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Biopharmaceutical Trends Report

ADVANSTAR PHARMACEUTICAL

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BioPharm INTERNATIONAL
The Science & Business of Biopharmaceuticals

Contents

Biopharmaceutical Trends Report

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Inside the National Institutes of Health

FRANCIS S. COLLINS

Francis S. Collins, director of the National Institutes of Health, talks about the institutes' global partnerships, innovation strategies, small-business funding, and plans for personalized medicine.

INTERVIEW BY ANGIE DRAKULICH

Editor's Note: The following is an excerpted transcript of an interview that took place in June 2011 between Francis S. Collins, director of the National Institutes of Health (NIH), and *BioPharm International*'s Senior Managing Editor Angie Drakulich, in preparation for the Biotechnology Industry Organization's (BIO) annual convention and Partnering for Global Health Forum, which was cosponsored by BioVentures for Global Health. Dr. Collins is noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project. The full recorded interview can be listened to at BioPharmInternational.com.multimedia.

GLOBAL HEALTH PARTNERSHIPS

BioPharm: Since you became director of NIH in 2009, you made it clear that you wanted to make global health a top priority. Could you summarize the role you saw then for NIH in global health and whether you feel that major strides have been made thus far?

Collins: Yes, in figuring out what were the themes that offered the greatest opportunity for progress in term of NIH research, I spent a lot of time speaking with experts, seeking advice, and trying to identify areas that would fit as being exceptional opportunities. Global health clearly emerged as one of them and certainly resonated with my own desires to see advances in medical research benefit not only people in high income countries but also throughout the world.

I do think, scientifically, the arguments are pretty compelling that this is a unique time for assisting that process through NIH research. After all, we're making discoveries about the nature of pathogens that cause infectious diseases, that suggest new ideas about vaccines and therapeutics. And I think we have increasing abilities also to look at noncommunicable diseases in new ways and try to interrupt what otherwise is going to be a cycle in which those cause an increasing amount of morbidity and mortality throughout the world.

When I came to this position in August 2009, I convened almost right away a major gathering of organizations that fund global health research to try to get a better handle on who's doing what and where the gaps might be. And that was quite instructive because there are a lot of players doing a lot of interesting things, and it's not trivial to figure out exactly where the opportunities lie.

There are two projects that have come out of that discussion that are now underway and that ... I think are going to be interesting. One of those is what's called the Medical Education Partnership Initiative [MEPI], which is now funding academic institutions in 12 countries, a total of 30 institutions, to build capacity, both for medical education and for research. We're doing this jointly with [the US President's Emergency Plan for AIDS Relief], PEPFAR.

Eric Goosby [the US Global AIDS Coordinator] and I have agreed that this is a shared area of real importance for that part of the world, and the kickoff of the MEPI program occurred in March [2011] in Johannesburg. It was very exciting to see how all of these investigators com-

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ing from institutions all over the continent—many of whom have never really been invited to come to the same meeting together and learn from each other—are really now going to be given a chance, with NIH support and support from PEPFAR, to build that kind of capacity.

The old model in which global health research is done by institutions in high-income countries and then sort of offered up to low-income countries has done good things. But in the future, we'd like to see that research capacity built in the countries where the medical needs are great, and I think we have a chance to do that through programs like MEPI.

BioPharm: And what is the second project underway?

Collins: The other program, which is going to be sponsored jointly by NIH and the Wellcome Trust, is called Human Health and Heredity in Africa, otherwise known as H3Africa. This is a bold effort to create a network of research activities that will look at environmental and genetic risk factors for both infectious and noninfectious diseases in the continent. It will adopt some of the same strategies that have been carried out more recently here in the US and other developed nations, but try to find out—in the cradle of humanity—how can we make the most of some of the new technologies that allow us to do genomics and environmental science and understand the causes of illness.

This will mean building capacity to do that kind of research, including information networks to share data and to carry out computational analyses. It will include setting up phenotyping capabilities to look at clinical consequences of various exposures and genetic risk factors. It will also mean establishing biorepositories to be able to store the samples that will be collected on what we expect will be thousands of individuals in Africa who will be the research participants in this bold new effort that will undoubtedly stretch over many years.

We'd like to see that research capacity built in the countries where the medical needs are great.

BioPharm: Have you found that countries and other groups are more willing to collaborate in recent years, and, if so, what do you think has led to that change?

Collins: I certainly do think that collaborative spirit is expanding in a wonderful way and it's driven, in part, by scientific opportunities. [For example, with our new consortium for rare-disease research], we are discovering the molecular causes at a prodigious rate. There are now some 4000 rare diseases for which we know, at a pretty detailed level, what the actual molecular problem is that leads to that illness, many of these being genetic diseases caused by mutations in the genome.

And, so, if you want to see that knowledge applied in terms of developing new therapeutics, that is something that is not trivial. You certainly don't want to waste the opportunity to bring groups together that might be able to do this faster, and you don't want to duplicate efforts and waste resources.

INNOVATION

BioPharm: In previous statements you've mentioned that innovation should not be limited to the work that's done for developing nations. How can we best capture the technology and knowledge that's used for developing-nation treatments and apply them to drug development and discovery in every region of the world?

Collins: I think of innovation very much as a two-way street. We shouldn't think that new inventions or new creative ideas come forth only in the US or in Europe. We can also learn, in what's being called 'reverse innovation', about how to adopt new ideas that are being developed in low-income countries. A particularly good example is the use of cellphone technologies for medical purposes....

For instance, we have a technology that's being developed and tested in Africa which is a simple method of assessing whether, in fact, individuals who are being treated for tuberculosis or HIV/AIDS are compliant with the therapy. So, you have a pill box which essentially is hooked up to the cellphone network, and every time the pill box gets opened, it sends a signal to the clinic where that patient is being cared for so that you can tell, was it, in fact, opened, and was it at the appropriate time of day?

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to follow through when they're not close by.

Collins: Exactly, and that, already, has spurred ideas about how we might adopt those same approaches here in the US for people who have, for instance, diabetes or hypertension. Medical compliance, we know, is critical for success in treating many conditions, and yet we haven't really had a good way of monitoring it.

BioPharm: Some other conversations going on in the pharmaceutical industry right now have to do with translational research, and NIH is a big supporter of that. How is NIH selecting projects to pursue in this area and how far can it take the projects, for example, through proof of concept in animals or Phase I clinical trials?

