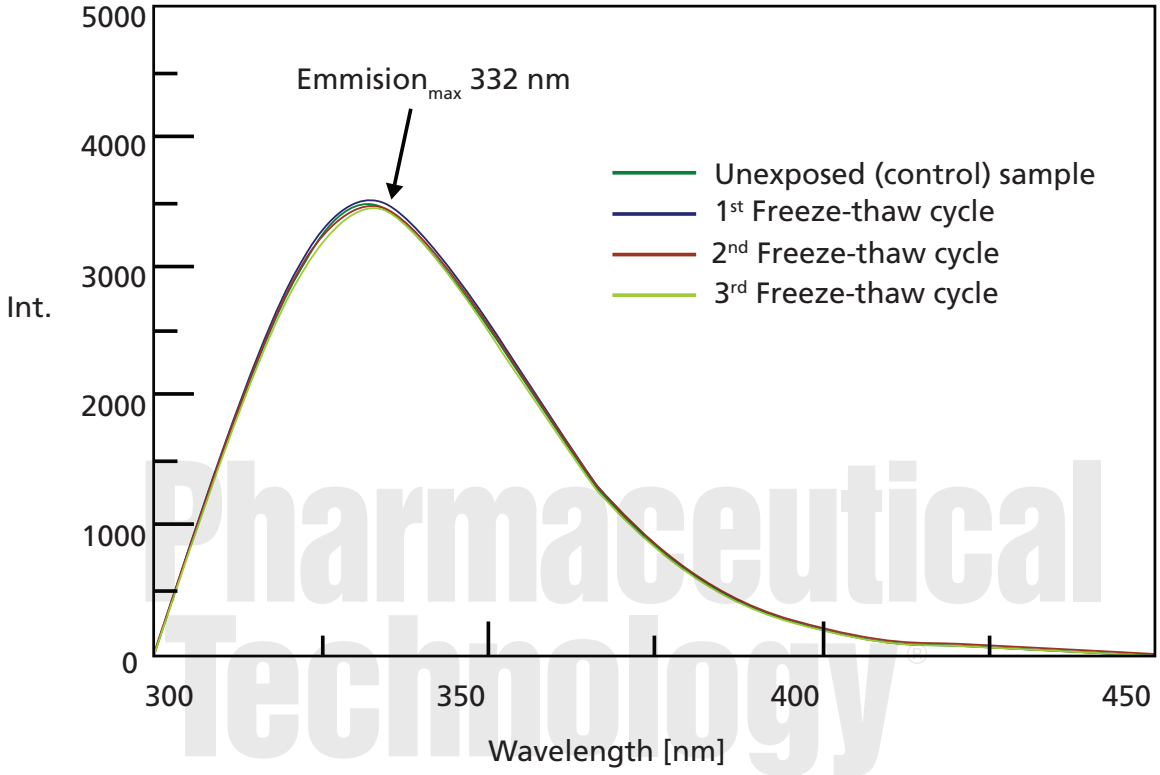
Figure 2: Overlaid Far-UV absorbance spectra of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples.



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Degradation of frozen vs. liquid peginterferon alfa-2b

Peginterferon alfa-2b's degradation pattern was assessed by analyzing results of repeated freezing and thawing cycles on the material. To check the effect of repeated freezing and thawing, peginterferon alfa-2b solution was aliquoted with 1 mL solution in a 10-mL container (Thermo Scientific) made of polytetrafluorethylene (PTFE) (Teflon, DuPont). Samples were frozen at or below –70 °C in the deep freezer (Thermo Electron Corporation, Model No.: ULT1740-3-V40). Thawing was done at room-temperature and was considered complete when the frozen mass had been completely converted into liquid. To check the degradation of liquid peginterferon alfa-2b protein, liquid samples were stored between +2 °C and +8 °C in the container, while samples that had been frozen at or below -70 °C were used to determine the stability of frozen material. Samples were withdrawn at different time intervals and analyzed by different test parameters.

Analytical evaluations

The presence of free interferon alfa-2b was assumed to indicate that depegylation had occurred in the test samples. High-performance size-exclusion chromatography (HP-SE), utilizing an ultraviolet (UV) detector, was used to measure samples to determine stability. Measurements were performed on a Shimadzu LC 2010-CHT series HPLC system equipped with a Tosoh Biosciences G3000SWXL column using a TSK gel (7.8-mm ID × 30.0 cm/L). Before injecting the sample, the column was pre-equilibrated with 0.2 M phosphate buffer containing 10% ethanol at a pH of 6.8 and a flow rate of 0.5 mL/min at an oven temperature of 25 °C. After the column was equilibrated, 10-µg samples were injected and analyzed in isocratic mode at a flow rate of 0.5 mL/min. Chromatographic separation was monitored at 214 nm utilizing the UV detector.

Test samples exposed to repeated freezing and thawing cycles were also tested to determine the structural integrity of peginterferon alfa-2b protein under these conditions by comparing them with initial sample that had not undergone freezing or thawing. Far-UV circular dichroism (CD) spectroscopy and spectrofluorometry (using a Jasco J-1500 instrument equipped with an MCB-100 Peltier-based temperature controlled assembly) was used to analyze the secondary structure of peginterferon alfa-2b samples.

A smoothing algorithm was used on the CD spectrum for baseline correction, and peak position was identified by using Spectra Manager software. Fluorescent spectroscopy (using a JASCO FP-8300 instrument equipped with a MCB-100 Peltier-based temperature-controlled assembly) was then used to evaluate the tertiary structure of peginterferon alfa-2b protein

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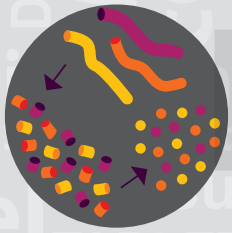

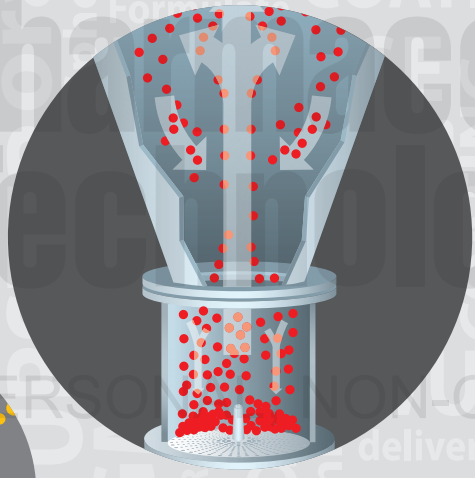

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Figure 3: Overlaid fluorescence emission spectra of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples

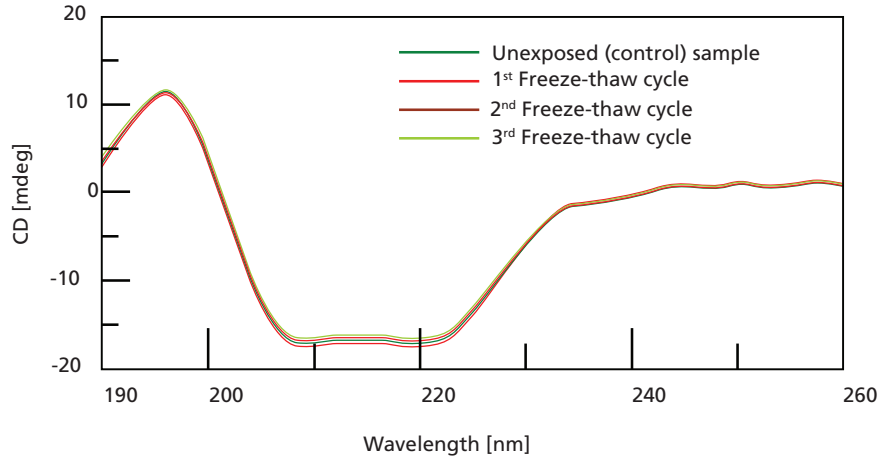
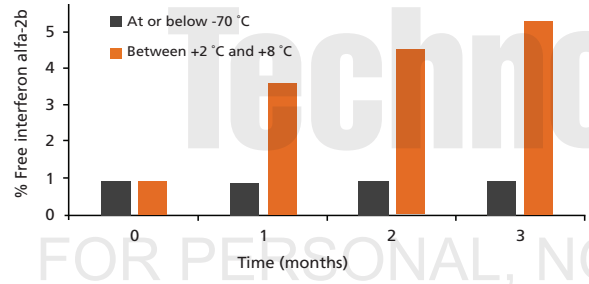


Figure 4: Stability of peginterferon alfa-2b under frozen condition and liquid form: Increase in level of interferon alfa-2b (depegylation) by HP-SEC.



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in the test samples. The temperature of the sample holder was controlled, and samples were incubated at 20 °C for 5 min under stirring conditions. Samples were then excited at 280 nm to capture total intrinsic fluorescence emission. Emission spectra were collected in the range of 300–450 nm. Again, a smoothing algorithm was used for smoothing and baseline correction, and Spectra Manager software was used to identify the maximum peak position.

Results

Effects of repeated freeze-and-thaw cycles on the stability of Peginterferon alfa 2-B. Peginterferon alfa-2b protein present in 10-mM sodium succinate buffer at a pH of 6.8 was exposed to freeze-thaw stress as described previously. Samples were exposed to three consecutive freezing and thawing cycles and evaluated to determine whether there had been an increase in the level of free interferon alfa-2b by HP-SEC. **Figure 1** shows the chromatographic profiles obtained with the samples of peginterferon alfa-2b before and after exposure to the freezing and thawing stress. The chromatogram obtained for the test samples exposed to freezing and thawing cycle shows no increase in the peak corresponding to free interferon alfa-2b, indicating no further increase in the level of free interferon alfa-2b upon repeated freezing and thawing compared to the result obtained with the unexposed initial sample.

Secondary structure analysis of the test samples of peginterferon alfa-2b exposed to repeated freezing and thawing was conducted by CD spectroscopy in the far-UV (260–190 nm) region to assess the effect on structural integrity of protein. As illustrated in **Figure 2**, CD spectra obtained with the test samples exposed to repeated freezing, and thawing cycles were observed to overlap with the spectra obtained for the unexposed initial sample in the far-UV region. The overlapping CD spectra obtained with all the samples showed absorbance minima at wavelengths 208 nm and 222 nm, typical for cytokine molecules, which remain unaltered upon repeated freezing and thawing of the peginterferon alfa-2b in presence of 10 mM sodium succinate buffer at pH 6.8. **Figure 3** shows results obtained with peginterferon alfa-2b test samples analyzed by spectrofluorometry to evaluate the effect of repeated freezing and thawing on tertiary structure. The fluorescence spectra obtained with the test samples that had been exposed to repeated freezing and thawing were observed to overlap with spectra obtained for unexposed initial samples, indicating no effect on tertiary structure of peginterferon alfa-2b protein.

Stability of peginterferon alfa-2b: frozen vs. liquid form

Peginterferon alfa-2b in 10-mM sodium succinate buffer at pH 6.8 was stored in liquid form between +2 °C and +8 °C, and in frozen form at temperatures at or below –70 °C for three months to check for any increase in the level of free interferon alfa-2b under both the storage conditions.

