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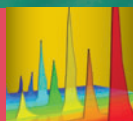
Sizing Up Big Pharma's Manufacturing Investment Strategies

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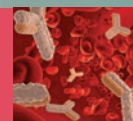
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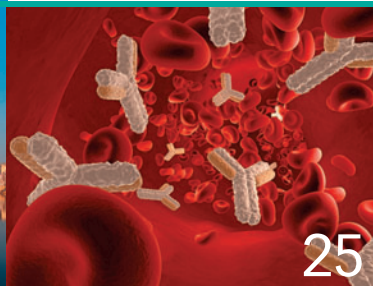
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16



25



20



28

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Features

COVER STORY

20 Sizing Up Big Pharma's

Manufacturing Investment Strategies

Pharmaceutical companies are investing in biologics manufacturing and emerging markets.

SOLUTIONS IN PHARMACEUTICS

25 Demonstrating Biosimilarity

Ensuring that biosimilars have comparable profiles to the reference products is key in their development.

TROUBLESHOOTING

28 Using Tandem LC-MS for Cleaning Validation

The author describes how liquid chromatography-mass spectrometry works and explains some of its advantages and disadvantages.

Peer-Reviewed

33 Alternative Solvents for Extractables and Leachables Evaluation

Solvents used for evaluation of process components may include surfactants that can interfere with chromatographic detection and contaminate the chromatographic system. The authors examine alternative solvents that provide extraction equivalence and do not interfere chromatographically.

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Columns

10 European Regulatory Watch

Seeking Harmonisation in Nanomedicines Regulatory Framework

16 Emerging Market Report from India

18 Emerging Market Report from South Korea

30 API Synthesis & Manufacturing

Advancing Peptide Synthesis

37 Outsourcing Review

Bioprocessing Advances in Vaccine Manufacture

42 Ask the Expert

Regulatory Inspections Get Serious

Regulars

5 Editor's Comment

Access to Medicines Rings Alarm Bells in Europe

6 Product Spotlight

8 Industry Insider

The Dilemma with Orphan Drugs

40 Product Showcase

42 Ad Index

Online exclusives

Generic Drugs Face Regulatory and Scientific Challenges

FDA funds research to further development of innovative generics, while working to address review and approval issues.

www.PharmTech.com/GenericDrugs

New Gene Patent Rules

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Access to Medicines Rings Alarm Bells in Europe



The issue of patients not receiving essential medicines because they are unable to afford them is becoming a serious problem in Europe. A briefing in May 2013 by the

European Public Health Alliance (EPHA) on *Access to Medicines in Europe in Times of Austerity* highlighted that two factors determine whether or not a patient gets his/her medicine—innovation and access. Innovation asks, “has a drug for a particular condition been developed?” whereas with access, the question is, “if the drug exists, can the patient have it?” Matters relating to affordability and availability will determine access. With the financial crisis hovering

over Europe and governments struggling to meet the increasing costs of healthcare, access to medicines appears to be slipping away in Europe.

So what can Europe do? According to the new president of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Christopher Viehbacher, Europe needs a different approach to healthcare. Viehbacher commented in a press release that “given the chronic deficits of healthcare systems, we must work differently, build collaborative policies and combine our strengths at both national and European levels.” He added that for healthcare to be a growth engine for Europe, the focus must be on three priorities—patient access, science and innovation and competitiveness.

As different policy approaches are implemented across Europe to reduce

public financing, it is important that governments evaluate the impact on medicines access and the health status of their citizens. In addition, Europe needs a regulatory and policy framework that supports collaborative research and helps translate scientific innovation into useful medicines for patients. Viehbacher noted that the European economy is stagnant and global competition for investment is intense; therefore, focusing on sectors that can drive growth, such as the healthcare sector, would benefit Europe. It is now time for the EU, member states and the industry to work together so that the potential promised by innovation-led growth can be realised.

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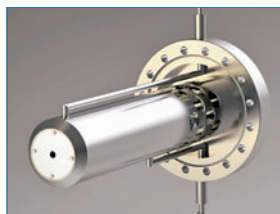


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The Dilemma with Orphan Drugs

Orphan drugs for rare diseases are a major area of investment for pharmaceutical companies but are they becoming too expensive for Europe to afford them?



Nathan Jessop

Rare diseases present an area of substantial unmet medical need. In Europe, a disease is defined as rare if it affects less than five people per 10,000 (1). More than 6000 different rare diseases have been identified to date, and it has been estimated that approximately 30 million people living in the EU suffer from a rare disease (2). Most rare diseases are caused by genetic defects, but environmental exposure during pregnancy or later on in life, often in combination with genetic susceptibility, could also be a cause (1).

Addressing unmet medical needs

Most pharmaceutical companies have shown little interest in developing drugs for rare diseases because these drugs were unlikely to generate sufficient return on investment. As a result, treatments for these disorders became known as 'orphan drugs'. To stimulate research in this area, a number of governments developed specific orphan-drug legislation, which provided incentives to companies who invested in this area. The types of incentives included are reduced fees for marketing-authorisation applications, scientific advice or protocol assistance, and protection from market competition once the drug is authorised (2). In 1983, the US adopted the Orphan Drug Act, with Japan and Australia implementing a similar legislation in 1993 and 1997, respectively. Europe followed relatively late in 1999 when it adopted Regulation (EC) N° 141/2000 on orphan drugs, but the legislation has been widely considered to be successful. Since its introduction, the European legislation has resulted in the review and approval of 69 treatments for some 55 different conditions (2, 3).

Despite improvements in the situation for patients with rare diseases and their families, efforts are continually being made by stakeholders to raise awareness of the condition, widen access to treatment and ensure appropriate medical representation. Due to the political make-up of the EU, competencies for healthcare are split across countries; hence, the authorisation of a particular orphan drug does not necessarily mean that it is available to all patients in the region. A key annual event to raise awareness is Rare Disease Day,

which is held on the last day of February (2). A main coordinator of this event is the European Organisation for Rare Diseases (EURORDIS), which represents 585 rare disease patient organisations in 54 countries covering over 4000 diseases (4).

A market too successful?

A controversial issue regarding orphan drugs is their pricing. Although they receive incentives to develop orphan drugs, particularly market exclusivity for 10 years in the EU, companies argue that they must still charge high prices to guarantee sufficient return. European healthcare systems are already struggling to cover the costs of treatment for citizens and there is a concern that orphan drugs are now placing too much pressure on the system.

Although the need for orphan drugs is recognised, critics argue that industry is taking advantage of the incentivised system to maximise profits and that healthcare systems cannot cope with such pricing in the long term. In the past, small specialised companies focused on orphan drugs, but in recent years, a growing number of large pharmaceutical companies have moved into this field. Thomson Reuters Life Sciences estimated that the current global market for orphan drugs is worth US\$50 billion and growing at 6% per year (5).