Collins: This ties into the conversation we were having about rare diseases [as part of the new consortium's goals to find treatments for 200 diseases by the year 2020] and the goal of having new therapeutics in a reasonable time. As you know, the current situation is a little scary when it comes to making such promises because, after all, the average time it takes from identification of a potential drug target to ultimate approval of that therapy is about 14 years, and the failure rate is about 98%. We think the time has come to look at that process the way that an engineer would and see if there are ways that we could optimize some of the steps that currently are slow, expensive, and likely to fail. That is part of NIH's effort now in putting together a new entity called the

Personalized medicine isn't the future, it's the present.

National Center for Advancing Translational Sciences.

We certainly will do this in a way that is complementary, and not competitive, with what the private sector would like to do, but we do expect that this kind of initiative may make projects that previously appeared too risky start to look attractive. So some of this is the idea of derisking projects which the private sector might otherwise not feel were economically attractive.

And certainly, when NIH sees opportunities for therapeutic development, working through the 27 institutes and centers that have a lot of knowledge about these areas, we will try to move projects forward to the point where they've become commercially viable and then license them out as quickly as possible in order to get them over the finish line.

Again, the goal here is to try to take advantage of remarkable scientific opportunities that might otherwise lie untouched but also to recognize the economic realities which means that companies, in general, are not going to go after projects that they don't think ultimately will become profitable.

FUNDING AND DEVELOPMENT

BioPharm: Do you think at some point you'll be able to recruit development partners in industry, such as any Big Pharma companies?

Collins: Oh, absolutely! I think already we're having some pretty interesting conversations with leaders of big companies about ways that we could work together in some areas that currently tend to be slow and inefficient.

One example is, how do we actually determine whether a new potential drug is safe to give to humans? Right now the way that that is done, as a sort of preclinical toxicology, depends upon the use of animal testing which is expensive, slow, and often not very reliable. We have a program already underway called Tox21, with 21 representing the 21st century, that is jointly done with FDA and EPA [the Environmental Protection Agency]. We're looking at potential environmental toxins and also with drugs to see if there are better ways that are higher throughput, depend upon human cells as opposed to other animals, and give a reliable signal about whether a compound is safe or not.

The Tox21 project is, I think, a good start in the direction of what could be a totally new science of doing preclinical toxicology in the era of having human cells that could be engineered into three-dimensional organoids.

BioPharm: You mentioned funding, and there has been some debate recently regarding the NIH grant program for small businesses. The Small Business Innovation Research (SBIR) program has been authorized by Congress until Sept. 30, 2011, but there are still disagreements in Congress about how venture capital affects those grants and the qualification of companies. In your

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opinion, what is best in that regard for drug discovery and development? Are there certain things you'd like to see happen with that particular bill and the program?

Collins: NIH has a long track record of supporting small businesses in a very productive fashion. We can point to some fairly major successes there that have resulted from that kind of starting support for the early phase of a company's development. Take the company Affymetrix, which has been a leader in the area of microarrays. That whole company was started on an SBIR grant and is now valued at quite a lot of money.

We could point to other examples as well. NIH's perspective is that we would like our SBIR dollars be used for projects that have the greatest chance of ultimately resulting in public benefit. Consequently, to have companies excluded on the basis of the amount of venture capital involved in their startup doesn't always make sense. So we are looking forward to seeing that limitation relaxed a bit because I think it has excluded some companies that might have been really good grantees. Obviously, that's a topic that's on an ongoing discussion on the Hill.

We would like SBIR dollars to be used for projects that have the greatest chance of ultimately resulting in public benefit ... to have companies excluded on the basis of the amount of venture capital involved in their startup doesn't always make sense.

PERSONALIZED MEDICINE

BioPharm: Another area of leadership and research for NIH is the Genome Project, which is supposed to provide the foundation for personalized medicine. How close do you think we are to truly having personalized medicine, and what do you think needs to happen to make it a reality?

Collins: I think we're there in some instances. It isn't one of those things where you don't have it one day and the next day you do. It comes along in various applications bit by bit. If you consider, for instance, a woman who's diagnosed today with breast cancer and has negative lymph nodes at the time of surgery, the question is, is the surgery she just had, the lumpectomy and the radiation that will follow, is that sufficient? Is she cured or does she also need adjuvant chemotherapy?

Well, personalized medicine is here because about half of the women in the US who are in that situation this year will have their breast-cancer cells analyzed to see whether there is a signature at the genetic level that would indicate that they are at a higher likelihood of recurrence and, therefore, need the chemotherapy or whether they're at low risk and can be spared the cost and the side effects of what can be a pretty unpleasant experience. That personalized medicine intervention right now is saving our healthcare system this year about $100 million in terms of the women who won't end up needing chemotherapy who otherwise would go through it. So it's a pretty good example.

Pharmacogenomics is another frontier. One example is abacavir for HIV, where it's now required on the label to do a genetic test before prescribing the drug for hypersensitivity. Or Plavix, which is one of the most highly prescribed drugs and where there's now an FDA label saying physicians should be aware that about one-third of the people given that drug will not benefit from it because of their genetics and should be offered some other alternative.

So, in those instances, I would say personalized medicine isn't the future, it's the present! It's here. **BP**

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Navigating the Biosimilars Market

The market landscape for biosimilars is in flux, with limited penetration now, but with the potential for growth for those who can navigate the market.

ALAN SHEPPARD

In 2009, the global market for biological products exceeded $125 billion, accounting for 17% of the total market for pharma/biopharma products. However, biosimilars last year only generated around $89 million in sales, with Sandoz's omnitrope accounting for the vast portion of those sales (33% market share). On a more positive note, growth in sales between June 2008 and June 2009 increased by a remarkable 200%.

Europe is by far the most advanced in terms of biosimilars approvals, but market penetration naturally varies considerably between the EU countries, with Germany accounting for the greatest market share in Europe and, indeed, worldwide (see Table I).

THE FUTURE MARKET LANDSCAPE

Sandoz is currently the global market leader in biosimilars sales, but Teva and Hospira are also developing a range of biosimilar products. Meanwhile, some Indian companies are using their experiences within the deregulated markets to produce dossiers and products suited for regulated markets. Certain R&D-based companies are also eyeing biosimilars as an opportunity for future growth; for instance, Merck has launched Merck Bioventures to develop biosimilars. Many companies have embarked on partnering and licensing deals in the area of biosimilars, but it will be those that already have in-house capabilities who will be in the best position. The cost of acquisition in this field is high and with the current limited penetration of biosimilars there is no guarantee of a return on investment in the short-to mid-term.