Samples were withdrawn at different time intervals and analyzed by HP-SEC. The level of free interferon alfa-2b in the test samples withdrawn at different time intervals from both the storage conditions is shown in **Figure 4**. When stored as liquid solution between +2 °C and +8 °C, the level of free interferon alfa-2b increased, with time indicating depegylation under these storage conditions. However, when stored under frozen conditions, even for up to three months, the material showed no significant change in the level of free interferon alfa-2b observed. In a separate study, stability of peginterferon alfa-2b was established at least up to 12 months when stored at or below –70 °C without any significant depegylation.

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Discussion

Experimental results demonstrate that peginterferon alfa-2b protein can withstand up to three multiple freeze-thawing cycles without showing any loss of structural integrity and depegylation. When stored under frozen conditions (i.e., at or below –70 °C), the material does not show any increase in level of free interferon alfa-2b for at least three months, showing that no depegylation had occurred. These results stand in contrast to what was observed with the liquid form.

For most biological products, drug substance is generally stored in the frozen form and known to have longer shelf-life of at least about two years before it gets converted into the drug product upon formulation. However, it is known that the manufacturing process of Oncaspar liquid drug product (Enzon Pharmaceuticals Inc.), involves continuous processing of the drug substance to produce drug product wherein the hold time stability of the drug substance material is established between +2 °C and +8 °C.

In a separate study, authors have found that pegaspargase does not show stability upon freezing and thawing (10). Unlike results obtained with pegaspargase, which is a multi-subunit protein highly susceptible to conformational changes upon freezing and thawing, peginterferon alfa-2b produced using mPEG-SC with carbamate linkage showed high stability when exposed to repeated freezing and thawing. These observations suggest that different protein molecules pegylated with different PEG reagents and using different pegylation chemistries may exhibit different degradation patterns when exposed to freezing and thawing stress. Therefore storage conditions during various manufacturing process steps must be selected very carefully, based on the pegylation chemistry utilized, the type of protein molecule involved (i.e., single subunit vs. multiple subunits) and degree of pegylation.

Oncaspar's susceptibility to conformational changes of the protein molecule upon freeze-thawing and depegylation when stored at +2 °C and +8 °C suggests that the drug substance material should be immediately and continuously converted to drug product during fill/finish manufacturing so that the material does not have to be stored.

Based on results obtained with the peginterferon alfa-2b samples stored at or below –70 °C, peginterferon alfa-2b can be stored in frozen form. This allows drug substance and drug product manufacturing to be decoupled, removing the need for continuous processing. The storage stability of peginterferon alfa-2b in frozen form can enhance manufacturing flexibility, particularly for production campaigns in a multi-product facility.

Another pegylated product, Pegasys (peginterferon alfa-2a) which is prepared by conjugating interferon alfa-2a with an NHS-activated, 40-kDa branched PEG molecule with stable amide linkage supplied as a liquid solution with the shelf-life of two years when stored between +2 °C and +8 °C whereas Oncaspar has a shelf-life of only eight months, due to removal of PEG from its protein backbone.

Like Oncaspar, peginterferon alfa-2b remains unstable when stored as a liquid solution between +2 °C and +8 °C and degrades through depegylation as these experiments confirmed. Due to the unstable linkages present in Oncaspar and peginterferon alfa-2b, it is crucial to produce the drug product material as a lyophilized powder and reconstitute it just before the injection.

Conclusion

Peginterferon alfa-2b exhibited stability after repeated freezing and thawing stress cycles, without the addition of any cryoprotectant. No impact was observed on the protein molecule conformation upon repeated freezing and thawing. When stored in liquid form, however, even at +2 °C to +8 °C, peginterferon alfa-2b shows significant depegylation. When stored in frozen form, it remains stable without any depegylation. Pegylated products may exhibit different storage stabilities when exposed to repeated freezing and thawing, based on the PEG reagent and pegylation chemistry utilized. It is thus very important to evaluate the storage stability of pegylated products at various steps of the manufacturing process. Identifying degradation patterns that will occur under different storage conditions can play important role in optimizing both drug substance and product manufacturing process designs.

Acknowledgement

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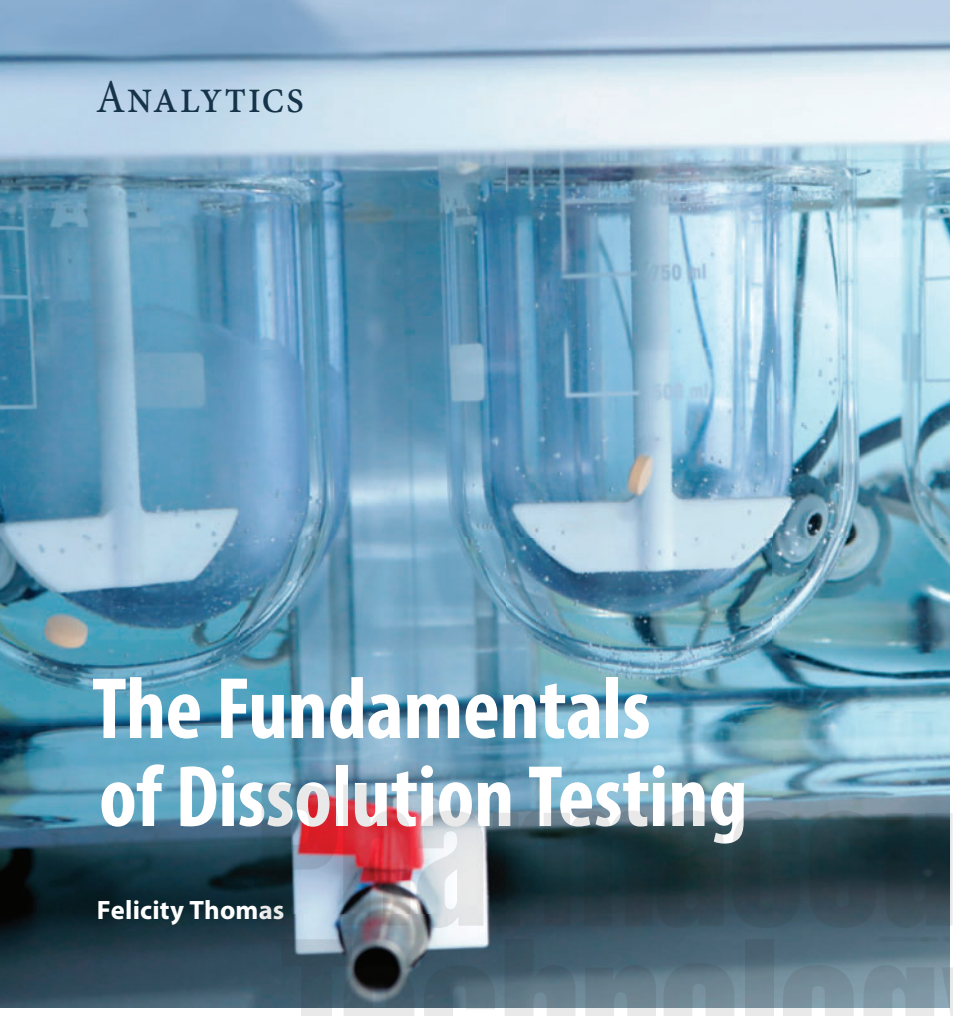

The Fundamentals of Dissolution Testing

Felicity Thomas

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In this article, experts discuss the fundamentals of dissolution testing and highlight the challenges that are surfacing as a result of the increasing numbers of poorly soluble molecules entering the development pipeline.

Because oral solid dosage forms are still the most common way in which drugs are administered, dissolution of the dosage form after it is swallowed, namely the rate at which the active ingredient is released into the body, is a critical facet of drug development. "Dissolution testing is an essential analytical procedure that's required as part of the final release investigation for solid oral dosage forms to control product quality, stability, and batch-to-batch consistency," confirms Meike Eckert, head of Dissolution Laboratories, Evonik Health Care. "As the rate of dissolution can significantly affect bioavailability, the goal of dissolution tests and associated acceptance criteria should be to identify batches with unacceptable bioavailability."

The primary functions of a dissolution test during early stages of development are to characterize therapeutic efficacy, bioequivalence, and bioavailability of API. During later stages of the development process, dissolution testing is also used for quality control (QC) purposes. "The type of dissolution testing performed along with the information required from the testing will change as the molecule progresses from the early stages of development to later in clinical development and towards product registration," says Charlotte Clay, head of Analytical Development, Pharmaceutical Analysis, Quotient Sciences.

Useful at every stage of development

"At the initial stages of characterizing and selecting the API, *in-vitro* dissolution testing can be performed to aid determination of the Developability Classification System (DCS) classification of an API, and in turn provide useful guidance on the best formulation development strategy for a molecule," Clay continues. "In later stages of development, dissolution testing is used as a QC procedure to detect the influence of critical manufacturing variables on a drug product."

During early drug development stages, it is possible to use a biorelevant dissolution method to determine how a formulation may react in media, such as fasted simulated gastric fluid (FaSSGF) and fasted simulated intestinal fluid (FaSSIF), that closely mimics conditions found inside the human body, Clay explains. "This methodology provides a prediction of how a formulation will behave within the body and ensure that the most appropriate formulations are taken forward into clinical trials," she says.

After the optimal formulation has been chosen to progress, dissolution methods specifically aimed at assessing quality and stability are developed. "These methods may not be biorelevant (standard acidic and phosphate buffered medias are typically used), but they are able to distinguish batch-to-batch variability as well as any changes in the formulations' dissolution performance that could affect product stability," Clay confirms.

Once pharmacokinetic (PK) data have started to be collected from clinical trials of the chosen formulation, it is appropriate to develop a biopredictive dissolution method. When used in combination with PK data, it is possible for developers to set up *in-vitro–in-vivo* correlations (IVIVC), which can be used to optimize formulations and determine equivalence for generic

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or modified versions of originator drug products, states Eckert.

"By following a quality-by-design (QbD) approach, risk assessments and definitions for quality target product profiles can be used throughout the clinical development and commercial lifecycle to identify potentially high-risk formulation and process variables," summarizes Eckert. "Dissolution testing can also achieve an improved product and process understanding to develop an appropriate control strategy."

Achieving meaningful dissolution

Of paramount importance for dissolution testing is the assurance that the conditions used for testing are appropriate and correct for the product that is being tested, as well as for the information that is hoped to be gained from the test, stresses Clay. "There are many variables when it comes to dissolution testing from the type of apparatus and the dissolution media used, through to the small but important decisions on parameters, such as paddle/basket rotation speed, the use of sinkers, and the number of sampling time points, to name but a few," she explains. "Small changes to these variables can have a big impact on the data generated; for example, the sinker mesh size used can have a direct impact on the release rate of the formulation, so it is therefore important to control these parameters and specify them in the analytical test method."

Additionally, Clay emphasizes that as a result of an increasing number of poorly soluble molecules entering the development pipeline, the number of ingredients falling into a DCS class II or IV are also rising. "As such, choosing the correct dissolution media where sink conditions can be achieved is becoming more of a challenge when developing dissolution methods," she says.