Companies continue to state that it costs around US\$1 billion to develop a new drug and that they need substantial revenue to cover the costs of developing drugs that fail during R&D (5). However, many observers believe that a number of the orphan drugs on the market have exceeded the costs of their development by a wide margin. A report by the BBC in January 2013, based on the views of Dr Carl Heneghan, director of the University of Oxford's centre for evidence-based medicine, suggested that approximately one in 10 orphan drugs has generated more than £620 million of revenues (6). Furthermore, the pricing of these drugs in relation to the patient population appears to be very high. For example, nine of the most expensive orphan drugs on the market, which cost more than £125,000 a year, treat diseases afflicting fewer than 10,000 patients (6).

Soliris (eculizumab), used to treat patients with paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome, was approved in 2007 and is frequently cited as one of the world's most expensive drugs, at £250,000 a year (6, 7). Nevertheless, the manufacturer, Alexion, believes that the price is fair. It states that one third of patients died within five years before Soliris was available (5).

One of the harder arguments for companies to justify in today's cost-conscious healthcare environment is when an existing therapy has been modified and adapted to become an orphan drug. In the BBC report, Dr Heneghan cited the example of oral ibuprofen, which costs approximately £0.08 per gram (6). The drug also exists on the market as an intravenous form (Pedea) for the treatment of the orphan disease patent ductus arteriosus, where it costs £6575 per gram (6). To account for this price variation, Orphan Europe, the manufacturer, explained that the drug was specially developed for a rare-disease population and should not be compared in such a straightforward manner with ordinary oral ibuprofen (6).

The case of Firdapse

In 2009, Firdapse, which contains the active substance amifampridine, was approved in the EU as an orphan drug for Lambert-Eaton myasthenic syndrome. However, a 2012 paper in the *Orphanet Journal of Rare Diseases* suggests that the branded product represents a slight modification of an unlicensed and low-priced compound that has been available for several decades (3). The unlicensed drug is 3,4 diaminopyridine (base form) whereas Firdapse is the phosphate-salt formulation of 3,4 diaminopyridine (7). It was suggested that the pricing of the Firdapse was 50- to 70-fold higher compared to the unlicensed formulation (6).

This issue prompted a number of physicians to write an open letter in the *British Medical Journal* (BMJ) to UK prime minister David Cameron complaining about the way in which companies were unfairly using orphan-drug legislation to their advantage (8). A series of exchanges between BioMarin, the manufacturer, and

the signatories to the BMJ letter took place, culminating in the lead author writing an FP10 prescription for the cheaper unlicensed drug, 3,4-diaminopyridine (8, 9). Although BioMarin then voluntarily cut its prices for Firdapse by 10%, the UK commissioners network did not recommend funding of the drug (8). The UK commissioners network took the view that although legally Firdapse and 3,4 diaminopyridine were two separate clinical entities, the two forms of the drug could be considered to be bioequivalent (7). It was calculated that on average, the base form of the drug costs £1200 per patient per annum, whereas Firdapse costs, on average, £44,000 per patient per annum (7). This development apparently led to some prescriptions of the unlicensed 3,4 diaminopyridine (base form), which could be legally challenged by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) or Biomar (8). However, as the lead author of the BMJ letter pointed out, such a legal challenge might prove embarrassing for these organisations (8).

So what's next now?

Despite the controversy concerning certain high-cost orphan drugs, at present, these treatments only account for a small percentage of the overall European drug budgets. In 2007, orphan drugs accounted for 1.7% of the French drug budget, 2.1% in Germany, 1.0% in the UK, 1.5% in Italy and 2.0% in Spain (3). However, healthcare systems need to be designed to cope with future demand, and given that most rare diseases are not well treated, there is a likelihood that countries will be asked to fund additional orphan drugs in the future. One study suggested that there will be between eight and 12 new orphan drugs approved in Europe each year (10). With patients wanting access to these treatments but companies seeking to maximise revenues, European governments are now placed in a difficult situation of over pricing. Although there has been speculation that governments will take a tough line with the industry, it remains to be seen what form such action will take and whether they will remove some of the specific market

incentives that were designed to stimulate orphan drug R&D in the first place (11). A delicate balance will need to be struck so as not to reverse the advances made in orphan-drug development and treatment access.

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Seeking Harmonisation in Nanomedicines Regulatory Framework

Nanomedicines have been authorised by the European licensing agencies for more than 30 years but they are still posing regulatory difficulties.

Planned launches of generic versions of first-generation nanomedicines and the emergence of a second generation of more-complex nanotechnologies in healthcare are now becoming a big challenge for licensing agencies. Unsurprisingly, the pharmaceutical industry has its doubts about the exact regulatory requirements for approval of innovative nanosubstances in medicinal products. The uncertainties are not only confined to Europe but also other developed regions such as North America, mainly due to the gaps in knowledge about the safety of nanomedicines derived from recent advances in nanotechnologies.

"The industry wants greater clarity among regulators, more uniform standards and more harmonisation," Beat Loeffler, chief executive of the European Foundation for Clinical Nanomedicine (CLINAM), Basel, Switzerland, told *Pharmaceutical Technology Europe*. "There is a feeling that the regulators do not know what they want." An annual international conference on clinical nanomedicines, organised jointly at Basel in June 2013 by CLINAM and the European Technology Platform on Nanomedicine (ETPN), called for greater consistency among regulators in dealing with new nanopharmaceutical products.

Safety requirements

In Europe, the safety rules on nanosubstances in medicinal products can be particularly perplexing because in many cases, the nanotechnologies are applied to drug-delivery systems, carriers and imaging agents. As a result, the products have been categorised as combination products or medical devices rather than medicines. In the European Union (EU), this categorisation has given much more scope for the regulatory authorities of the 28 EU member states to approve nanomedicines rather than the European Medicines Agency (EMA), whose main responsibility is the approval of pharmaceuticals.

Some national governments have been taking their own regulatory initiatives on the management of nanosubstances in medicines and other products because of the reluctance of the European Commission (EC) to tighten up EU rules in the area. Last year, after a regulatory review on controls of nanomaterials, the EC decided to leave EU legislation on nanotechnology unchanged. Instead, the EC stated that the safety of nanomaterials should be assessed on a case-by-case basis on the grounds that they are similar to normal substances in that some may be toxic and some may not.

In an earlier recommendation, made in October 2011, the EC provided leeway for national governments to apply their

own controls on nanomaterials by recommending a broad definition of "nanomaterial." A material was defined as "nano" when it contained 50% or more particles in the size range of 1–100 nm. The EC also acknowledged that because of "special circumstances" in the pharmaceutical sector, the recommendation of an upper limit of 100 nm should "not prejudice the use of the term nano when defining certain pharmaceuticals and medical devices."

France has been among the most ambitious EU member states in introducing a new nanotechnology legislation, which came into effect in May this year, but which has, so far, not raised any significant opposition among French pharmaceutical companies. Its main requirement is that manufacturers, importers and distributors of engineered nanosubstances make annual declarations to the French government of the amounts they are placing on the national market with details of their uses.