Based on a contribution by ALAN SHEPPARD, principal of Thought Leadership, Global Generics at IMS Health.

Forecasting biosimilar sales is complex because of various factors including the imprecise classification of a biosimilar and pricing policies of the originator resulting in the use of the brand in place of the biosimilar. Some estimates show the market growing from $66 million in 2008 to $2.3 billion in 2015. Others see sales exceeding $5.6 billion in 2013. Whatever the forecast, there remains a $50 billion potential for biosimilars. **BP**

Table I: Market share value for marketed biosimilars by country in Q2 2009.

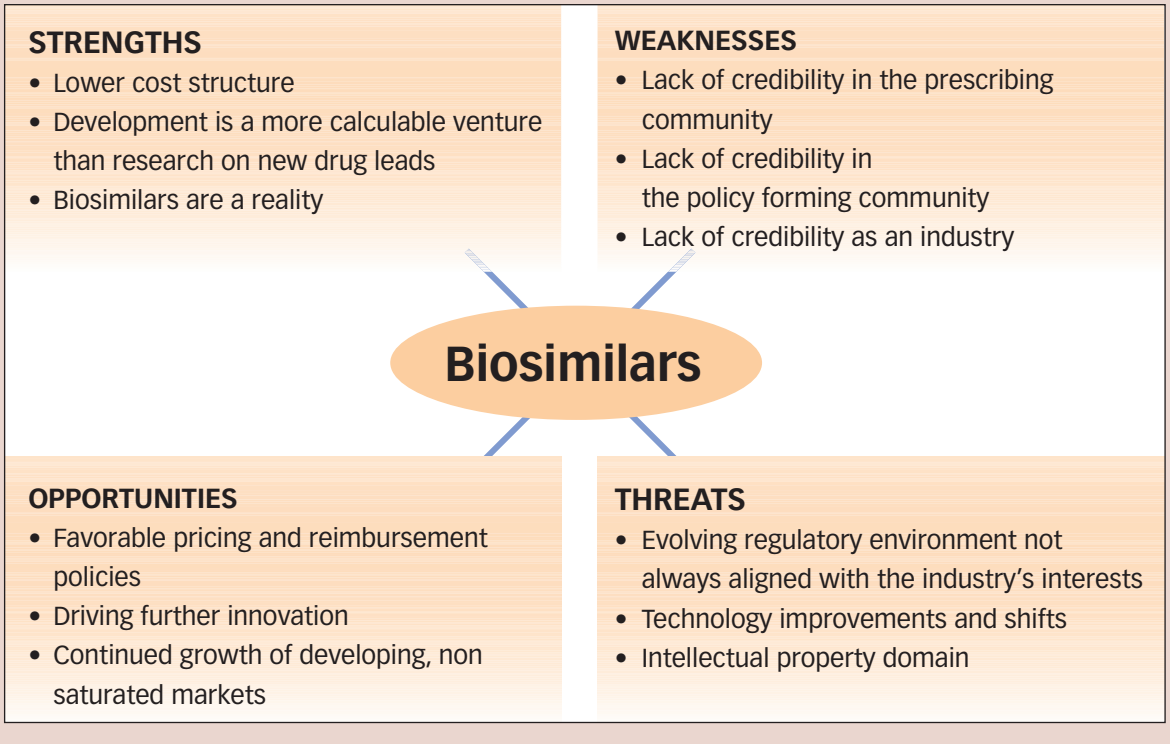
	Human growth hormone	Erythropoetin	Granulocyte hormone colony stimulating factor
US	6.6%	0	0
Japan	0	0	0
France	12.5%	2.0%	3.8%
Germany	5.1%	52.1%	31.0%
Italy	15.3%	0.2%	18.5%
Spain	1.4%	1.6%	7.1%
UK	1.0%	0.9%	24.0%

A SWOT analysis of the biosimilars market

Biosimilars present an attractive opportunity for small biotech companies seeking to capitalize on the success of originator biotechnology products with proven safety and efficacy. The biosimilar model, however, will not provide sustained market success unless biosimilars manufacturers take certain additional risks to differentiate their products in more ways than on price alone. A Strengths (S), Weaknesses (W), Opportunities (O), and Threats (T) analysis of the biosimilars market is shown below.

Key recommendations for small biotech firms that are considering developing a biosimilar:

- **Timing matters**: Market awareness will be highest for the first biosimilar to compete with a given originator.
- **Dare to be different**: Try to find targets where you can positively differentiate your biosimilar; for example, with an optimized formulation, delivery modes, packaging variants, sizes, and service aspects of the product offering.
- **Keep it simple:** Try to find targets for which you can access the knowledge around the product, its development and production processes, and then try to stay as close as possible to this foundation because such an approach has proven its viability through the originator for many years.
- **Don't play on IP**: There are not many defense strategies available to the originator firm, so you may expect it to fully exercise its options. As a result, you must find a way around IP issues or you may be taking part in a game too heavy to play for a small company.
- **Prepare deep pockets for financing the unexpected**: Eventually, at the beginning of your development you draw a plan that nicely sums up to an interesting investment. Don't sell this plan to your board as the final bill. You have a high chance of funning into additional costs during development.



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Contributed by **ANJAN SELZ**, CEO at Finax AG.

Chris Stein/Getty Images

Challenges and Innovations with Prefilled Syringes

Market considerations and new technologies must be recognized to achieve the full benefits of manufacturing prefilled syringes.

RAUL SOIKES

The pharmaceutical industry is constantly seeking drug-delivery technologies that can increase compliance, improve the quality of delivered care, reduce medication errors, and reduce the possibility of admixture-related contamination. Prefilled syringes, along with premixed infusion bags, are single-dose, ready-to-use delivery systems that have the potential to positively impact patient care. From a pharmaceutical company's point of view, prefilled syringes can also contribute to a product's overall success.

Advantages of prefilled syringes include:

- Ease of use: Prefilled syringes meet the demands of physicians and patients for effective and easy-to-use administration methods.

RAUL SOIKES is senior director of program management at Baxter.

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- Reduction in medication errors: A medication in a ready-to-use format, in conjunction with other related initiatives, can help reduce medication errors.
- Improved life-cycle management: Moving a product from a vial to a syringe may provide differentiation from competitive agents in the same therapeutic category.
- Better pricing: Economic advantages may also be possible for pharmaceutical manufactures. Prefilled syringes meet the stated demand for increased safety and convenience, and may present the opportunities for premium pricing compared with vials.