In agreement, Eckert highlights that it can often be necessary to add solubilizers, such as sodium lauryl sulfate, at an appropriate concentration to achieve meaningful dissolution results when dealing with poorly soluble ingredients. "During the formulation development process, it can be challenging to identify the right dissolution test methods to predict how the target formulation will perform *in-vivo* to reduce risk during future clinical studies," she continues. "Based upon the physicochemical characteristics of the API and the type of formulation, the use of media with different rates of complexity can be employed. These media options can range from plain buffers up to biorelevant media and the potential addition of digestion enzymes."

Defined dissolution apparatus and development of new tools

Currently, there are seven different types of dissolution apparatus defined in the *United States Pharmacopeia* (*USP*)—basket type, paddle type, reciprocating cylinder, flow through cell, paddle over disc, rotating cylinder, and reciprocating disc. Of the seven apparatus, basket type (apparatus I) and paddle type (apparatus II) are most commonly used for oral solid dosage forms but many different product types, from capsules to creams, can be testing using the apparatus defined in the *USP*.

"*USP* Apparatus I and II are the most commonly used dissolution apparatus for solid oral dosage forms and are versatile in enabling the development of many types of dissolution methods, from those for formulation development purposes to those used for QC testing of commercial batches," confirms Clay. "There are also a number of more bespoke dissolution apparatus/techniques being developed and used as drug products become more complex and the search for a more biopredictive technique continues."

In concurrence, Eckert notes that development of newer *in-vitro* tools has occurred as a result of the rising number of APIs with more complex physicochemical characteristics and the more stringent regulatory requirements being demanded for the prediction of *in-vivo* behavior. "In addition to Apparatus III and IV (reciprocating cylinder and flow through cell), which are candidates for the prediction of detailed gastrointestinal transit with multiple test media or bioequivalent volumes, there is a growing toolbox of other emerging systems that are now offered by university spin-offs, such as Physiolution or other specialized companies for certain specific challenges," she says.

Giving an example, Eckert explains that multiple providers now offer services to combine dissolution testing with simulated mechanical stress. "These combination tests offer additional benefits for dosage forms that are sensitive to mechanical stress, such as delayed release capsules," she adds. "They can also be useful in the development of generic products to compare eroding and non-eroding matrices."

Volumes can be problematic when determining the most appropriate dissolution test to use, stresses Eckert. The commonly used apparatus are limited for use with media volumes of between 500 mL and 1000 mL, which can restrict the physiological relevance. However, using high volumes for dissolution testing can lead to an overestimation of *in-vivo* performance. "To better reflect conditions within the human gastrointestinal tract, the use of mini-paddles combined with smaller vessels can sometimes be advantageous," Eckert says. "However, this method is not yet considered by the pharmacopeias."

Clay continues by highlighting the fact that there has been an escalating use of modified and non-compendial apparatus in the field of dissolution testing over recent years. "These apparatuses are being utilized to offer novel perspectives on different dosage types, delivery devices, and formulations, with the goal being to make dissolution results more biorelevant," she states. "As a result, previous 'fringe' techniques such as intrinsic dissolution, small-volume dissolution, and dissolutions using enhancer, immersion, or extraction cells are becoming more widely adopted."

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Furthermore, advancements in detection techniques are also enabling testing, either online or in real-time, of more complex, multi-component formulations, Clay confirms. With the added capabilities afforded by these new detection techniques, developers can achieve a comprehensive data set, which provides a better understanding of the interactions of APIs and excipients in product formulations.

A harmonized technique

Globally, various pharmacopeias provide clear outlines for apparatus, procedures, and evaluations that will help developers to fulfill the dissolution testing criteria of regulatory bodies. For example, *USP* has several chapters, including 711, 1092, and 1225, detailing preliminary assessments, method development, analysis, automation, validation, and acceptance criteria (1–3). In *European Pharmacopoeia* section 2.9.3 (4), developers can find information on apparatus, procedures, and evaluations for acceptance criteria also.

"Since 2014, Europe has also started following the *USP* approach of publishing individual formulation monographs containing dissolution methods and acceptance criteria," adds Eckert. "In the US, additional information is also publicly available in the dissolution methods database (5) of FDA."

Further information can also be found on the physical operating conditions of the dissolution testers, confirms Clay, with guidelines covering dissolution testing for immediate release, delayed release, and extended release drug formulation types. "However, given the complexities of the human body, physiology, and chemical/biological interactions that take place, it can be difficult to solely rely on the dissolution test as a way of predicting how a drug formulation may perform *in-vivo*," she stresses. "The use of biorelevant media can aid such assessments, but there is no way of understanding how closely the dissolution test may predict *in-vivo* performance without performing clinical studies."

The European Medicines Agency (EMA) also provides guidelines on the investigation of bioequivalence, reveals Eckert. "These guidelines describe the use of dissolution studies to waive a bioequivalence study in applicable cases and the evaluation of similarity of dissolution profiles," she says. "The use of dissolution data in IVIVC approaches is also explained in EMA's guideline (6) on the pharmacokinetic and clinical evaluation of modified release dosage forms."

Because dissolution testing is fundamental for the assessment of the performance of oral formulations and is widely used around the world, much work has been done to create a globally uniform approach. The International Council for Harmonization (ICH) has worked with various pharmacopeias to harmonize many of the dissolution testing methodologies (specifically *USP* I and II Apparatus) so that they are standardized across many different regions, Clay iterates.

"Dissolution is a harmonized technique across many pharmacopeias in which dimensions of the equipment used and operating parameters are clearly defined and documented," Clay continues. "Thanks to this harmonization, successful transfer of validated dissolution methods from one laboratory to another is made to be relatively straightforward."

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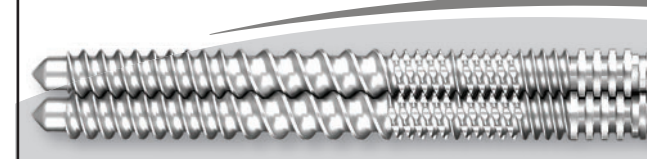

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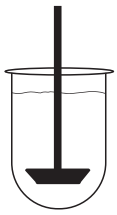

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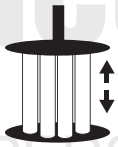

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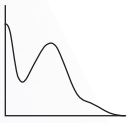

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The global market for injectable drug delivery is growing at a compound annual growth rate of 10.9% (1). A report from Future Market Insights attributes the anticipated growth rate to the rising prevalence of chronic diseases such as diabetes, cancer, and rheumatoid arthritis along with increasing demand for point-of-care devices where prefilled, needle-free injectors are most preferred (1).

Beyond self-dosing, other factors influencing market growth include shorter runs, sensitive products, and labor constraints, which are driving parenteral drug makers to streamline operations. Tactics include maximizing container quality and adoption of ready-to-fill technology. On the equipment side, robotics are assuming a bigger role as are integrated systems. Simulation expedites design and engineering on the front end and supports training, operation, and maintenance functions during and after installation. *Pharmaceutical Technology* reviews new technologies for parenteral packaging, including several displayed at INTERPHEX (April 2–4, 2019, Javits Center, New York, NY).

Hallie Forcinio is *Pharmaceutical Technology*'s Packaging Editor, editorhal@sbcglobal.net.

Container features

To address rising demand for ready-to-use (RTU) containers, DWK Life Sciences has developed the Workflow Solutions portfolio of glass and plastic containers, with Solutions Packs for research and for production (2). The Wheaton Complete Pak provides a complete kit of off-the-shelf, RTU packaging components for short runs. Contents include approximately 220 certified sterile and particulate- and endotoxin-free, crimp-top vials in one of three sizes (2, 5, or 10 mL), with seals in red or blue and a coated, uncoated, or lyo stopper. "We are planning an amber version and also planning a ModPak six-pack," says Jay Harkins, senior product manager at DWK Life Science.

For self-dosing, an on-body injector being developed by Nemera combines a disposable needle and drug container with a reusable element that contains the electronics and mechanics. "The device customizes infusion speed and depth of injection and communicates with a smartphone to track doses and provide reminders," says Lauren Mudrak, business development manager at Nemera.

Also under development, the S.A.F.E. Syringe Kit from Morimoto Pharma combines a vial filled with liquid, a pre-attached needle syringe filled with powder, and a compact tube-shaped container. Expected to be commercial in a few years, the design allows injection preparation to be performed inside a closed environment, thereby protecting caregivers from accidental needlesticks and exposure to the drug (3). Dissolving the drug powder inside of the syringe rather than the vial is quicker and ensures all the drug is injected (zero-loss). According to the company, this design also allows a syringe size that is significantly smaller than recent dual-chamber syringes, which makes it easy to administer and lessens patient needle phobia. Because the syringe is returned to the container immediately after administration and extra supplies are not needed, waste is reduced and disposal is safer.

Equipment innovations

Although traditional fill/finish equipment continues to be popular, robotic systems and machines that handle nested, RTU vials, syringes, and cartridges appear to be gaining ground, as they streamline operations by eliminating the need for a washer and depyrogenation tunnel.

New options for handling nested containers include the Dara NFL/2-RDL aseptic filling and closing machine from NJM, a ProMach product brand. De-

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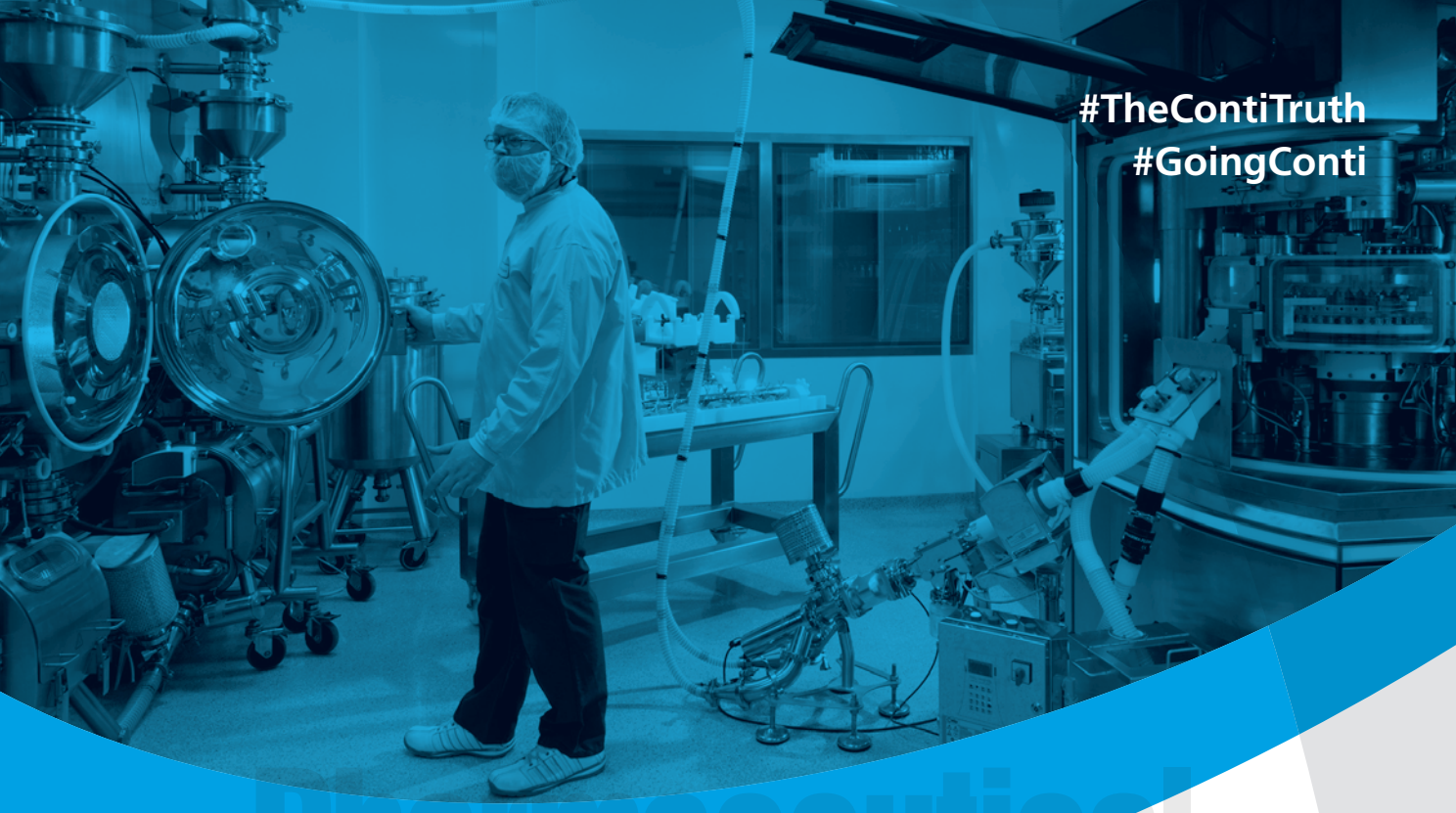