"This legislation is not a hurdle and the provision for annual declaration encourages transparency, which is a desirable objective," explains Laurent Levy, chief executive of Nanobiotix, Paris, a nanomedicine company and a member of the biotechnology committee of the French Pharmaceutical Companies Association. The increase in new nanomaterial legislation at the national level in Europe is, however, causing some nanomedicine companies to see regulation as being an obstacle to innovation.

"Small and medium enterprises (SMEs), in particular, are regarding regulation in nanotechnology as a barrier," Levy, who is also vice-chairman of the ETPN, an EU-funded research organisation, said in an interview with *Pharmaceutical Technology Europe*. "But once they start interacting with the regulatory authorities about their new products, they become much less concerned because they are in a dialogue with the authorities during the development of their nanoproducts, and therefore, will know what is expected of them."

Nanobiotix has been keeping in close contact with the French National Agency for the Safety of Medicines and Healthcare Products (ANMS) in the development of a nanoparticle-enhanced radiotherapy technology. In June 2013, ANMS authorised the company to start a clinical trial of the technology for the treatment of head and neck cancer.

The Nanobiotix technology, however, is an example of disparities outside Europe in the international classification of nanomedicines. In Europe, it has been categorised as a medical device, while in the US, FDA considers it to be a drug. As a result, Nanobiotix reckons its first products will reach

the market more quickly in Europe than in the US because European national authorities responsible for licensing medical devices require fewer clinical trials than with pharmaceuticals.

"There may be a bit of a difference in the time to market between Europe and the US, but in the end, you have to meet the same regulatory requirements of demonstrating an acceptable benefit-to-risk ratio," explained Levy.

EMA takes charge

Meanwhile, EMA has been stepping up its efforts to ensure a consistent EU-wide approach to nanomedicines in the two areas for which it has responsibilities—pharmaceuticals and combination products, defined as devices with a predominant pharmaceutical application. So far, EMA has only evaluated 11 marketing-authorisation applications for nanomedicines, of which eight have been approved and three withdrawn. This number is fewer than in some of the larger EU countries. In France, for example, 36 nanomedicines, 21 of them being drug-delivery products, have been licensed.

EMA has recently drafted reflection papers (i.e., discussion documents on the principles underlining the risk assessment of groups of products that may provide a basis for later guidelines) on generic nanomedicines or nanosimilars. The agency is also planning reflection papers on new second-generation nanotechnologies, on which it has already published discussion documents on block-copolymer micelles and nanomedicine coatings. As a coordinator of evaluation strategies throughout the EU's network of national licensing authorities, EMA believes it is in a strong position to boost assessment standards in areas like nanomedicines.

"The agency has access to the best available scientific expertise in Europe, which it can consult during the evaluation of the quality, safety and efficacy of all new compounds, including nanomedicines," an EMA official told *Pharmaceutical Technology Europe*. "EU-wide harmonisation is one goal of EMA. However, the agency's main intention is to ensure that only safe

and efficacious medicines enter the EU market."

EMA's Committee for Medicinal Products for Human Use (CHMP) has a multidisciplinary expert group on nanomedicines, which can tap into the evaluation experience among member states. The agency has also been extending its regular contacts with non-European agencies on nanomedicines. CHMP chairs regular meetings on the matter with FDA and the licensing authorities of Japan, Canada and Australia. "There are no official recommendations from these meetings," said the EMA official. "The focus is on knowledge-sharing and finding common areas for collaboration."

The reflective paper on block-copolymer micelles, written jointly by the agency and Japan's Ministry of Health, Labour and Welfare (MHLW), was an idea that came out of one of the international meetings. The EMA's investigations of nanomedicines have highlighted the need for more public-sector assistance in Europe on the characterisation of nanoparticles in medicinal products. The micelles reflective paper pinpointed the importance of characterisation of approximately 15 properties of block-copolymer micelles and properties related to the manufacturing process and *in-vivo* behaviour, as well as of the chemical structure and nature of the polymer raw materials.

The ETPN is currently exploring the idea of setting up a European Nano-Characterisation Laboratory that would act as the centre of a network of characterisation facilities across Europe. It would be modelled on the US National Cancer Institute's (NCI) Nanotechnology Characterisation Laboratory (NCL), which has close links with FDA.

Europe is gradually putting together an evaluation structure that should accelerate the development and commercialisation of the next generation of nanomedicines. "Like with all new technologies, there have inevitably been areas of uncertainty with nanomedicines," said Levy. "But ultimately, as knowledge of the technology increases, there will be a high level of consistency and clarity in the way it is regulated across Europe." **PTE**



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CPhI Worldwide 2013

An invitation to the global pharma industry

The global pharmaceuticals market is currently worth US\$300 billion a year, and is forecast to grow to US\$400 billion within three years. It is an ever developing sector in which more and more companies are seeking outsourcing services and looking to invest in target areas such as R&D and formulation development. Considering this, the formation of solid contacts and relations from company to company is becoming increasingly vital to augment the growth which is being witnessed within the industry. CPhI Worldwide, the leading pharmaceutical exhibition and global meeting point for the world's pharma community returns, providing an exceptional platform for innovation and growth in the pharma industry.

Presenting an unrivalled opportunity for visitors and exhibitors to build new relationships, explore and evaluate pharmaceutical products and learn about the latest industry trends, CPhI Worldwide alongside co-located ICSE, InnoPack and P-MEC Europe is being held at Messe Frankfurt, from 22nd- 24th October 2013. The three day event is unique in bringing together senior executives from the international pharma market alongside global pharmaceutical suppliers and buyers.

The show attracts a quality audience from all of the industry's sectors looking for innovation and eager to find new pharmaceutical ingredients, contract services, technology and packaging to their business. CPhI Worldwide and co-located events will host senior pharma professionals from over 140 countries under one roof and offer over 30,000 potential leads in 72 hours. Impossible? Not at the pharma industry event...

Three days to drive business for the rest of the year

CPhI Worldwide will co-locate with three additional shows making the event, undoubtedly, the best place to network with the entire global pharmaceutical community. Whilst CPhI focuses primarily on pharma ingredients with exhibitors covering ingredients, APIs, excipients, finished dosage and more, co-located show ICSE is a dedicated outsourcing event designed to connect the pharmaceutical community with contract service providers including specialist clinical trial companies, CROs, logistics providers, data management firms and CMOs. P-MEC Europe delivers innovative pharmaceutical machinery, equipment and technology to a worldwide forum of decision makers and incorporates LABWorld for laboratory, analytical and biotechnology instrumentation. It is the must-attend networking event for any business in the pharmaceutical machinery, equipment and technology industry. The final co-located event is InnoPack which offers the pharma community innovative and diverse packaging solutions to satisfy the changing way we package and deliver medication.