Manufacturing benefits and cost savings can also be realized because prefilled syringes help increase the saleable yield of the active pharmaceutical ingredient (API). API filling in prefilled syringes is precise to the dose required. Only trace amounts of API remain in the needle of a prefilled syringe after injection, as opposed to single- or multi-use vials, where it is necessary to overfill the API by 20–24% to ensure that an accurate dose is pulled into the syringe each time.

Prefilled syringes also offer savings from a capital-investment perspective. Vial washing, depyrogenation, and vial-component preparation equipment are not required because the syringes come presterilized and ready for use. Also, increased efficiency can be achieved by leveraging modern automated filling technology with barrier isolation systems, which can offer fill–finish lines with smaller footprints, higher throughputs and longer validation windows.

MANUFACTURING CHALLENGES

Biotech products, in particular, provide a number of unique manufacturing challenges compared with big therapeutic classes, such as anticoagulants and vaccines. The trend towards ready-to-use delivery systems combined with the decreasing manufacturing volume associated with biotech products and more targeted therapies poses an efficiency challenge. Batch sizes are typically smaller, requiring potential innovation and manufacturing optimization to provide sustainable value.

There has been an increase in the requirements for documented processing and control of the glass syringe throughout manufacture.

For CMOs, there are also complexities related to global regulatory compliance because there are marked differences in the expectations and best practices of key regulatory agencies. For example, specific structural changes needed for one client to ensure regulatory compliance may impact others using the same manufacturing line. Finding appropriate solutions to accommodate the broad spectrum of client and regulatory requirements is an intricate responsibility of utmost importance.

As with other sterile filling, such as vials, another challenge that can arise is the need to calibrate automated inspection equipment to meet the standards of multiple regional regulatory agencies, as well as client expectations. There is also often a lack of validated data to adequately handle product physico–chemical limitations, such as air and light sensitivity, time-out from refrigeration, shearing concerns, and others.

INNOVATION

There have been several recent innovations in prefilled syringes. For example:

- Restricted access barrier systems have had one of the biggest impacts on the sterility assurance of prefilled syringes.
- Electron-beam sterilization tunnels for the aseptic transfer of prefilled syringe tubs provide benefits by delivering high throughput and high levels of sterility assurance.
- Nondestructive control and inspection advances, coupled with improved cold-chain management, are of great advantage to minimize the waste of high-cost biologic APIs.
- Enhanced readability of fluid levels and accuracy of fluid draw helps ensure appropriate dosing.

Despite the advances made thus far, there is still room for further improvement. There has been an increase in the requirements for documented processing and control of the glass syringe throughout manufacture including: tube processing, forming machines (including closed-loop controls), ammo-

nium sulfate treatment, coating and annealing controls, leachable and extractable analysis, dimensional and cosmetic inspection, needle assembly control, water-for-injection washing, siliconization, shield assembly, and nesting. The systems that support the timely availability of this data will need to evolve and improve to support the requirements of pharmaceutical and biotech companies.

As drugs evolve to more targeted applications, manufacturing flexibility will be crucial. From a CMO's perspective, innovative equipment that supports this flexibility and optimization (e.g., equipment that can handle multiple safety shield vendors with minimal change parts) will be important. Another improvement that would be welcomed is easy interchangeability in fill and inspection equipment for glass and plastic syringes, which would increase efficiency and provide more flexibility.

Specifically for biologics, a siliconization process or suitable substitute is needed that has zero to minimal impact on the biological material. New tools for funnel forming, combined with lower forming temperatures, currently provide the lowest tungsten content, but alternates are needed, as this would improve stability by eliminating the potentially detrimental tungsten–protein interaction. Further understanding of product–container interactions is also required to ensure hydrolytic resistance of the syringe to prevent delamination, an issue in recent product recalls seen in the market.

As drugs evolve to more targeted applications, manufacturing flexibility will be crucial.

PREFILLED-SYRINGE MARKET DYNAMICS

To understand prefilled syringe growth, we look to external expertise from companies such as IMS and Frost and Sullivan. These sources generally agree that the US market is growing at twice the speed of the European market. According to IMS data on prefilled syringes and pens (IMS MIDAS injectables data 2003–2009), the share of total injectable volume is roughly the same in the US and Europe (top five countries) at 20% and 18%, respectively. The market for prefilled syringes has been growing at 10% and 5.5% in the US and the European Union, respectively, from 2003 to 2009. At the same time, the overall injectable volume (excluding vaccines) has been growing at 6% in the US and 2.5% in Europe.

Both regions have expressed the same desire to have ready-to-use delivery systems, such as prefilled syringes, widely incorporated into healthcare systems. However, economic uncertainty and related budgetary austerity measures are in place in both the US and Europe, and it is not immediately clear what impact, if any, these factors will

Prefilled syringes' success

Even though they have been available for almost 20 years, prefillable syringes are still an ongoing success story and represent one of the strongest growing segments in the pharmaceutical primary packaging market. These products, however, still pose many manufacturing challenges. In particular, quality requirements for prefillable syringes are continuously on the rise because of the increase in more sensitive drug products. Additionally, there is ongoing interest from pharmaceutial companies in increasing their product yields. These demands impact all steps of the syringe manufacturing process.

—Claudia Petersen, Gerresheimer

Extractables and leachables analysis

Multiple materials are involved in the packaging of drug products in prefillable syringes. With regard to extractables and leachables, manufacturers need to consider the materials used for the barrel, plunger, tip cap or needle shield, the needle itself, and any adhesives or lubricants, such as silicone oil. Because so many of these materials are in direct contact with the drug product, prefillable-syringe systems may require a more involved extractables and leachables analysis. It is also crucial for manufacturers to use the highest quality packaging materials.

—Frances DeGrazio, West Pharmaceutical Services

The growth of autoinjectors

Convenient, fully disposable autoinjectors, including needle safety devices for biotech drugs, have been on the market since 2006. Newer autoinjection devices include integrated needle safety and provide the patient with enhanced visual and audible injection feedback, which makes handling and the injection process more intuitive for the patient. Today, the main innovation focus is on improving the handling and reliability of disposable autoinjectors and prefillable syringes—now that they have been on the market for a number of years—to reduce patient complaints.

—Ian Thompson, Ypsomed

have on the adoption rate of prefilled syringes or other preferred methods of drug delivery.

The world market outlook from 2010 to 2025 shows a range of therapeutic agents—vaccines, insulins, analogs, and other biologicals—driving growth in the injectable and prefilled syringes sector. Important innovations will include advances in liquid formulation technology that enable protein drugs to be stable, as well as liquid prefilled packages and developments that enable the simple and cost-effective production of lyophilized formulations.