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Figure 1: The Flexicon FPC60 fill/finish machine from Watson-Marlow Fluid Technology Group uses a peristaltic pump and custom, precision tubing.

signed for RTU vials and the RayDyLyo cap, the machine handles nests of presterilized vials and eliminates the crimping required with traditional aluminum closures. The machine fills solutions, suspensions, diagnostics, or vaccines in glass or plastic vials in sizes ranging from 2R–50R with dose volumes from 0.1–50 mL and can be programmed for full stopper insertion for non-lyophilized products or half stopper insertion for lyophilized products. Developed for biotech companies and 503B pharmacies, the servo-driven system streamlines the packaging operation to reduce capital costs, minimize footprint, and speed changeover. Volume capabilities suit scale-up through small batch commercial manufacturing.

A highly configurable fill/finish system, the Flexicon FPC60 machine from Watson-Marlow Fluid Technology Group can be set up from outside the cleanroom via wi-fi or hard wiring and automatically adjusts for height and width for hands-free calibration (see **Figure 1**). "We want to remove the operator from the process as much as possible. Operators are the biggest source of contamination," explains Peter Lambert, filling division manager at Watson-Marlow Fluid Technology Group. Each operator also tends to set up the machine differently, so automating changeover eliminates that variability. Compatible with a traditional or single-use product path, the unit handles a range of containers, stoppers, and caps with a minimum of change parts. Designed to handle a range of vial sizes (0.2–100 mL) without change parts, the system outputs up to 45 vials/min. Vibrator bowls for stoppers (injection or lyo) and caps (flip-off or plain) are similarly flexible and capable of handling either 13-mm or 20-mm diameters.

A tabletop fill/seal system for low-volume needs, the EDM3611 from Bausch+Ströbel can be housed in a tent-like disposable isolator. A sterile connection provides air, carbon dioxide, nitrogen, or HEPA-filtered laminar flow. A touchscreen-equipped operator interface houses machine settings and provides 100% in-process control batch recording (4).

Robotics also minimize the need for operator intervention. The GENiSYS R filling and closing system from AST accommodates up to five robots in a compact footprint and minimizes moving parts. Designed to process small batches of presterilized, nested vials, syringes, or cartridges, the machine offers fast, tool-less changeover in less than 30 minutes. A high-definition, user-friendly human/machine interface holds recipes, step-by-step instructions, videos, and standard operating procedures and can eliminate paper documents. An in-process control system ensures accurate fills, minimizes waste, and maximizes product yield.

Decontamination systems

Decontamination systems work in conjunction with fill/finish systems. The Eziflow UV-C aseptic transfer from Ezidock sterilizes to log 6 within minutes using ultraviolet (UV)-C light to ensure that product or components transferring to the fill/finish machine are sterile.

Pulsed UV light treatment offers several advantages. Effective against all known microorganisms, including those that are chlorine resistant, the chemical-free process also can remove free chlorine and chloramines, break down ozone, and reduce total organic carbon without leaving any residue, odor, or coating on treated surfaces.

The Pulsed UV Light Chamber Type 411 from Bausch Advanced Technology Group mounts in the wall to serve as a pass-through to the cleanroom. When the door on the cleanroom side is closed, presterilized containers are placed in the chamber. The outer door is closed, and the pulsed-light decontamination cycle runs for approximately 30 seconds. When the cycle is complete, the inner door can be opened and the operator or a robotic arm removes the containers in preparation for the fill/finish process. The compact, easy-to-install system needs minimal maintenance and cleans quickly to minimize downtime. Energy costs are low (5).

The RTDS2 robotic tub decontamination system from Steriline also uses a pulsed UV light and is designed to decontaminate nests of RTU syringes, vials, or cartridges. The robotic arm ensures all tub surfaces are exposed to the lamp flashes. The system can operate as a standalone machine or be integrated with any RTU filling machine, particularly Steriline's robotic nest filling machine (6).

Virtual reality

As Industry 4.0 takes hold, simulation via virtual reality (VR) or augmented reality (AR) is assuming larger roles in machine design, engineering, construction, operation, and maintenance. VR offers an immersive experience in a fully simulated setting; AR overlays digital elements on a real-world environment.

Bausch & Ströbel is already using AR and VR technologies. VR is helping its design teams fix problems in the development phase before machine construction begins. Using VR, the design team can reduce turbulence and areas of low velocities, avoid cross-flows above containers, and show static pressure and upward flow to optimize air-flow and ensure the cleanest possible environment for filling. VR also can help check ergonomic features, such as reachability for machine access by short or tall operators. "VR allows earlier decision making and helps determine if adaptations are needed," explains Florian Naser, an engineer in the Data Processing Organization, Systems Product Creation, Applications at Bausch & Ströbel.

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AST's line of table-top machines includes a Container Filling System, Container Closing System, and Vial Sealing System. Each machine is designed to minimize risk in aseptic processing by automating the critical aseptic operations for vial, syringe and cartridge processing. They can be installed on the bench of a biosafety cabinet or LAF, or integrated with a full isolator. GENiSYS Lab systems are simple to use, and offer a perfect balance between automated features, size, and affordability.

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VR can be used to train operators before the machine is installed and whenever new hires come onboard. There are several advantages. VR training doesn't tie up the machine, and all operators are trained the same way. VR can also support maintenance because it can ensure that the proper spare parts are on hand and help optimize machine modifications.

AR also can assist with machine troubleshooting by highlighting the problem area on a tablet computer that is brought to the machine. AR can identify the correct part and part number, zoom in, offer different views, present the virtual view next to the actual machine, and provide visual instructions for the operator or maintenance person, eliminating the need to search through paper-based standard operating procedures. "Nothing is forgotten or out of sequence, and the program is easily edited if changes are needed," says Naser.

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BEST PRACTICES IN PACKAGING AND TRACKING RAW MATERIALS IN BIOPHARMA MANUFACTURING

Raw material tracking is a crucial component of making a quality product efficiently. Supply-chain visibility and documenting that raw materials meet quality specifications are both important.

"Maintaining consistent, high quality in both the supply chain for materials and in the end products themselves are two major challenges in raw materials management for biopharmaceutical manufacturers," says Dr. Nandu Deorkar, vice-president, Technology & Innovation at Avantor.

Best practices

Understanding the supply chain is crucial. "Long lead times can be a challenge for certain raw materials," notes Deorkar. "It is important for manufacturers to work with their suppliers to understand their outlook and foster investments to increase critical capacities worldwide. Additionally, managing the correct methods for packaging and process efficiencies is also critical for handling materials, reducing demands on storage at facilities, and reducing the capital expenditures required at new facilities."

Avantor has implemented flexible packaging sizes using modular packaging systems to help its biopharmaceutical manufacturing customers. Preweighed materials in ready-to-use packaging allow companies to reduce storage of bulk or hydrated buffers as well as reducing testing and material handling processes.

Deorkar notes that another best practice is transparency for the supply chain and for management of change procedures for materials made under current good manufacturing practice (CGMP). Adoption of electronic data systems enables this practice.

Electronic data

Although the bio/pharma industry has traditionally used paper-based tracking systems, leading manufacturers are transitioning to electronic systems, which offer significant benefits for efficiency and quality, as part of digitalization efforts.

"It's important to have full supply-chain visibility and management of change across the entire supply chain during the manufacturing process, and this is where data [are] coming in to help," agrees Claudia Berron, senior vice-president, Biopharma Production at Avantor. "The new frontier of biopharma is being driven by e-data: the electronic delivery of critical documents related to the material, with full tracking capabilities by package and by pallet. As the industry is adopting this technology, it is benefiting from the experience of other industries that are more advanced in this space."

"Paper-based documentation can be problematic when tracking and managing materials through the production process," explains Richard Soltero, president of InstantGMP, which offers software for GMP manufacturing. "In a paper-based system with different information kept in different locations, people can find themselves spending valuable time verifying material status and inventory levels or tracking down the right person. Manufacturers can avoid these problems by transitioning to a cloud-based inventory software that automates material tracking, inventory levels, material statuses, purchase orders, and staging materials for production."

Using inventory management software enables automation of material receiving and specifications, says Soltero. Automation eliminates human errors and helps to remove poor-quality materials before they enter inventory, and it can be used to maintain inventory history in real-time. "In InstantGMP's inventory software, each material has a unique profile and a system-generated receipt number that comes with a barcode label to check materials throughout the production process," explains Soltero. "The real-time status update alerts personnel that material is ready for use, where it is, how much is available, from what vendor, and what the vendor lots are. Every use of inventory or change appears within that material's inventory record."

A new software feature for material resource planning includes the ability to make a picklist. "Through the picklist, manufacturers can start allocating materials for production, setting materials aside to prevent confusion, verifying stock level and material status, preventing double counts, and performing additional quality reviews. Picklists can be used for bridging the tracking gap in assembling kits and for those that want to take advantage of traceability within the software but want to connect data to their legacy system," says Soltero. The software is designed to work in tandem with other systems, including paper-based systems, to help companies that are transitioning to electronic systems.

—Jennifer Markarian

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Lessons from FDA 483s and cGMP Inspection Data

Ajay Babu Pazhayattil, Marzena Ingram, and Naheed Sayeed

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Production and process controls, organization and personnel were the top problems found, while packaging and labeling citations increased in 2017 and 2018.