Together, the shows provide a distinctive structure and platform to reflect the current trends within the pharma industry. Increasingly, more companies are looking to outsource services and the co-located events ensure that attendees are able to generate business leads and partnerships in all sectors to drive business for the short and long term.



Navigate your way with industry dedicated zones and country pavilions

A zone-based layout at CPhI and co-located events will make your search for the right business partners much easier.

Alongside already established zones at the event, including APIs, LABWorld and Bioservices, this year will see new zones inspired by your feedback. Building upon the layout of the event, this year's edition introduces a Natural Extracts Zone, Pallets (within the logistics zone) and Packaging Ingredients Zone to further focus attention on the specialised products on offer.

The Natural Extracts Zone will be devoted to all things natural, incorporating companies that offer products including plant extracts, animal extracts, herbal teas, functional food ingredients, dietary supplement ingredients, nutraceutical ingredients, cosmeceutical ingredients, food additive and dietary fibre.

CPhI recognises the importance of international partnerships within the pharmaceutical industry as being key to drive innovation and augment growth across the market in its entirety. With this in mind, the event is host to 14 country pavilions, in order to help attendees to establish partnerships and source suppliers from a certain geographical area. Featured this year will be pavilions from India, North America, China, Argentina, Brazil, Egypt, Portugal, Morocco, Korea, France, United Kingdom, Scotland, Malaysia and Russia.



Your chance to meet senior level executives

CPhI is the leading meeting point for worldwide senior level executives across the entire pharmaceutical industry. With company representatives from marketing and sales, general management (CEO/President/Director/GM etc.), business development and purchasing, the opportunities to attendees to meet the right people are invaluable. Around 87% of CPhI Worldwide visitors have purchasing power with 8 out of 10 visitors planning to source products or services from an exhibitor. The event provides excellent exposure to potential clients, with 78% of exhibitors agreeing that they meet the right visitors at the event.

“ Exhibitors are satisfied that the show increases brand awareness for their company and the majority (92%) agree that the show is ‘the’ meeting place for the pharma industry. ”

Source: CPhI Worldwide Exhibitor Survey, 2012

Celebrating tomorrow's innovations today

In conjunction with providing a meeting point to generate business opportunities, CPhI is committed to honouring the innovation and hard work that comes out of these ventures. Celebrating its 10th consecutive year, the award entries are now open to the entire pharma industry and will celebrate the most innovative and dynamic areas across the global pharma community. The Awards recognise thought leadership on a global scale, unveiling top pharma innovators to global trade. They honour companies who are driving forward industry changing initiatives across innovation within three broad categories - 'Formulation', 'Process Development' and 'Packaging' - with just one winner to each prestigious award. CPhI is now accepting applications for the 2013 CPhI Pharma Awards through to 26th July, open to individuals and companies who have developed innovations in pharma over the past year. Winners will be announced at a ceremony during the evening on October 22nd. To learn more about the awards or to submit an award entry, please visit www.cphi.com/pharma-awards.



CPhI Global meetings- let us do the matchmaking for you

Attendees are offered the chance to take advantage of the Global Meetings matchmaking programme to help make the most of their time at the event. It allows for direct access to individual exhibitors that meet your needs. The customised programme facilitates high quality meetings, boosting ROI for all participants, across the three show days. Every year, over 94% of visitors make new business contacts. The matchmaking programme is a great way to facilitate these connections. This free programme enables suppliers and buyers to maximize time by bringing them together with the most relevant business contacts. Participants will have access to the most suitable pre-selected buyers, who can meet and discuss valuable business proposals. Meetings are arranged prior to the event using sector specific knowledge in combination with the objectives of attendees to identify key business areas.

“

If the normal experience of being at CPhI is 'shake and run', then Global Meetings is 'breathe and meet'! It's very nice to have a base where you can stay for a while. Secondly, the ambience of the venue is pleasant, with refreshments available, which is much appreciated when you have a hectic schedule and you're running from one appointment to another.

”

Krishna Poojari, Head of Strategic Sourcing and Business Development, Neuca,
and Andrzej Schoenert, CEO of group subsidiary Synoptis Pharma.

Conferences and seminars

As you prepare your itinerary to attend this year's CPhI Worldwide, make sure you factor in attending the CPhI Pre-Connect Conference on 21st October. Comprised of 6 modules featuring API sourcing, Drug Delivery Systems and Biosimilars and Biobetters, the Pre-Connect Conference offers the exclusive opportunity to join senior executives and influential speakers from across the pharma industry. Representatives from Wockhardt, Novartis, Merck and PwC to name just a few, will help you get a head start on your networking in an informative and interactive environment.

One key theme at the CPhI Conference this year is the generics and super generics industry in emerging markets. The sessions were set up in order to help you expand into or strengthen your position in developing regions and provide the unique opportunity to discover the key trends, drivers, challenges and opportunities in this market.

Attendees will also obtain critical information about recent and upcoming advances in drug delivery systems, examine the complexity of regulations and find out about latest innovations in drug formulation, as well as exploring key considerations for successful strategic partnerships in times of open innovation, from risk management to quality assurance and control of alliances.

Additionally, the show features a constant stream of informative content on the latest key developments via the free sessions in the Speaker's Corners. You will have the opportunity to hear first-hand from exhibitors across the globe about the latest trends within the pharma industry whilst also finding out about their latest products, innovations, services and more!

CPhI Pharma Evolution- the global community for smart pharma

This year CPhI has launched Pharma Evolution- an online platform to provide a community base for CPhI exhibitors, visitors and the wider pharma industry. Designed to aide innovation between industry professionals, it provides real world best-practice advice. Anyone in the global pharma community can take advantage of Pharma Evolution to debate issues any time of the day, from any location on the globe.

CPhI Pharma Evolution will be present at this year's show, blogging live and keeping attendees up to date on all the latest news. To learn more visit: <http://www.pharmaevolution.com/>

Willkommen in Frankfurt

When not at CPhI attendees can explore the beautiful city of Frankfurt, from the unmistakable Römerberg, the gothic "Imperial Cathedral" and the Main Tower to the Frankfurt Zoological Garden. Visitors can also enjoy the shopping opportunities on "The Fifth Avenue of Germany"- the Shopping Street Zeil.





EMERGING MARKET REPORT

Report from: India

Jane Wan

Industry players brace themselves to face challenges as India's new drug-pricing policy kicks in full gear.

On 1 July, India's new Drug Pricing Control Order (DPCO) 2013 replaced the 1995 version. Under this new regime, the National Pharmaceutical Pricing Policy 2012 will regulate prices of 348 drugs covered under the National List of Essential Medicines (NLEM) 2011 compared with 74 drugs in the former list. Adopting the market-based price mechanism, the policy is based on the simple average price for all brands with a market share above 1% in their segment.