In the author's opinion, several factors will converge that ultimately impact the prefilled syringe market:

- The trend towards development of longer acting therapies will reduce the volume of prefilled syringes required.
- Scarce economic healthcare resources may contribute to a slowing rate of adoption of ready-to-use delivery systems. Prioritizing relevant therapies in these delivery systems will also increase.
- Innovation and technical requirements relative to the potential for glass incompatibility with biologics could result in a volume shift between glass and plastic, without an expansion of the overall market.
- Legislation will be an important driver in the demand for prefilled syringes, and it will be interesting to see what effect EU laws designed to reduce needlestick injuries have on the availability, pricing, and share of doses delivered in prefilled syringes.
- Lastly, in Europe, glass syringes are considered to be a pharmaceutical component of the prefilled syringe, whereas the US FDA mainly regulates prefilled syringes under pharma product regulations. As such, for Europe, the glass supplier is the starting point in the production chain. It will be interesting to see what future developments hold for the glass-syringe suppliers, and whether this leads to shared responsibility with pharmaceutical companies for a drug's integrity and efficacy. **BP**

Coming next month:

A special issue of *BioPharm International* focuses on facilities and single-use technologies.

TEK IMAGE/SPL/Getty Images

Trends in Prefills

An interview with Oskar Gold, vice-president, key account management and corporate marketing, at Vetter.

INTERVIEW BY FEDRA PAVLOU

WHAT HAVE BEEN THE KEY DRIVERS FOR THE GROWTH OF PREFILLS?

In general, the prefilled market has been growing at a promising rate in recent years. Looking at projections from our clients for the next four years, although sales growth won't be in double digits it will be at the higher end of the single-digit range—around 5–7% per annum, depending on the segment.

One of the key drivers at the moment is injectable biologics. If you look at the pipeline in the biotech world, roughly a third of all new projects are injectable biologics. The other driving factor is globalization. Many of our clients have international expansion plans and we're also seeing a strong focus on pharmerging markets. In the past, the ratio of growth in the established markets was in aggregate about double that of the pharmerging markets. For the next 4–5 years, however, projections show that the markets are basically on a par; the pharmerging markets will see growth of about $120–$140 billion until 2014 and the figure is similar for the established markets. In percentage terms, the pharmerging markets will grow at an annual rate of 14–17%, while the established markets vary between 3–6%.

HOW IMPORTANT DO YOU THINK PREFILLABLE SYRINGES ARE AS AN ALTERNATIVE TO INJECTABLES THAT ARE GOING OFF-PATENT FOR COMPANIES THAT ARE LOOKING TO EXTEND THE BRAND LIFE OF THEIR PRODUCT?

We always have clients coming to us for life-cycle propositions. I don't see it as more or less compared with the past, but in the pipeline reviews we do with our clients we find that a number of them want to upgrade the products they already have on the marketplace by changing the form of administration. For instance, we're in discussion with a number of customers to propose that they move from a vial to a syringe (single or dual-chamber) or to a cartridge.

One important factor driving companies towards prefillable devices is the healthcare market's need for cost containment. Healthcare payers want to reduce costs by making products more convenient to administer at home. If you're a patient needing an injectable medication and you always have to go to a doctor for administration, this is a huge cost. Because of this, reimbursement authorities and insurance providers are happy if people can administer medicines at home. A syringe, a pen, or an auto-injector supports patient convenience, and both the handling and overall treatment costs can be significantly reduced. This is one of the key reasons for the industry to develop more of these systems. Indeed, within the prefilled area, this is the segment that is growing the strongest.

One important factor driving companies towards prefillable devices is the healthcare market's need for cost containment. Healthcare payers want to reduce costs by making products more convenient to administer at home.

IS THE US THE BIGGEST MARKET FOR PREFILLED SYSTEMS?

Actually, the US and Europe are almost level if you look at the syringe market. In a recent study, we found that the US accounts for 43% of the global prefilled market sales, while Europe accounts for 42%. Only part of this market, is for pens and auto-injectors, but it's a growing segment that is seeing double-digit sales growth. Single-digit growth is only being experienced in the conventional syringe area.

WHAT ARE THE THERAPEUTIC AREAS WITH MOST GROWTH POTENTIAL?

In the injectable world, the therapeutic areas with the most growth potential are multiple sclerosis, diabetes, HIV, and oncology. Indeed, the requests we get are mainly for finding the most convenient drug-delivery system for these areas.

WITH MORE ADVANCED PREFILLED SYRINGES, IS COST AN OBSTACLE WHEN CONSULTING WITH CLIENTS?

Initially, cost is not an obstacle, but it becomes a point of heavy discussion in later stages. First, companies need to understand the technical challenges involved in the project. How long does it take? What are the benefits? What is the optimal drug-delivery solution from a patient's point of view? As soon as the client knows exactly what solution or option they want to pursue, they ask about the cost and begin weighing up the benefits.

We try to make our clients aware that it's the total cost of doing business that's important. It's also vital to consider the robustness of the supply chain, as well as quality. Whenever the supply chain or quality become disrupted, cost is usually no longer an issue as companies are willing to do whatever it takes to mend the situation.

ARE CLIENTS PLACING ANY PRIORITY ON ENVIRONMENTALLY FRIENDLY SOLUTIONS FOR THE DISPOSAL OF INJECTABLE SYSTEMS?

Looking back over our consultations during the past year, there is usually a small discussion about a product's environmental impact, but it's not really a major concern. It's not that companies are ignoring the issue, but there is huge pressure on too many other factors.

SUPPLY CHAIN SECURITY IS ONE OF THE TOP ISSUES OF CONCERN ON PHARMA COMPANIES' LIST. ARE YOU INNOVATING IN THE AREA OF TAMPER-EVIDENT SYSTEMS?

We offer the opportunity for tamper-evident features, but not all companies use these. In general, we find that it's not the main priority, but discussions about it

can fluctuate. If three or four tampering cases appear in the press then every discussion we have will involve tamper evident systems.

HOW ARE YOU PLANNING TO DEAL WITH THE LATEST TRENDS IN THE PREFILLED MARKET?

The world of injectable processing and syringes has a lot to do with the materials used. At the moment, siliconization is important so we're continuing to optimize this process by, for example, defining the optimal degree of siliconization that matches the active ingredient.