To provide insight into regulatory trends and factors contributing to noncompliance, the authors analyzed data from Form 483 observations issued by FDA during routine investigations of finished drug and API manufacturing sites between 2014 and 2018. The goal was to provide pharmaceutical quality compliance professionals, managers, and operators with insights into how they can best strengthen compliance and develop appropriate solutions for key regulatory compliance issues. This article summarizes results of the study.

Ajay Pazhayattil is a management consultant (ajpazha@gmail.com). **Marzena Ingram** is senior manager, quality and compliance at Eurofins CDMO. **Naheed Sayeed** is deputy director, validation services at Sanofi.

To review the basics, form 483s are issued by FDA's Office of Regulatory Affairs (ORA), which is responsible for field activities such as site inspections and enforcement (1). ORA inspectors issue Form 483 observations when they find current good manufacturing practice (cGMP) violations during a facility inspection. These observations are then presented to the company's senior managers to notify them of the need to correct compliance deficiencies.

Inspection observations are crucial, because they define the site's state of compliance. Companies that receive 483s are expected to ensure that steps are taken to correct problems and address the observations and any auxiliary systems that are also deficient but not cited. The final establishment inspection report (EIR) then determines the resulting regulatory actions, considering the observations, proposed corrective measures, and evidence collected.

Three different types of observation classifications (2) are possible:

- No Action Indicated (NAI) indicates that no objectionable conditions were found during inspection and that no further regulatory action required.
- Voluntary Action Indicated (VAI) shows that objectionable conditions were found, but the agency is not yet willing to take any regulatory action.
- Official Action Indicated (OAI) shows that ORA will recommend specific actions.

This study used data from FDA's Inspection Classification Database, which was established in 2009 as part of a transparency initiative (3). The analysis used data classified as final, which is updated by FDA and posted on the agency's website each month. Any undisclosed inspections are not captured in the list. The inspectional observation data set files for years 2014, 2015, 2016, 2017, and 2018 provided the full list of audit observations. For instance, the 2014 list of inspectional observations included inspections that ended between Oct. 1, 2013 and Sept. 30, 2014.

FDA recorded a total of 2997 audit observations in 2014, including 645 Form 483s issued for finished formulation and API sites, which, in turn, were classified into nine categories (4):

- Subpart B, organization and personnel
- Subpart C, buildings and facilities
- Subpart D, equipment
- Subpart E, control of components and drug product containers and closures
- Subpart F, production and process controls
- Subpart G, packaging and labeling control
- Subpart H, holding and distribution
- Subpart I, laboratory controls
- Subpart J, records and reports.

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The inspection classification database detailed the number of official and voluntary actions (OAIs and VAIs), whether at US manufacturing sites or at sites outside of the United States.

The authors used the Pearson correlation coefficient to identify any positive correlation between the variables, where positive correlation indicates that as the values of one variable increase the values of the other variable increase (5).

cGMP observations provide quality professionals, managers, and operators with insights into how best to strengthen compliance.

Figure 1: Final classified form 483 observations, final drug product and API.

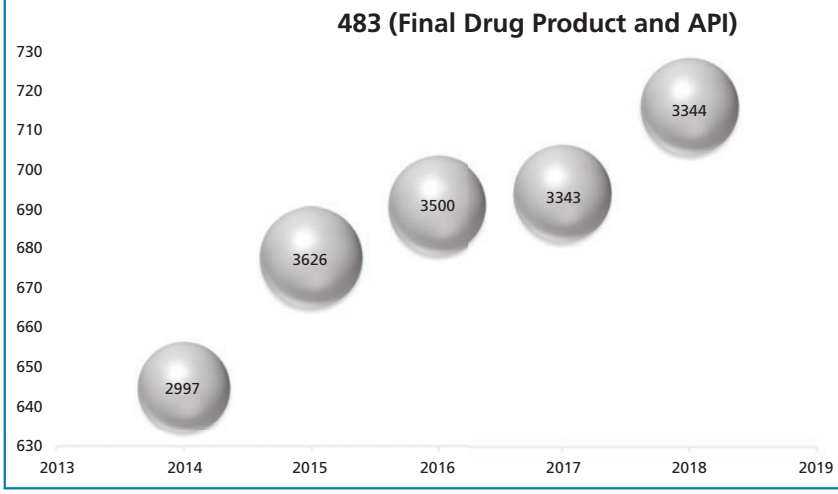

Table I: 483 observations, final drug product and API 2014–2018

Year	483 (Drug)	Observations
2014	645	2997
2015	678	3626
2016	691	3500
2017	694	3343
2018	716	3344
Total	3424	16810

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Results and discussion

Between 2014 and 2018, the total number of FDA Form 483 audit observations was found to range from 2997 to 3626, with an average of 3362 observations per year. The agency issued a total of 3424 Form 483s, an average of 685 per year. However, 716 483s were issued in 2018, a higher number than seen in previous years (**Figure 1** and **Table I**).

Figure 2 and **Table II** summarize the nine categories of inspection observations and associated subsections.

The data provide a clear indication that most 483 observations were related to Subpart I–laboratory controls, which accounted for 2603 observations, and Subpart J–records and reports, with 2530 observations. The other top contributors were Subpart F–production and process controls (with 2088 observations), Subpart B–organization and personnel (with 1902 observations), and Subpart D–equipment (with 1621 observations).

Figure 2: Number of observations by good manufacturing practice (GMP) subsections.

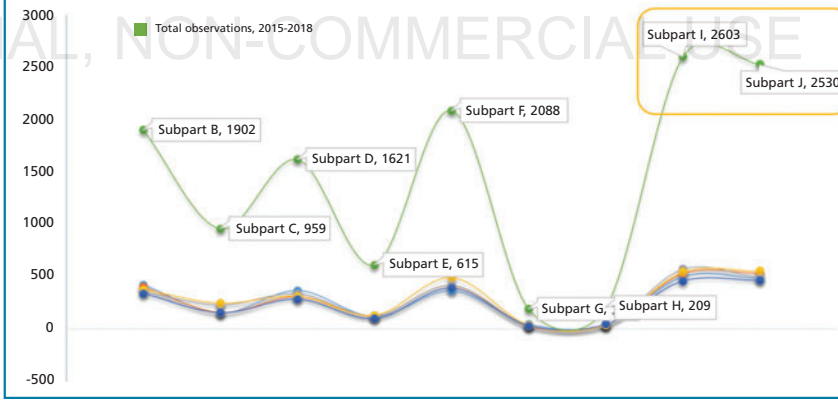

Figure 3 illustrates the percentage changes in the identified observation categories. The most relevant fluctuations would be the increase in FDA observations for packaging and labeling control (Subpart G) in 2017 and 2018. Also noteworthy is the spike in equipment (Subpart D) observations, which went from 311 to 370 between 2017 and 2018. However, laboratory control observations decreased during the same period, which may reflect the implementation of improved system and data integrity laboratory controls.

VAI and OAI trends

VAI and OAI are critical for companies, because they indicate non-compliance and the need for critical actions, which may have implications for product quality and supply. Data showed that there has been a consistent reduction

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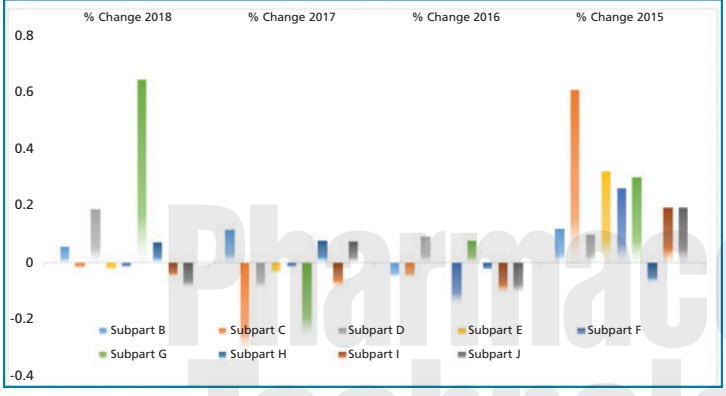
Table II: 483 observations, final drug product and API 2014-2018.

Subpart	Subpart B	Subpart C	Subpart D	Subpart E	Subpart F	Subpart G	Subpart H	Subpart I	Subpart J
2018	424	158	370	124	367	51	45	501	485
2017	401	161	311	127	415	31	42	526	532
2016	359	236	342	132	422	42	39	575	495
2015	379	249	313	132	493	39	40	544	554
2014	339	155	285	100	391	30	43	457	464
Total	**1902**	**959**	**1621**	**615**	**2088**	**193**	**209**	**2603**	**2530**

Figure 3: Change of observation types, year over year (in percentages).



in the issuance of VAI and OAI since 2017, suggesting a higher rate of compliance with regulatory guidance requirements,as found during inspections.

The finished formulation and API site inspection trend (**Figure 4**) indicates a declining domestic inspections trend; however, there was no corresponding increase in foreign site inspections, which may reflect the fact that FDA has adopted a risk-based inspection management process. The data were also analyzed to determine whether there were any correlations between the variables: number of VAI/OAI, number of domestic inspections, and number of foreign inspections.

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Figure 4: Voluntary Action Indicated (VAI), Official Action Indicated (OAI) and domestic, foreign inspections of finished formulation and API sites.

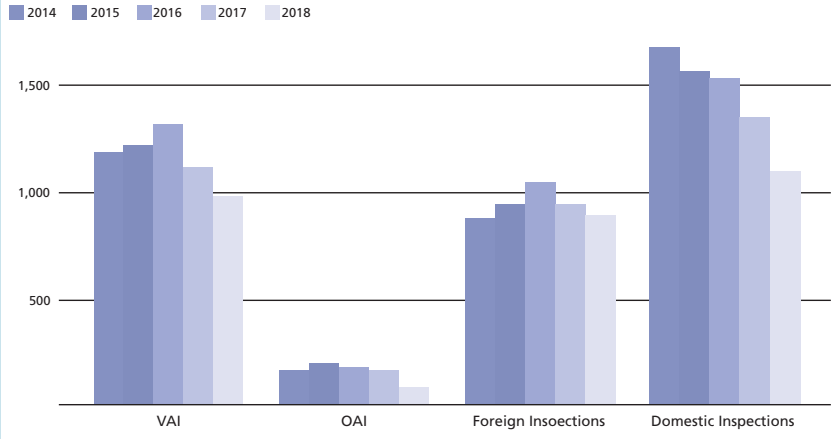

Figure 5a: Pearson correlation coefficient.

X Values	Y Values
1117	1117
1362	1362
1545	1545
1581	1581
1690	1690

Figure 5b: Result details and calculation.

X Values	Y Values	X and Y Combined	R Calculation
Σ = 7295 Mean = 1459 Σ(X - Mx)2 = SSx = 202014	Σ = 6758 Mean = 1351.6 Σ(Y - My)2 = SSy = 117347.2	N = 5 Σ(X - Mx)(Y - My) = 145385	r = Σ((X - My)(Y - Mx)) / √((SSx)(SSy)) r = 145385 / √((202014)(117347.2)) = 0.9443

Based on the Pearson correlation coefficient calculation of X values (domestic inspections) and Y values (number of VAI/OAI), the value of R is 0.9443, suggesting a strong positive correlation between X and Y variables. The p-value is 0.015648, hence statistically significant (<0.05). The correlation was not seen when VAI/OAI numbers were compared with foreign inspection trend. It can be, therefore, concluded that there is a higher tendency to generate VAI/OAI observations if the domestic inspection rate increases.