According to industry sources, the new drug-pricing policy will affect two thirds of the Indian pharmaceutical industry. Consumers, on the other hand, will benefit greatly. Tapan Ray, director general of the Organisation of Pharmaceutical Producers of India (OPPI), said in an interview with *Pharmaceutical Technology Europe*, "Ceiling prices will now be based on approximately 91% of the pharmaceutical market by value, resulting in more than 20% price reduction in 60% of the NLEM. The prices of some drugs will fall by up to 70%." According to Ray, DPCO 2013 will "achieve the objectives of the government in ensuring essential medicines are available to those who need them most by managing prices in the retail market and balancing industry growth on a longer-term perspective."

Impact on consumers

While consumers could potentially benefit from price cuts, it may not necessarily lead to easy medicines access, which is based on patients' socioeconomic strata. Amit Backliwal, general manager of IMS Health, South Asia, told *Pharmaceutical Technology Europe*. The effect will not be as pronounced for those in the upper strata who can afford the pre-2013 DPCO prices; whereas, patients who are on the other end of the spectrum will continue to be unable to afford the medicines even after the revision. Only

the middle-income groups will reap maximum benefits from the changes of the new drug-pricing policy.

Impact on the industry

With the new policy in force, IMS Health estimates that the erosion in overall market revenue will be approximately \$290 million on an annual basis, which is a 2.2% drop of the entire market. Inevitably, the policy will affect profit margins and sales of medicines. Sujay Shetty, executive director and India pharma life sciences leader of PricewaterhouseCoopers, comments, "As NLEM drugs account for nearly 60% of the market, value erosion of the pharmaceutical market would be anywhere between 2% to 5% of the current pharmaceutical market. However, the extent of effect will vary from company to company depending on their current product portfolio and exposure to NLEM. This short-term effect will last between 12 to 18 months. In the long term, companies will devise suitable strategies to overcome this impact."

Multinational companies (MNCs) will be greatly affected by the new pricing regime. For example, Centrum Broking, a financial-solutions provider based in India, projected that the profit margins of GlaxoSmithKline and Novartis could drop between 2% to 7% under DPCO 2013. On the other hand, Indian companies such as Sun Pharma and Dr. Reddy's Laboratories would be less affected due to their focus on export market.

Backliwal says, "The bigger pharma companies will likely take the brunt of the revenue erosion but they will also be more able to balance the drop in profits with higher volumes due to greater market reach and brand value. The major impact will be felt by mid-level pharma companies who will need to draw up new strategies and look beyond the price-differential advantage that they currently leverage to grow



sales. Also, companies with brands under the older DPCO 1995 regime will be now able to take annual price increases and make up for the losses (to some extent) from their portfolio, which will fall under the newer regulation."

Shetty adds, "Companies may carefully examine their current portfolio for the exposure to NLEM and level of diversification and realign to negate the effect of the new policy. They can look at ramping up chronic portfolio to reduce their dependence on acute therapies, which have been growing at a slower pace. Enhanced focus on over-the-counter products, vaccines and biosimilars would start gaining importance in overall business strategies. Companies will look at in-licensing initiatives, comarketing and alliances with MNCs over the long run."

Outlook

Despite the implications of DPCO 2013, foreign companies are not likely to move away from India given its promising market. With a 12.5% (± 4.0%) estimated compound annual growth rate over the next few years, India is the second fastest growing country among the emerging markets, ranked only behind China.

The Indian market is driven by rising incomes, macroeconomic expansion and increasing access to medicines, supported by a range of government policies and programs. Revenue may be eroded as a result of DPCO 2013, but Big Pharma's greater challenge is to obtain and enforce intellectual-property protection

IMPORTANT FACTS

- Under the new drug-pricing policy, the maximum price of each drug will be limited to the weighted average price of all its variants having a volume-based market share of more than 1%. The new policy covers 30% of India's drug market, which is worth approximately \$13.1 billion annually.
- The revised drug-pricing policy will encourage small- and medium-size domestic players to invest in R&D. Drugs that are locally discovered and developed using indigenous R&D and granted patent under Indian law can seek exemption from price control for five years from the commercial production date in the country.

rights. Compulsory licensing, patentability, patent enforcement, regulatory approval and data exclusivity are issues that they will need to grapple with.

The revised drug-pricing policy will encourage small- and medium-size domestic players to invest in R&D. It will also help some small players achieve price parity in certain niche segments. Locally discovered and developed drugs are eligible to avoid price control for five years. Drugs developed using indigenous R&D and granted patent under Indian law can seek exemption from price control from the commercial production date in the country. **PTE**

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EMERGING MARKET REPORT

REGULATION & COMPLIANCE

Report from:

South Korea

Jill E. Sackman

The bio-pharmaceutical business outlook in South Korea remains positive.

South Korea is a rapidly growing pharmaceutical market. Previously considered a developing economy, this country was reclassified as a developed economy in 2010, though it is still considered an emerging market. In recent years, South Korea's high growth rate has continued amid worldwide economic downturns and is expected to continue in years to come. It is estimated to be the fastest growing developed market in the world. Other characteristics, such as recent free-trade agreements strengthening intellectual property rights and an aging population, make the market attractive for multinational companies. There are, however, considerable challenges. While South Korea's overall economy has outpaced other countries in the years since the worldwide economic downturn, rapidly rising healthcare costs caused the government to cut drug prices in 2011. Because the government is the single payer, this rise in costs has had a profound impact. South Korea's new president, Park Geun-Hye, has made building a safe and happy population a centerpiece of her platform. As a result, the Ministry of Food and Drug Safety (MFDS) has highlighted their own goal of becoming an international model for drug safety.

South Korea health and pharmaceutical market overview

The International Monetary Fund (IMF) considers South Korea to be a "graduated" developing economy, with the 15th highest gross domestic product (GDP) per capita worldwide and the 12th highest purchasing power parity (PPP). It is now the fourth largest healthcare market in the Asia-Pacific region, following Japan, China and Australia (1). According to the Korean Pharmaceutical Traders Association, Japan and China are also the largest buyers of exported drugs from South Korea (2).

Over the past four decades, South Korea's population has consistently migrated from the countryside to cities, especially the capital, Seoul. With 9.8 million inhabitants at the last census in 2005 and more than 24.5 million people in the surrounding areas, Seoul is the most densely populated city in the OECD. The population is one of the most ethnically homogeneous, but low birth rates and a rapidly aging population have resulted in increasing immigration since 2000, largely from other Asian countries, with government projections that the immigrant population could be as high as 6% in 2030 (3). The government has also created incentives for fertility and adoption in recent years to balance the rapidly aging population.

Population demographics have two particular implications for pharmaceutical companies looking to expand in the region: first, the labour participation rates of the Korean population will decrease, and second, the aging population will face greater health needs.