Another issue is the stability of all the compounds used. Glass breakage, in particular, is a big topic. It has always been an industry issue, but has extremely high visibility at the moment because the FDA is giving it a very strong focus. To deal with this, we have intensive discussions with all suppliers along our supply chain to finding ways of reducing glass breakage, such as by making the glass components more optimal for use with combination products. In parallel, we have increased the number of our automated visual inspection systems to help detect and minimize glass breakage. We're putting programs in place and are considerably increasing our quality teams.

FDA's view has changed quite rapidly compared with the past. With FDA's 2007 Safety Act, companies are requested to conduct ongoing stability monitoring and to have risk-evaluation processes in place. The tolerance of minor defects has also decreased significantly. If you make 6 million units and after half a year there is a report of three broken units in a pharmacy, you need to detect when it happened and how. This requires investment in infrastructure and technology, which adds costs to the supply chain.

With FDA's 2007 Safety Act, companies are requested to conduct ongoing stability monitoring and to have risk-evaluation processes in place. The tolerance of minor defects has also decreased significantly.

Several years ago, there were clear contracts that outlined the responsibilities of the different parties involved, such as the component manufacturer and the secondary packager. Now, however, we are made co-responsible. If there is a problem then we have to show documented proof that we have done everything we can to resolve the matter. As a CMO, this means we have to have dialogue with all our supply chain members.

DO YOU THINK THE INCREASINGLY STRINGENT REGULATIONS WILL CAUSE A PHASING OUT OF SMALLER CMOS/CDOS THAT CAN'T KEEP UP?

If you look at press releases from the last year, you'll notice that FDA has put out a number of serious observations to manufacturing organizations that can't keep up with quality standards or new regulatory expectations, leading to market recalls, for example. If you look at the number of events that have happened globally, companies who have not been able to correct their problems have been severely punished from a financial perspective.

This is where the shake out takes place: the company either operates to cGMP and cGLP standards and has a future, or doesn't and gets punished! Companies have to find the financial resources to make sure their quality systems and operating processes are state of the art. For CMOs, there is increased pressure to do this for the client—if the CMO is producing their product, then the client will want to ensure that the CMO can keep up with industry developments and GMP. The ones who can't keep up will not be in the business for long. **BP**

Getty/Nick Koudis

Single-use Technology: Balancing the Risks and Rewards

Developing a quality agreement template for single-use systems.

JEROLD MARTIN

Single-use systems are being used more and more in manufacturing. The time savings, reduced incidence of cross-contamination, reduced need for cleaning, and increased overall efficiency, to name a few advantages, make these technologies a very attractive proposition for manufacturers. There are, however, several obstacles to implementing the single-use systems; a key obstacle being manufacturers' unwillingness to replace fully installed and validated technologies, while the lack of clarity in understanding the regulatory requirements for single-use technology presents another barrier.

Notwithstanding the potential hurdles, a recent poll of *Pharmaceutical Technology* readers confirmed that the majority of companies (56%) are already using single-use technologies. Of the remaining respondents, 18% admitted that they planned to use single-use technology in the future (1). So it is clear that, not only is single-use here to stay, but it could fully replace certain stainless-steel technologies in the future.

The development of quality agreements between biopharmaceutical companies and contract manufacturers has long been recognized as a critical activity to ensure that a product's quality meets regulatory requirements. Quality agreements are used to clearly establish each party's responsibilities and assure that manufacturing processes are controlled according to mutual understanding. For outsourced biological

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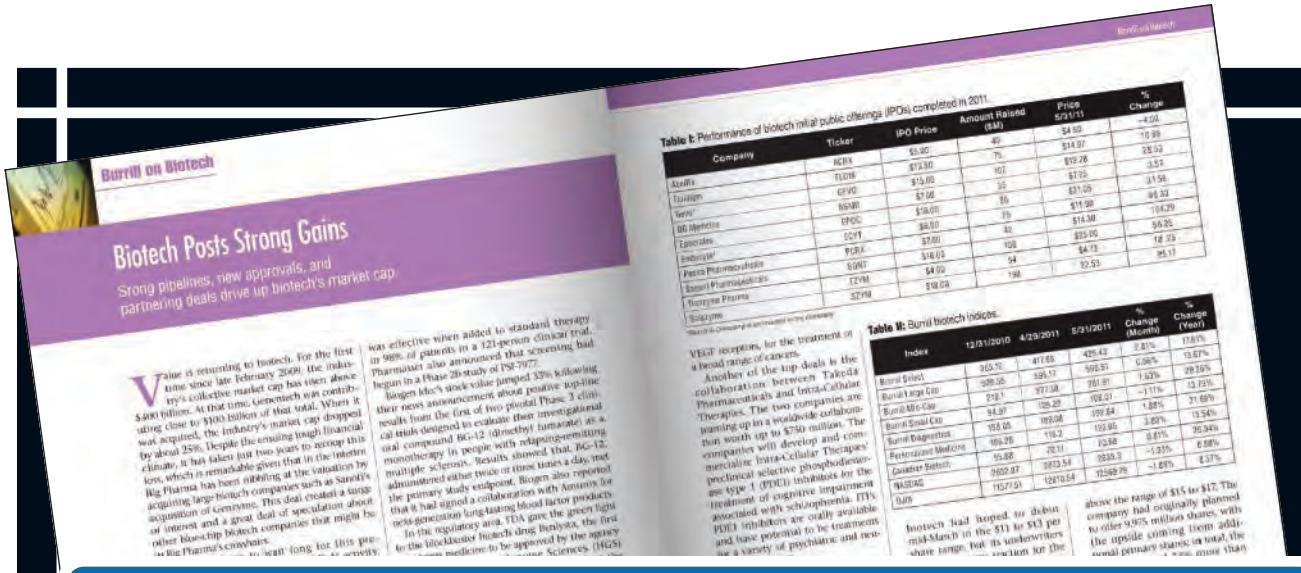
Burrill on Biotech

Biotech Posts Strong Gains

Strong pipelines, new approvals, and partnering deals drive up biotech's market cap

Table I: Performance of biotech initial public offerings (IPOs) completed in 2011

Company	Ticker	IPO Price	Amount Raised ($M)	Price 5/31/11	% Change
Alnylam	ALNY	$5.00	40	$4.60	-4.00
Trovagen	FLDN	$13.00	75	$14.97	15.08
Verro*	CEVO	$7.00	107	$7.05	28.93
BG Medicine	BGMI	$16.00	35	$21.05	-3.57
Lpscodex	EPOC	$16.00	75	$11.98	31.56
Endocyte*	PCRX	$8.00	82	$16.30	96.33
Pacira Pharmaceuticals	KNRT	$7.00	108	$23.00	104.29
Ensert Pharmaceuticals	EZYM	$16.00	94	$4.73	56.25
Trovagene Pharma	SGYM	$4.00	198	$2.53	18.25
Sangamo		$16.00			85.17