The Pearson Correlation Coefficient for individual GMP observations associated with the nine subparts (B through J) were analyzed for 2014 through 2018 (**Figure 5 a** and **b**). A positive correlation could be ascertained across laboratory control observations (Subpart I) and records and reports (Subpart J). This may suggest that increased regulatory scrutiny of laboratory controls may have resulted in improved good documentation practices, because there appeared to be an improvement in records and reports observations as well. A summary of statistics is found in **Figure 6**.

Although additional analysis might be required to confirm the correlation, it is safe to assume that laboratory data integrity-based inspection assessment extends from GMP sections Subpart J to Subpart I. As an inspection readiness strategy, organizations should provide equal weight to laboratory electronic controls, procedures, specifications, and methods as well as to data access and integrity (6), and to the storage of raw data and reports, whether electronic or paper.

Increased regulatory scrutiny may have resulted in improved good documentation practices.

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Conclusion

Analysis of FDA Form 483 observations issued from 2014 to 2018 revealed that the number of 483 forms issued has increased during this time period, while the number of observations has declined. The number of VAI and OAI observations issued has also fallen since 2017.

Over this period, there has been a decrease in domestic inspections, and a positive correlation was found between the number of domestic inspections conducted and the number of VAI/OAI observations issued. The highest number of observations were related to Subpart I–laboratory controls and Subpart J–records and reports, Subpart F–production and process controls, Subpart B–organization and personnel, and Subpart D–equipment.

Increased inspection of laboratory controls (Subpart I) may also result in

Figure 6: Summary statistics.

Subpart B–Organization and Personnel		*Subpart C–Buildings and Facilities*		*Subpart D–Equipment*		*Subpart E–Control of Components and Drug Product Containers and Closures*	
21 CFR 221.22-34		21 CFR 221.42-58		21 CFR 221.63-72		21 CFR 221.80-94	
Mean	380.4	Mean	191.8	Mean	324.2	Mean	123
Standard Error	14.99867	Standard Error	20.82162	Standard Error	14.57875	Standard Error	5.949789912
Median	379	Median	161	Median	313	Median	127
Standard Deviation	33.53804	Standard Deviation	46.55857	Standard Deviation	32.59908	Standard Deviation	13.3041347
Sample Variance	1124.8	Sample Variance	2167.7	Sample Variance	1062.7	Sample Variance	177
Kurtosis	-1.14213	Kurtosis	-3.06251	Kurtosis	-0.35406	Kurtosis	3.699224361
Skewness	0.119981	Skewness	0.643347	Skewness	0.454282	Skewness	-1.883361658
Range	85	Range	94	Range	85	Range	32
Minimum	339	Minimum	155	Minimum	285	Minimum	100
Maximum	424	Maximum	249	Maximum	370	Maximum	132
Sum	1902	Sum	959	Sum	1621	Sum	615

Subpart F–Production and Process Controls		*Subpart G–Packaging and Labeling Control*		*Subpart H–Holding and Distribution*		*Subpart I–Laboratory Controls*		*Subpart J–Records and Reports*	
21 CFR 221.100-115		21 CFR 221.122-137		21 CFR 221.142-150		21 CFR 211.160-176		21 CFR 211. 180-198	
Mean	417.6	Mean	38.6	Mean	41.8	Mean	520.6	Mean	506
Standard Error	21.18868	Standard Error	3.854867	Standard Error	1.067708	Standard Error	19.95645259	Standard Error	16.28803
Median	415	Median	39	Median	42	Median	526	Median	495
Standard Deviation	47.37932	Standard Deviation	8.619745	Standard Deviation	2.387467	Standard Deviation	44.62398458	Standard Deviation	36.42115
Sample Variance	2244.8	Sample Variance	74.3	Sample Variance	5.7	Sample Variance	1991.3	Sample Variance	1326.5
Kurtosis	1.767949	Kurtosis	-0.62246	Kurtosis	-1.11727	Kurtosis	0.059894877	Kurtosis	-1.54527
Skewness	1.098318	Skewness	0.566635	Skewness	0.205753	Skewness	-0.425902662	Skewness	0.375057
Range	126	Range	21	Range	6	Range	118	Range	90
Minimum	367	Minimum	30	Minimum	39	Minimum	457	Minimum	464
Maximum	493	Maximum	51	Maximum	45	Maximum	575	Maximum	554
Sum	2088	Sum	193	Sum	209	Sum	2603	Sum	2530

increased good document practices, records and reports observations (Subpart J) based on the positive correlation observed. It is also noteworthy that there was an increase in packaging and labeling control (Subpart G) observations in 2018.

Note: This article was prepared by the authors in their personal capacities. The opinions expressed are the authors' own and do not reflect the view of their employer, government, or any agency with which they are affiliated.

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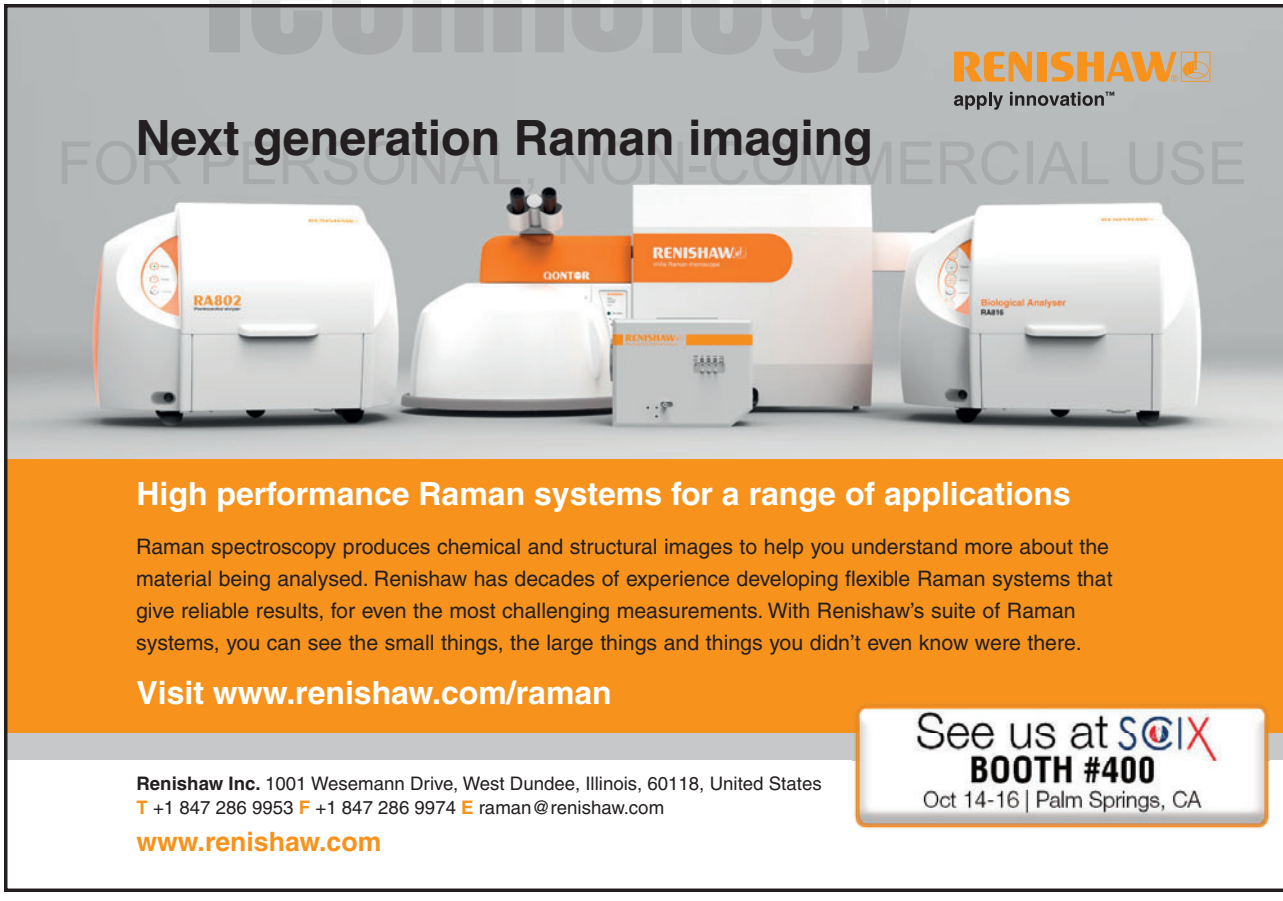

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Distribution of Data: The Central Limit Theorem

Chris Burgess

Using the central limit theorem concerning the distribution of means allows one to justify the assumption of the normal distribution.

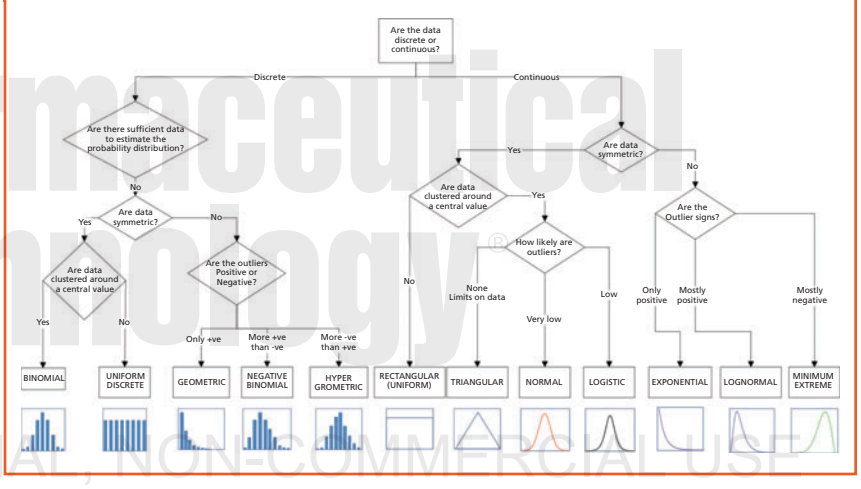
Analytical people tend not to worry too much about the nature of the distribution of their data. Statisticians, on the other hand do worry. Some 10 years ago, Rebecca Elliott, a senior statistician with Eli Lilly, gave an excellent presentation on some ways users drive statisticians crazy (1). This column is about just one method to prevent that happening, as we do need statisticians occasionally.

The central limit theorem (CLT)—actually theorems as there are more than one—is at the heart of much statistical methodology. The CLT is a lifesaver for analytical data, be it continuous or discrete. The good news is that the part that must be understood is very simple. The really good news is that if the CLT did not exist, many familiar statistical methods would not be valid. The first lesson for analytical people to learn is that, from a statistical point of view, there is a world of difference between individual or replicate data from a sample and means of those data.