Healthcare is paid for by National Health Insurance (NHI) with financing help from employee/employer contributions and is compulsory. Eligibility extends to all residents of South Korea, regardless of their nationality. This program does require copayments for pharmaceutical products, set at 35–40%. Because the copay is a percentage, some individuals also purchase private plans to offset additional costs in the case of expensive diseases such as cancer.

Key regulatory considerations

The MFDS has established a number of specific goals for the pharmaceutical industry in South Korea. First, as part of President Park's goal to "open a new era of safe society and happiness for all people," the Minister of the MFDS, Chung Seung, has stated



EMERGING MARKET REPORT

that his goal is “to become a globally recognised nation for food and drug safety” (4). Strategies for his work include promoting consumer participation in safety efforts.

There have also been changes to Korean pricing for drugs that have had the effect of slowing pharmaceutical market growth in recent years. In the past, Korean pharmaceutical companies had primarily focused on generics, with name-brand drugs produced by international companies. In January 2012, in response to rapidly rising healthcare costs, the government announced its plan to cut the price of drugs dramatically once patents expire. Previously, drug prices had been capped at 80% of original prices once the patent expired for original drugs, with generics capped at 68%. The new pricing scheme lowered those caps to a range of 59.5% to 70% for innovator drugs for the first year, and additional cuts after that (5). The stated goals of these cuts were twofold: to reduce the percent of government spending for drugs and to encourage Korean companies to pursue more innovative research. The Ministry of Health and Welfare also pledged financial incentives to companies that make innovative drug development a priority.

The MFDS has also worked in recent years to expand the manufacture of biosimilars. In 2009, the Ministry introduced regulatory guidelines and funding to promote biosimilar development. The stated goal of the government is for South Korea to achieve 22% global market share by 2020. The government’s funding has been supplemented with private funding, with investments from companies such as Samsung Electronics (\$389 million over five years) (6).

Other regulatory changes include the Korea-US Free Trade Agreement, which went into effect in March 2013. This agreement reduced tariffs between the two countries, and creates additional protection for patented drugs from generics-drug competition by increasing the testing requirements (and associated expenses) for generics and specifies additional data protection requirements.

Implications for successful market entry and in-region partnering

South Korea, with its pharmaceutical market ranked in the global top 10 with sales of approximately \$16.5 billion in 2011, clearly offers significant business opportunity. Trade has become significantly easier with the recent signing of the South Korea-EU Free Trade Agreement (FTA) in July 2011 and South Korea-United States (KORUS-FTA) in March 2012. KORUS is widely seen as the most significant free-trade agreement ratified by the US since the North American Free Trade Agreement (NAFTA). For the US, KORUS-FTA opens up Korea’s \$1 trillion economy to “America’s workers and businesses, while also strengthening our economic partnership with a key Asia-Pacific ally,” said US Trade Representative (USTR) Ron Kirk (7). Along with KORUS-FTA, there has also been a significant commitment to strengthening to intellectual property rights and enforcement provisions.

For the biopharmaceutical market, KORUS is important because it not only focuses on intellectual property rights but also establishes discipline in the Korean Government’s approach to drug reimbursement and pricing. As a single-payer system, gaining access to the Korean national healthcare system is a crucial element for success in this market.

On a cautionary note, Pharmaceutical Research and Manufacturers of America (PhRMA) CEO John Castellani is on the record as stating that, “while this FTA represents a 21st-century standard that should be a model for other agreements including the Trans Pacific Partnership (TPP), we [PhRMA] are highly concerned that the Korean government has not implemented certain provisions requiring transparency and due process in the manner that Korea prices and reimburses biopharmaceutical products” (8).

Also on the horizon is reform of the pharmaceutical reimbursement process. Recently the national health system announced reimbursement reform aimed at increasing “rational resource use in drug spending” (9). Following policies similar to those set in many EU economies, South Korea’s national health system aims to take cost-effectiveness and budget impact of new drugs into consideration in payment decisions. If these policies are implemented, South Korea will be the first Asian country to officially use economic evaluation in healthcare.

Moving forward in South Korea

South Korea has sustained rapid growth, low debt, and resilience to global financial stress. South Korea’s high-quality healthcare system has stimulated demand for medical tourism with strong government support. Implementation of free-trade agreements with the EU and US will likely have a considerable positive impact on the healthcare market through IP protection, opening of access to the single-payer government system, and a reduction in trade tariffs (estimated to eliminate 95% of tariffs within five years). Overall, the pharmaceutical and biotech business outlook in South Korea remains positive.

On the flip side, manufacturers will need to keep a close eye on reimbursement reform as it progresses, and be prepared to provide both strong clinical and economic data to justify pricing and market access.

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Sizing Up Big Pharma's Manufacturing Investment Strategies

The pharmaceutical majors target biologics and emerging markets in their manufacturing expansion activities.

Patricia Van Arnum
is Executive Editor of
Pharmaceutical Technology
Europe.

Restructuring and manufacturing rationalisation has been the recent norm for many bio/pharmaceutical companies. Despite such cost-cutting, particularly in small-molecule API and solid-dosage operations, there are some bright spots. A review of leading companies (see **Tables I and II**) show key trends. Several Big Pharma players are investing in biologic drug-substance, vaccine and parenteral drug manufacturing and are also making select investments in emerging markets.

Company activity

Pfizer. Pfizer is investing \$130 million (EUR 98 million) in two Irish manufacturing sites: \$100 million (EUR 76 million) at its Grange Castle site in Dublin and \$30 million (EUR 23 million) in the Ringaskiddy site in Cork, according to a 11 July 2013 press release from IDA Ireland, Ireland's industrial development agency. The \$100-million (EUR 76-million) investment in Grange Castle is for additional mammalian-cell manufacturing capacity with the addition of a new production line, scheduled to be operational in 2015, when the first process validation batches will be made. In 2011, Pfizer invested \$200 million (EUR 151 million) in the Grange Castle site to develop a new suite to expand the manufacturing process for an invasive pneumococcal vaccine, according to IDA.

Bristol-Myers Squibb. Bristol-Myers Squibb is spending \$250 million (EUR 189 million) to expand its large-scale biologics manufacturing facility in Devens, Massachusetts. The expansion will introduce biologics development and clinical-trial manufacturing capabilities to the site. The Devens site is home to the company's large-scale bulk biologic manufacturing facility. Construction of the Devens site was completed in 2009. It was the company's largest single capital investment (\$750 million [EUR 567 million]) and provided

the company with large-scale bulk biologics production capacity. In May 2012, the company received US Food and Drug Administration approval to manufacture its arthritis drug Orencia (abatacept) at the Devens facility. The new \$250-million (EUR 189-million) investment will be used to construct two new buildings: one for process development and one for clinical manufacturing. The two buildings will add approximately 200,000 ft² of laboratory and office space to the Devens site.

Bristol-Myers Squibb also announced plans to locate a North America Capability Centre in Tampa, Florida, according to a 18 July 2013 press release from the Office of the Governor of Florida. The 70,000-ft² facility will open in January 2014 with approximately 250 employees with plans to add more than 325 additional jobs at the site by 2017.