Table II: Burrill biotech indices

Index	12/31/2010	4/29/2011	5/31/2011	% Change (Month)	% Change (Year)
Burrill Select	353.10	417.65	429.43	2.81%	17.81%
Burrill Large Cap	388.56	395.13	399.91	1.63%	13.67%
Burrill Mid-Cap	212.1	217.58	201.97	-7.11%	-12.75%
Burrill Small Cap	94.97	105.29	108.21	1.88%	21.69%
Burrill Diagnostics	158.85	169.08	169.84	3.89%	13.54%
Personalized Medicine	169.26	178.3	182.85	0.81%	20.34%
Countries Biotech	55.88	70.11	70.58	-1.33%	6.58%
NASDAQ	2652.87	2873.54	2840.3	-1.89%	8.57%
DJIA	11577.51	12810.54	12568.79		

VEGF receptors, for the treatment of a broad range of cancers.

Another of the top deals in the collaboration between Takeda Pharmaceuticals and Intra-Cellular Therapies. The two companies are teaming up in a worldwide collaboration worth up to $750 million. The companies will develop and commercialize Intra-Cellular Therapies' preclinical selective phosphodiesterase type 1 (PDE1) inhibitors for the treatment of cognitive impairment associated with schizophrenia. ITI's PDE1 inhibitors are orally available and have potential to be treatments for a variety of psychiatric and neu-

biotech had hoped to debut mid-March in the $11 to $13 per share range, but its underwriters

above the range of $15 to $17. The company had originally planned to offer 9.975 million shares, with the upside coming from addi-

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products, this is supported by the 2008 FDA Guidance, *Cooperative Manufacturing Arrangements for Licensed Biologics*. More recently, biopharmaceutical companies have looked to establish quality agreements with raw material and API suppliers as a means to guard the supply chain from counterfeit or adulterated materials. This drive has led to the recent publication of a *Quality Agreement Template for API manufacturers* by the Bulk Pharmaceutical Task Force (BPTF), an affiliate of the Society for Chemical Manufacturers and Affiliates (SOCMA).

Considering the increased reliance that single-use manufacturing technology places on suppliers to ensure biopharmaceutical quality, quality agreements have also begun to be established between single-use process equipment suppliers and users—particularly for critical single-use equipment, such as filters, biocontainers, tubing manifolds, and other integrated single-use systems. While some companies have negotiated agreements on a case-by-case basis, there is a recognized need within the industry for a common quality agreement template (QAT) specific to single-use manufacturing that highlights key performance criteria. With this in mind, the Bio-Process Systems Alliance (BPSA), also an affiliate of SOCMA, has formed a Quality Agreement Template Task Force (QATTF) to develop a suitable template for single-use technologies for the benefit of users and suppliers.

BPSA is an industry trade organization for suppliers and users of single-use technologies for production of biopharmaceuticals and vaccines. Its primary objective is to facilitate the implementation of single-use manufacturing through networking, recognition, and publication of best-practice guides, to provide clarification of current regulatory requirements, and to interact with governmental agencies on emerging issues that may impact BPSA members. The BPSA QATTF is composed of quality department personnel from member companies that are system suppliers and end users. This is a global initiative because many BPSA member participants on the committee represent global companies.

… the BPSA estimates that 60–70% of the work undertaken to establish quality agreements between supplier and user is redundant and does not serve any added value.

WHY IS A QUALITY AGREEMENT TEMPLATE NEEDED?

One of the major challenges with quality agreements that users and suppliers have experienced is that no two companies request the same information, resulting in many hours spent filling out and modifying each company's unique forms. Single-use system suppliers are considered more responsible for the user's processes than stainless steel component or system suppliers because single-use components could conceivably vary from lot to lot, with users being highly dependent on the quality and delivery (and repeat quality) of such systems. Consequently, users are requesting to be kept more informed of supplier process changes beyond what has been previously acceptable practice. Single-use equipment suppliers and users must find ways to ensure suitable change notification on custom-assembled systems for users, while enabling sufficient flexibility of suppliers for updating standard products and processes. Based on a BPSA informal survey of single-use supplier QA managers, the BPSA estimates that 60–70% of the work undertaken to establish agreements between supplier and user is redundant and does not serve any added value.

Adoption of single-use technologies for biopharmaceutical manufacturing is growing every day, and many user and supplier companies have expressed the need for an easier way to execute quality agreements in a more timely and low-cost manner. By streamlining the process, the adoption of single-use technologies can progress more efficiently and rapidly, with a higher sense of process consistency and product quality, at lower cost. The BPSA has already helped the industry significantly by educating and providing best-practice guides for the adoption of single-use technologies. BPSA documents such as extractables/leachables guides, white papers on component quality test methods, irradiation/sterilization, disposal, and the economic advantages of single-use are good examples of what the BPSA has been able to accomplish in a relatively short period of time.

The BPSA QAT will be a consensus document that identifies commonalities of various templates existing today and will be more effective as a starting point for negotiations. Application of the BPSA QAT will be voluntary (as

a trade association, BPSA has no mandate authority).

PROGRESS TO DATE

At the moment, the BPSA QATTF is comparing existing templates and will be creating subsections to the document that cover the key points that the QAT must have. Some of the issues to be addressed will be identification of critical changes, change control and notification, subcomponent supplier qualification, component origin information, customer involvement in changes to standard products, levels of disclosure, and custom-product quality specifications. Rather than hinder uptake, we envision the BPSA QAT will provide higher assurance of quality supply and facilitate faster uptake of single-use equipment by reducing the time, cost, and effort to establish agreements.

The BPSA QATTF has been working to define a process for developing the document, which is expected to be completed over the next 4–6 months. This template will be another tool that biopharmaceutical companies and suppliers can use to ensure that high quality, safe drug and vaccine products can be delivered to patients at the time they are needed, to save and improve the quality of peoples' lives. Interested parties are invited to contact the BPSA for corporate membership and participation information.

Based on preliminary feedback from single-use suppliers and users, we anticipate that, when published, the impact of the BPSA QAT will be positive. Smaller companies are more likely to accept it as offered while larger companies are likely to demand customization, but the consensus is that the BPSA QAT will facilitate the finalization of agreements in a more expedient manner. Requests for quality agreements are likely to increase as regulatory agencies come to expect these to be in place between users and suppliers of single-use process equipment.