It is visually apparent, therefore, that to use methods based on the assumption of normality would be invalid in many instances. Fortunately, the CLT comes to our aid.

It is the mathematical model (shape) of data population which determines the applicability (suitability) of the statistical methodology. A summary of some commonly met distributions are shown in **Figure 1** (2).

Figure 1: Some data distributions for continuous and discrete data (adapted from reference 2).



Central limit theorem (CLT)

The simple part of the CLT is that for any sample of N independent determinations, the means of n values tend to a normal distribution irrespective of the underlying population distribution. In addition, the overall or grand mean tends to the population mean. Note that the bigger n is, the more this is true. Unlikely though this seems, some calculations can be performed in Microsoft Excel to demonstrate this property. This is not well described in books on statistics, but *Basic Statistics and Pharmaceutical Statistical Applications* does describe this well, albeit somewhat hidden away in the 800 pages (3). The following is one way to visualize the value of the CLT.

Let us consider a small data set of 15 integer numbers far away from a normal distribution, namely 8,8,8,9, 9,9,10,10,10,11,11,11,12,12,12, which are shown as a histogram in **Figure 2**.

Let us take the decision that n is to be two and we know that there will be 105 means of two combinations of these 15 numbers. In Excel, this would be calculated using the combination formula;=COMBIN(15,2). Sadly, there is no function currently

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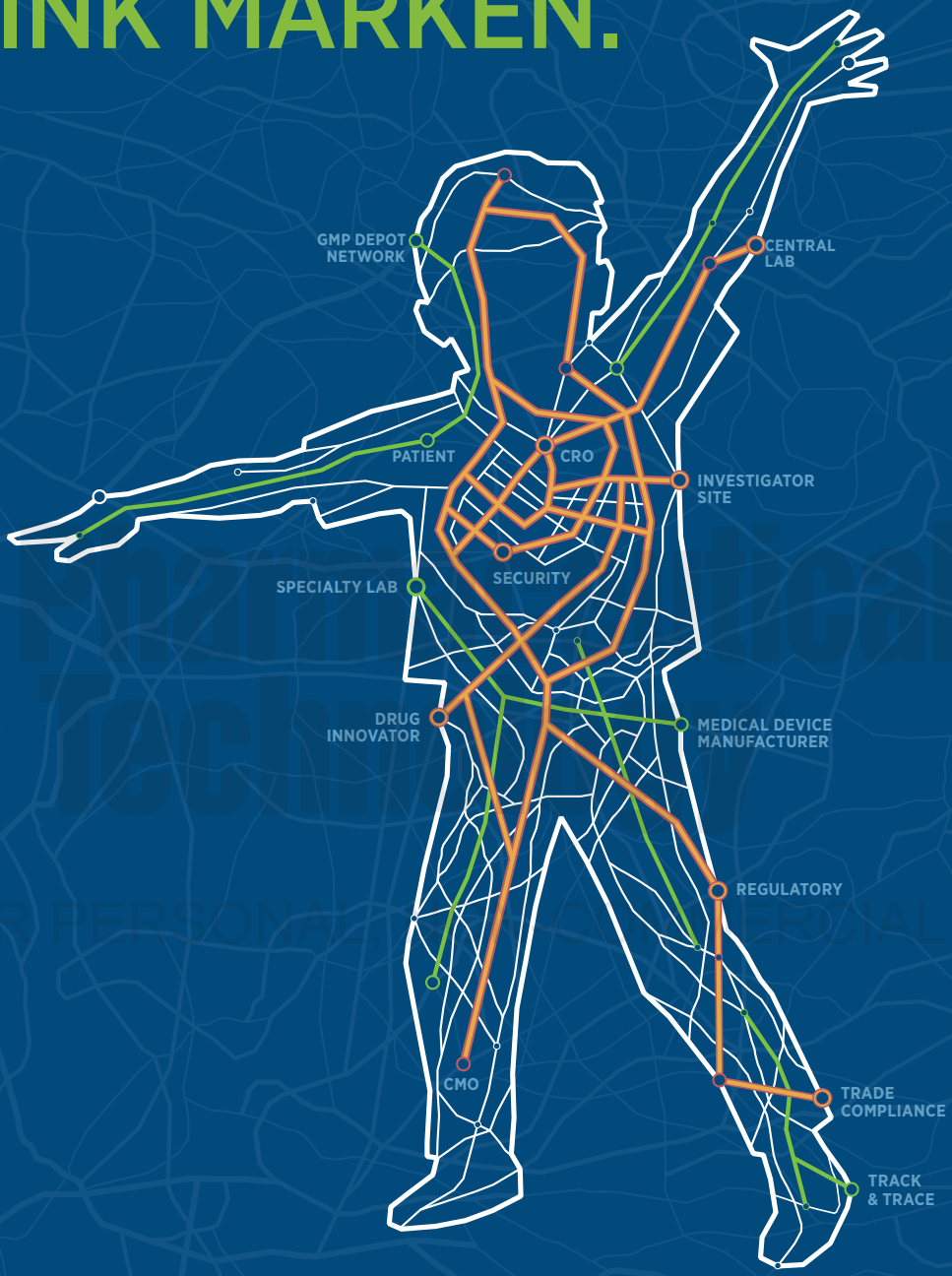

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Figure 2: Histogram of the rectangular distribution of the 15 numbers in our data set.

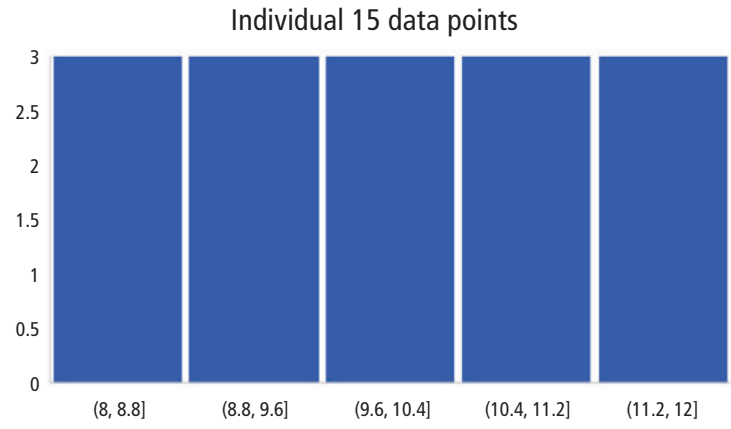


Figure 3: Histogram for the 105 means for n=2.

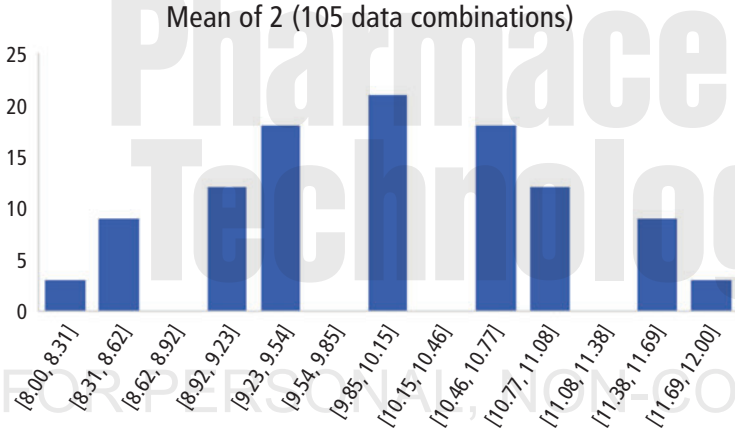
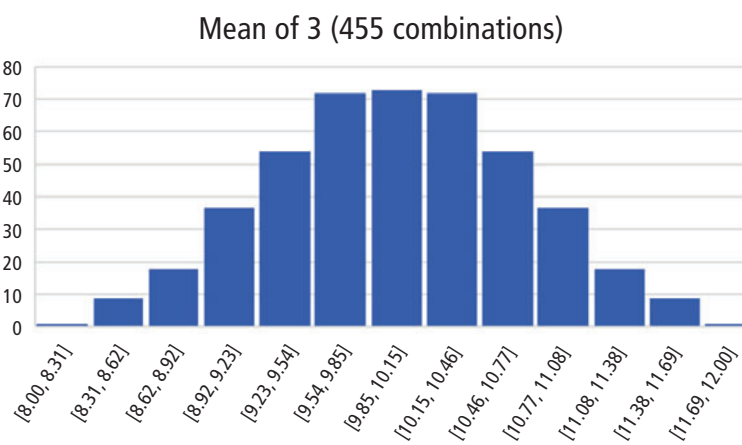


Figure 4: Histogram for the 455 means for n=3.



in Excel to list all of these 105 combinations, but fortunately there is a macro available on the Internet to do just that (4). Once you have these combinations listed, then you can calculate the means. The result is shown in **Figure 3**.

Looking good so far; so what about n=3? In Excel, this is calculated from the formula =COMBIN(15,3), which gives 455 combinations. Modifying the macro works well and generates the 455 combinations listing. We proceed as before by calculating the means of 3 resulting in the histogram shown in **Figure 4**.

The approximation to the normal distribution becomes even more apparent. The normal approximation becomes good when n is in the region of 25 to 30. This was demonstrated in an earlier column using the t distribution (5). This particular calculation cannot be performed in Excel because if one used N=50 data points and n=30, one would have 47,129,212,243,960 combinations, which would take, at one calculated mean per second, just under 1.5 million years to achieve even if Excel allowed that many rows.

Conclusion

The central limit theorem concerning the distribution of means allows one to justify the assumption of the normal distribution so that we can use many of the statistical formulae that require normality on our datasets. As long as mean and individual data are clearly differentiated, we will help our statistician colleagues remain sane.

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A Q&A

N-1 Bioreactor Perfusion Capability

Kenneth Green, PhD
Cell Culture Manufacturing Operations
Samsung Biologics

Perfusion can boost productivity for large-scale commercial applications.

Perfusion is gaining broader biopharmaceutical application at small scale with clinical development, but few companies have reported utilization at large scale for commercial applications to intensify bioprocessing and boost productivity.

Samsung Biologics recently added N-1 bioreactor alternating tangential flow (ATF) perfusion, which enhances bioreactor capabilities and service provision to clients, enabling process intensification to achieve high cell culture densities (up to 10-fold) and product titers. In fact, Samsung Biologics successfully performed N-1 (3,000-L) perfusion with ATF to supply the 15,000-L commercial production process in the Plant 3 facility at its manufacturing site in Songdo, South Korea. The use of ATF perfusion reduced production time by up to 30%.

Pharmaceutical Technology recently spoke with Kenneth Green, PhD, at Samsung Biologics to learn more about how ATF perfusion improves productivity and reduces production time.

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Pharmaceutical Technology: Can you explain what perfusion bioreactor culture is?

Green: Perfusion is a continuous bioreactor production mode that allows for fresh growth medium to be supplied to the mammalian cell culture while removing waste medium and metabolites. Cells are retained in a perfusion device and then returned to the bioreactor. The fresh growth medium provides the required sugars and nutrients to sustain cell growth over extended periods and reach much higher cell densities (up to ten-fold) when compared with a traditional batch operation.