Novartis. In the fourth quarter of 2012, Novartis announced plans to construct a new biotechnology production site in Singapore with an investment valued at more than \$500 million (EUR 378 million). The new facility will focus on drug-substance manufacturing based on cell-culture technology. Construction begins in 2013, and the site is expected to be fully operational in 2016. It will be colocated with the company's production site in Tuas, Singapore. Novartis expects its Singapore site to be a technological competence centre for both biotechnology and pharmaceutical manufacturing.

In December 2012, Novartis acquired a 16,000-m² FDA-approved manufacturing facility in Morris Plains, New Jersey from the biopharmaceutical company Dendreon. The facility and certain former Dendreon personnel that were retained will support clinical and commercial production of products from the Novartis–University of Pennsylvania (Penn) collaboration. Under the Novartis–Penn pact, the parties will research, develop and commercialise targeted chimeric antigen

receptor immunotherapies as well as build on the Penn campus in Philadelphia, Pennsylvania, the Centre for Advanced Cellular Therapies, which will be dedicated to developing and manufacturing adoptive T-cell immunotherapies.

On the vaccine side, Novartis is proceeding with a multiyear vaccine-production project. In 2008, it broke ground on a new rabies and tick-borne encephalitis \$330-million (EUR 250-million) manufacturing facility in Marburg, Germany. Construction is complete, and the facility is in the process of executing the necessary validation activities with regulatory approvals for products planned for 2013. In 2009, Novartis opened a new cell culture-based influenza vaccine-manufacturing site in Holly Springs, North Carolina. As of 31 Dec. 2012, the total amount spent on the project was \$426 million (EUR 322 million), net of grants reimbursed by the US government. The total investment in this new facility is expected to be at least \$900 million (EUR 681 million), partly supported by grants from the US government and prior investments in influenza cell-culture technologies at the Novartis vaccines site in Marburg, Germany. Novartis is also building a new \$475-million (EUR 359-million) vaccine-manufacturing facility in Recife, Brazil. The technical start-up of the facility is planned for 2015.

Novartis is moving forward with other investments. The current phase of the long-term redevelopment of its St. Johann headquarters site in Basel, Switzerland is expected to be finalised in 2015. This project was started in 2001 with the aim of transforming the site from one designed mainly for pharmaceutical production into a centre of knowledge with an emphasis on international corporate functions and research activities. Novartis expects that through 2015 it will spend more than \$2.3 billion (EUR 1.74 billion) on the project and will transfer production from the site to other facilities in the Basel region. In the second quarter of 2012, Novartis began construction of a CHF 500 million (EUR 404 million) solid-dosage manufacturing facility in Stein, Switzerland. The new facility will replace an older facility that will be partially demolished by 2016.

Rank	Company	2012 global prescription drug sales (US\$ billions)	2012 R&D spending (US\$ millions)
1	Pfizer	\$47.404	\$7046
2	Novartis	\$45.418	\$8831
3	Merck & Co.	\$41.143	\$7911
4	Sanofi	\$38.370	\$6117.8
5	Roche	\$37.542	\$8032.2
6	GlaxoSmithKline	\$33.107	\$5255.7
7	AstraZeneca	\$27.064	\$4452
8	Johnson & Johnson	\$23.491	\$5362
9	Abbott*	\$23.119	\$2900
10	Eli Lilly	\$18.509	\$5074.5
11	Teva	\$17.681	\$1283
12	Amgen	\$16.639	\$3318
13	Takeda	\$15.173	\$3720.5
14	Bayer	\$14.734	\$2522.7
15	Boehringer Ingelheim	\$13.686	\$3012
16	Novo Nordisk	\$13.478	\$1882.3
17	Bristol-Myers Squibb	\$13.155	\$3715
18	Daiichi Sanyko	\$11.019	\$2287.2
19	Astellas Pharma	\$10.835	\$2224.3
20	Gilead Sciences	\$9.398	\$1682.7
21	Baxter International	\$8.857	\$1015
22	Otsuka Holdings	\$8.385	\$1869.5
23	Merck KGaA	\$7.709	\$1551.6
24	Mylan	\$6.697	\$388.9
25	Eisai	\$6.181	\$1423.5

*Source: The Pharma 50, *Pharm. Exec.*, May 2013. Data were compiled using companies' annual reports and US SEC filings, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys. For privately held companies and in some other instances, the numbers reflect a best estimate based on a consensus methodology that includes forecasts from brokers covering these companies. All data represent the fiscal year that ended in 2012. For most US and European companies, this means the year ending 31 Dec. 2012 and for many Japanese companies, the fiscal year ending 31 March 2012. Historic averages were used in the conversion of companies' native currency to US dollars. R&D is research and development. Note: Effective January 2013, Abbott spun off its research-based pharmaceutical and biologics businesses into a separate company, AbbVie. Abbott is now a separate company consisting of the company's medical products, including branded generic pharmaceuticals, devices, diagnostics and nutritional businesses.

Stein is planned to be a technological competence centre for sterile and solid dosage drugs. In 2012, Novartis began a series of projects in which the company expects to invest more than \$300 million (EUR 227 million) during the next several years in three areas: implementation of a serialisation product-tracking program across its pharmaceutical operations network, a GMP upgrade for its milling

and blending centre at Stein and an upgrade of change-control systems. The company is continuing a multiyear upgrade of its campus in East Hanover, New Jersey. The company expects that through 2013, it will have spent more than \$545 million (EUR 412 million) to complete the construction and consolidate operations there.

In emerging markets, Novartis is investing \$140 million (EUR 106 million)

Table II: Top 50 pharmaceutical companies (Rankings 26–50).

Rank	Company	2012 global prescription drug sales (US\$ billions)	2012 R&D spending (US\$ millions)
26	Celgene	\$5.369	\$1412.1
27	CSL	\$5.345	\$423.5
28	Les Laboratoires Servier	\$4.931	\$1232.7
29	Allergan	\$4.756	\$926.8
30	Actavis	\$4.716	\$401.8
31	Mitsubishi Tanabe Pharma	\$4.547	\$853.2
32	Shire	\$4.407	\$848.8
33	Chugai Pharmaceutical	\$4.359	\$761.1
34	Biogen Idec	\$3.783	\$1326.3
35	Dainippon Sumitomo Pharma	\$3.625	\$732.2
36	UCB	\$3.566	\$1064.6
37	Fresenius	\$3.445	\$270
38	Menarini	\$3.045	\$220.7
39	Grifols	\$3.000	\$137.7
40	Valeant Pharmaceuticals	\$2.957	\$79.1
41	Forest Laboratories	\$2.903	\$891.4
42	Purdue Pharma	\$2.678	\$434.4
43	Kyowa Hakko Kirin	\$2.575	\$551.2
44	Hospira	\$2.570	\$303.6
45	Lundbeck	\$2.349	\$503.5
46	Endo Health Pharmaceuticals	\$2.329	\$137.7
47	Warner Chilcott	\$2.306	\$103
48	Stada Arzneimittel	\$2.241	\$69.0
49	Shionogi	\$2.162	\$647.5
50	Ranbaxy Laboratories	\$2.049	\$112.9