ACKNOWLEDGMENTS

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For further information about BPSA's publications and activities, please visit www.bpsalliance.org.

REFERENCE

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Perception and Costs of Biotech Innovation

The lower price of biosimilars will not only increase patient access to medicines, but also will spur innovation in the development, manufacturing, and commericalization of biologics.

AMEET MALIK

We believe that all stakeholders are increasingly realizing that marketed biosimilars offer comparable quality, safety, and efficacy to their reference products. Indeed, this is the basis on which they were approved by the centralized European procedure. To quote Nicolas Rossignol, the (former) European Commission pharma division administrator: "We are confident that if a product meets all the requirements and gets a marketing authorization from the Commission, it means that the product is as safe and effective as any other product authorized by the Commission."

In parallel, antibiosimilar campaigns are also beginning to lose their bite and there is a growing understanding that biopharmaceutical originator companies also effectively create changes in their products similar to biosimilars when they modify their original manufacturing processes.

LABELING AND SAFETY

The centralized European biosimilar regulatory pathway recognizes that existing biosimilars can and should have the same INN (International Non-Proprietary Name) as their reference product. Reference products that change through major manufacturing or process modifications also have the same INN. Provided that the mechanism of action is equivalent for all indications, biosimilars should also be approved for the same indications as the reference product.

Based on a contribution by **AMEET MALIK**, Global Head, Sandoz Biopharmaceuticals. www.sandoz.com

Biosimilars manufacturers will play a vital role in driving the next biologics revolution.

HOW LOW CAN BIOSIMILARS BE PRICED COMPARED WITH THE ORIGINAL?

Development costs, which include clinical trials, for biosimilars, typically equate to around $100 to $150 million per product and the payback period for the industry can be up to 10 years. In comparison to standard generic drugs, biosimilars offer less leeway for substantial price cuts because of the high barriers to entry—particularly on the financial side.

The European Unions's biosimilars are currently priced at about 30% below their reference products, but the important thing to remember is overall costs—the total savings to healthcare systems at this level of reduction are substantial, with one study in Germany conducted by the IGES Institute, projected potential savings in Germany alone of +€8 billion ($13.2 billion) through 2020.

IMPACT ON BIOTECH INNOVATION

Biopharmaceuticals have revolutionized modern medicine and will continue to do so, with many innovative new medicines still to come. Biosimilars manufacturers will play a vital role in driving the next biologics revolution by dramatically broadening patient access to affordable, high-quality medicines through innovative approaches to development, manufacturing, and commercialization of biosimilars. **BP**

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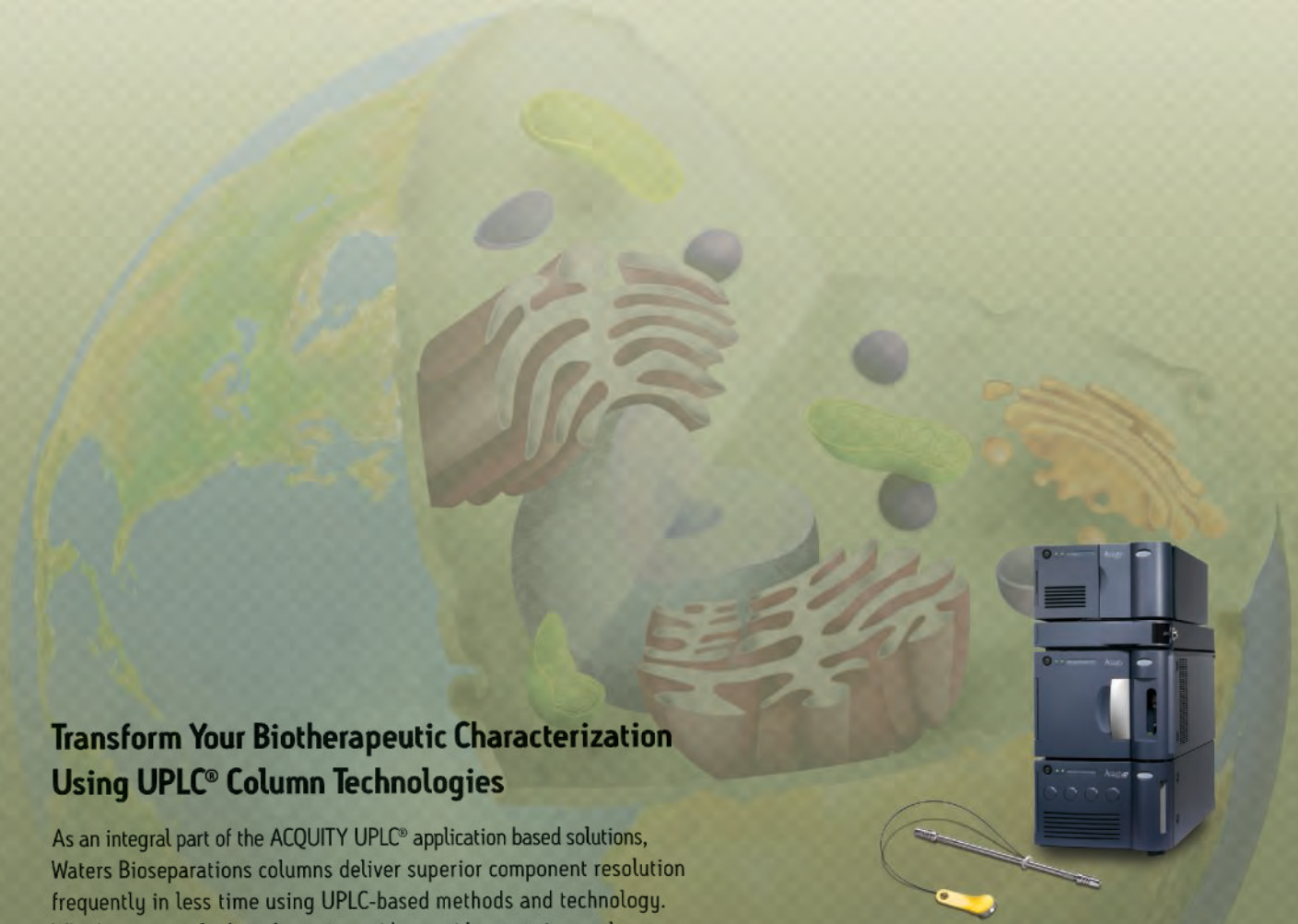

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