Pharmaceutical Technology: What is alternating tangential filtration or ATF?

Green: ATF is perfusion technology that utilizes hollowed fiber filters to retain cells while suspended culture medium is filtered out into waste. The cells are then returned to the bioreactor by alternating the flow such that the cells are continuously withdrawn and returned to the bioreactor with the alternating flow achieved by use of a diaphragm pump. Fresh growth medium is then continuously added to the bioreactor to replace the spent medium at the same rate. The fresh medium allows for continuous cell growth and high cell densities. During perfusion mode bioreactor controls—such as volume, temperature, dissolved oxygen, and pH—are all kept constant.

Pharmaceutical Technology: How is ATF different from other perfusion technologies?

Green: The ATF system differs from other perfusion technologies with the application of hollow fiber filters and alternating

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flow as opposed to Tangential Flow Filtration (TFF) or centrifugation. ATF provides a low-shear environment such that cell viability is maintained during the perfusion process. In addition, the ATF system is operationally robust and scalable with different ATF units available from development to production scale.

Pharmaceutical Technology: What then are the benefits of ATF?

Green: ATF can be applied at the production bioreactor stage or also at the seed stage, what we call the N-1. By working at the N-1 stage, high cell densities can be achieved, thus allowing the following bioreactor production stage to be seeded at high cell densities. This shortens their production cycle as cell growth is accelerated, and reaches peak cell density and protein production much earlier than traditional fed batch production. This also results in higher protein titers in the overall product yield.

> "The ATF system differs from other perfusion technologies with the application of hollow fiber filters and alternating flow as opposed to Tangential Flow Filtration or centrifugation."

Pharmaceutical Technology: What are the process considerations?

Green: There are several process and scale considerations when applying perfusion for cell culture. First, the cells must be stable for extended cell generations with a retention of protein expression. Second, the cell line must exhibit sufficient robustness with regard to shear stress or sensitivity to the micro-environment. Cells are continuously removed, retained, and returned to the bioreactor, which is operated under controlled conditions. Controlled perfusion also requires extensive process development and characterization to determine perfusion rates to achieve optimal growth and production. The ATF perfusion system is available with different filtration areas and configurations to allow for predictable scale up from the lab to commercial levels.

Pharmaceutical Technology: What are the manufacturing considerations?

Green: With large-scale commercial manufacturing, the criteria for introducing new technologies such as perfusion is to ensure that a system is fully compliant with cGMP operations and also can be operated reliably within specified process controls. At Samsung Biologics, the ATF system was carefully designed with consultation and support from the vendor.

With the ATF system deployed at SBL, we use a stainless-steel filter housings and validations were completed within a six-month period. This included extensive autoclave cycle development and sterility performance testing. In addition, we conducted ATF system water and media tests to fully qualify the operational controls and provide assurance for closed-system integrity and sterility. Perfusion cultivation has also been developed in full automation mode by integrating the ATF system with bioreactor control logic so that manual intervention is reduced to a minimum during the cultivation duration.

Pharmaceutical Technology: Is this technology appropriate for single-use devices, too?

Green: Yes, ATF is applicable to single-use bioreactors and the ATF system can also be supplied in a single-use format. Single-use ATF can help to reduce implementation time as autoclave cycle development and validation are not required.

Pharmaceutical Technology: Can you provide some details about the N-1 perfusion commercial applications?

Green: N-1 perfusion is gaining broader biopharmaceutical application at small scale with clinical development however few companies have reported utilization at large scale for commercial applications to intensify bioprocessing and boost productivity. With increasing pressure on maximizing productivity and reducing costs, I expect broader utilization of N-1 perfusion for future commercial products.

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ALCOA+ and Data Integrity

Data supporting the quality and safety of product must meet the ALCOA+ elements in order to avoid regulatory citations for data integrity issues, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am familiar with the term ALCOA as it relates to data integrity, but lately, I have heard people refer to ALCOA+. Can you explain what impact this new acronym has on my company's data integrity program?

A. ALCOA requires data be attributable, legible, contemporaneous, original, and accurate. ALCOA+ adds the concepts that data also need to be complete, consistent, enduring, and available. It is important to understand what each element of ALCOA and ALCOA+ mean in order to apply the concepts to a company's records. The following are definitions, paraphrased from the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (1):

- Attributable: The data generated or collected must be traceable back to the individual who generated the information.
- Legible: The data recorded must be readable and permanent.
- Contemporaneous: The results, measurements, etc. must be recorded at the time the work is performed.
- Original: Original or source data are the record, report, notebook etc. where the data point was initially recorded.
- Accurate: The data recorded must be complete, consistent, truthful, and representative of facts.
- Complete: Information that is critical to recreating and understanding an event. This would include any repeat or reanalysis performed on a laboratory test sample.
- Consistent: The data are presented, recorded, dated, or time-stamped in the expected and defined sequence.
- Enduring: The data or information must be maintained, intact, and accessible throughout their defined retention period.
- Available: The data or information must be able to be accessed at any time during the defined retention period.

Data integrity has always concerned regulatory authorities, but it is important to understand what is prompting the renewed discussion of ALCOA and the introduction of ALCOA+. Many of the concepts for ALCOA have been captured in the regulations as far back as 1978. Since that time, the industry has changed dramatically. The generic-drug industry has grown and in the United States alone accounts for more than 80% of the prescriptions written today (2). Coupled with the emergence of biosimilars, virtual companies, contract manufacturing organizations, rapid advances in automation and information technology, and the globalization of the industry have resulted in reinterpretation of the attributes associated with maintaining the integrity of data throughout the product lifecycle, whether those data are generated from electronic, paper-based, or hybrid systems. In addition, there has been an increase in citations internationally by the FDA, European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA), World Health Organization (WHO), and other health authorities. These changes and increased violations have brought about a need to reeducate the industry on the concepts of proper data control.

The ALCOA acronym has been used since the 1990s; however, the requirements governing data elements have been in regulations for a much longer period of time. *EudraLex* chapter 4 states, "Suitable controls should be implemented to ensure the accuracy, integrity, availability, and legibility of documents. Instruction documents should be free from errors and available in writing" (3). The US *Code of Federal Regulations (CFR)* refers to these elements in various sections of the regulations (4–8). An example for language speaking to the element of attributable is in 21 *CFR* 211.194(a)(7), which states, "The initials or signature of the person who performs each test and the date(s) the tests were performed." Language in 21 *CFR* 58.130 (e) addresses the elements of contemporaneous and legible by stating, "All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data."

Documents issued by WHO (9) and PIC/S (1) have added to the original ALCOA attributes. The PIC/S document actually states, "Some key concepts of GDocPs are summarized by the acronym ALCOA: Attributable, Legible, Contemporaneous, Original, and Accurate. The following attributes can be added to the list: Complete, Consistent, Enduring, and Available. Together, these expectations ensure that events are properly documented and the data can be used to support informed decisions." WHO refers to ALCOA+ in the title of Appendix 1 to their 2018 document. The last two documents also address the concept of quality culture (10). The impact to your organization is that the quality culture must ensure that data supporting the quality and safety of your product must now meet the ALCOA+ elements in order to avoid regulatory citations for data integrity issues.

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4. 21 *CFR* 11: Electronic Records; Electronic Signatures
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8. 21 *CFR* 820: Quality System Regulation
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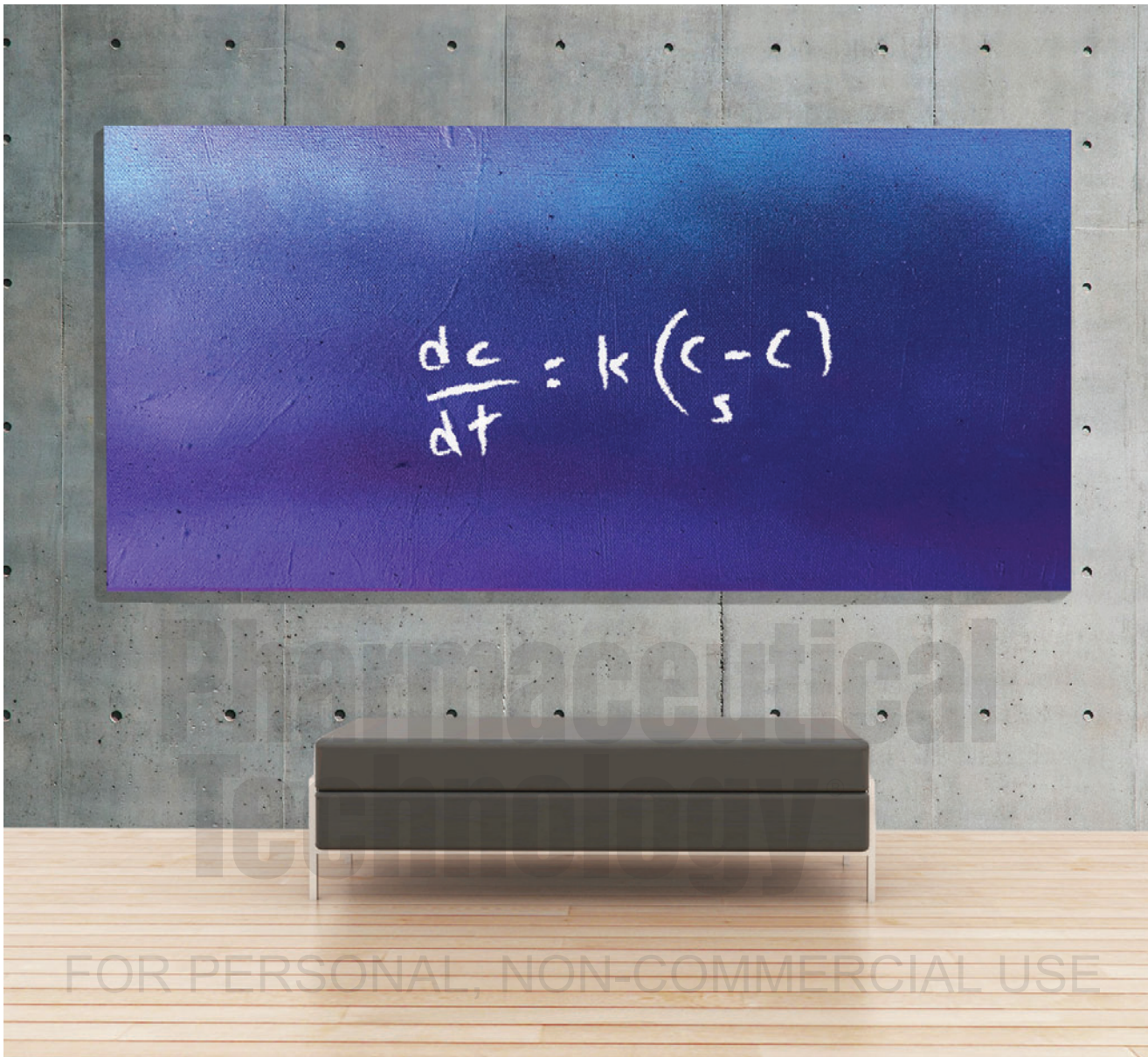

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