Source: The Pharma 50, *Pharm. Exec.*, May 2013. Data were compiled using companies' annual reports and US SEC filings, other *Pharm Exec* estimates, and contributions from the EvaluatePharma industry sales surveys. For privately held companies and in some other instances, the numbers reflect a best estimate based on a consensus methodology that includes forecasts from brokers covering these companies. All data represent the fiscal year that ended in 2012. For most US and European companies, this means the year ending 31 Dec. 2012 and for many Japanese companies, the fiscal year ending 31 March 2012. Historic averages were used in the conversion of companies' native currency to US dollars. R&D is research and development.

for a new pharmaceutical plant in St. Petersburg, Russia. Annual production is expected to be 1.5 billion units per year (oral solid dosage forms), of which the majority will be for generic-drug products. Product registration for production at the site is expected to begin in 2014.

In China, Novartis is moving ahead with an expansion of its research facilities. Novartis is investing \$1 billion (EUR 756 million) to increase its R&D operations in Shanghai. Based on a

re-evaluation of the site made in 2010, the company expanded its Phase 1 plan to include two buildings to house 800 offices and 400 laboratory work places. As of 31 Dec. 2012, structural work was finished, and the first above-ground buildings began to be built. Novartis also began construction in April 2012 for new laboratory and office space at its research facilities in Cambridge, Massachusetts as part of a multiyear \$600-million (EUR 454-million) investment at that site.

Sanofi. Sanofi's Frankfurt, Germany site, its principal manufacturing center for diabetes products, is being equipped with a new aseptic processing area that uses isolator technology to improve the aseptic-filling process. This investment will be operational in 2016. Sanofi's Frankfurt site is one of three dedicated biotechnology hubs that the company is developing in Europe. In 2012, its facility in Vitry-sur-Seine, France, the company's largest integrated cell-culture facility, produced the first technical batches of aflibercept, the API in the anticancer drug Zaltrap. Its facility in Lyon Gerland, France, is a new world centre dedicated to the production of thymoglobulin, a drug to prevent and treat transplant rejection. During 2012, teams at Lyon prepared a dossier for the healthcare authorities to transfer production to this site.

In the United States, Sanofi, through its subsidiary Genzyme, has major investments underway, including at its Framingham, Massachusetts biologics site, which was approved by FDA and the European Medicines Agency in 2012 for the manufacture of Fabrazyme (agalsidase beta). Its site at Allston, Massachusetts moved forward with a major investment programme in connection with the implementation of a compliance-remediation workplan approved by FDA in January 2012. Also, in 2012, Sanofi's Genzyme acquired the Bayer Healthcare facility in Lynnwood, Washington, which specialises in the manufacture of Leukine (sargramostim).

Sanofi is undergoing a major investment phase, which includes a new dedicated dengue-fever vaccine facility in Neuville, France scheduled to produce its first batches in 2014. In response to observations made by FDA during routine inspections conducted in 2012 at Sanofi's facilities in Toronto and Marcy l'Etoile, France, Sanofi initiated a compliance program to address quality issues.

Sanofi is moving forward with other investments in emerging markets. Two new dedicated influenza vaccine-manufacturing facilities are in the start-up phase. Sanofi's facility in Shenzhen, China is testing its production processes, and its facility in Ocoyoacac, Mexico was approved by Mexican regulatory authorities at the start of 2012 and began production

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for the Mexican influenza vaccination program in September 2012.

The Sanofi diabetes industrial network also is expanding its manufacturing footprint in Russia as well as in China (Beijing), where a new facility that was inaugurated in 2012 began assembly and packaging of SoloSTAR, the prefilled injection system for Lantus (insulin glargine). Also, during 2012, Sanofi's pharma site in Ankleshwar, Gujarat State, India, handled packaging and quality control through to release for the first commercial batches of AllSTAR, the company's insulin pen specifically intended for the India market.

Earlier this year, Sanofi began construction for a new \$75-million (EUR 57 million) manufacturing in Saigon, Vietnam. The plant, which is scheduled to be operational by the end of 2015, will have an initial capacity of 90 million units per year with a possible extension up to 150 million units. In the Middle East, Sanofi is investing in a new solid-dosage manufacturing facility in Saudi Arabia; products from the facility are expected in 2015. The company is also investing in a new hormonal-products facility in Brasilia, Brazil. The company's Goa site in India expanded solid dosage production capacity to approximately 2.5 billion pills a year. And in Algeria, Sanofi signed an agreement with the local authorities for a major industrial investment that will lead to the construction of a large industrial complex in the Africa-Middle East region.

Roche. Roche is investing CHF 240 million (EUR 194 million) at its facility in Penzberg, Germany to expand raw-material manufacturing for its Elecsy immunoassays, to be completed by the end of 2014, as well as to increase compounding, filling and lyophilisation capacity, which is planned for 2016. At its sites in Basel and Kaiseraugst, Switzerland, Roche is investing CHF 230 million (\$186 million). Three projects were completed in 2012: a new pharmaceutical quality control and assurance building, expansion of cold-chain storage capacity and a filling line upgrade for Herceptin (trastuzumab) subcutaneous formulation. The company is also expanding capacity for high-potency drugs. Also, Roche plans to upgrade the filling line for the cephalosporin

antibiotic Rocephin (ceftriaxone) in 2013 and 2014. Roche is investing CHF 260 million (\$210 million) to expand its Shanghai pharmaceutical facilities, including new laboratory, warehouse, office and training facilities, to be completed in 2014.

These moves come as Roche restructures. In 2012, Roche announced that it is closing its R&D facility in Nutley, New Jersey, which is expected to be completed by the end of 2013. The R&D activities at Nutley are being consolidated at existing sites in Switzerland and Germany and at the planned Translational Clinical Research Centre at the Alexandria Centre for Life Science in New York.

GlaxoSmithKline. In 2012, GlaxoSmithKline (GSK) announced it was investing more than £500 million (EUR 581 million) in the United Kingdom across its manufacturing sites, which included selecting Ulverston in Cumbria as the location for the first new GSK manufacturing facility to be built in the UK in almost 40 years. The company also will invest in sites in Montrose and Irvine, Scotland. GSK will locate a new £350-million (EUR 407-million) biopharmaceutical manufacturing facility in Ulverston, Cumbria. Detailed planning and design of the new facility is underway with an anticipated start date for construction of 2014-2015, dependent on portfolio timing and obtaining necessary planning and related consents. Once construction starts, it is likely to take at least six years before the plant is fully operational, according to GSK.

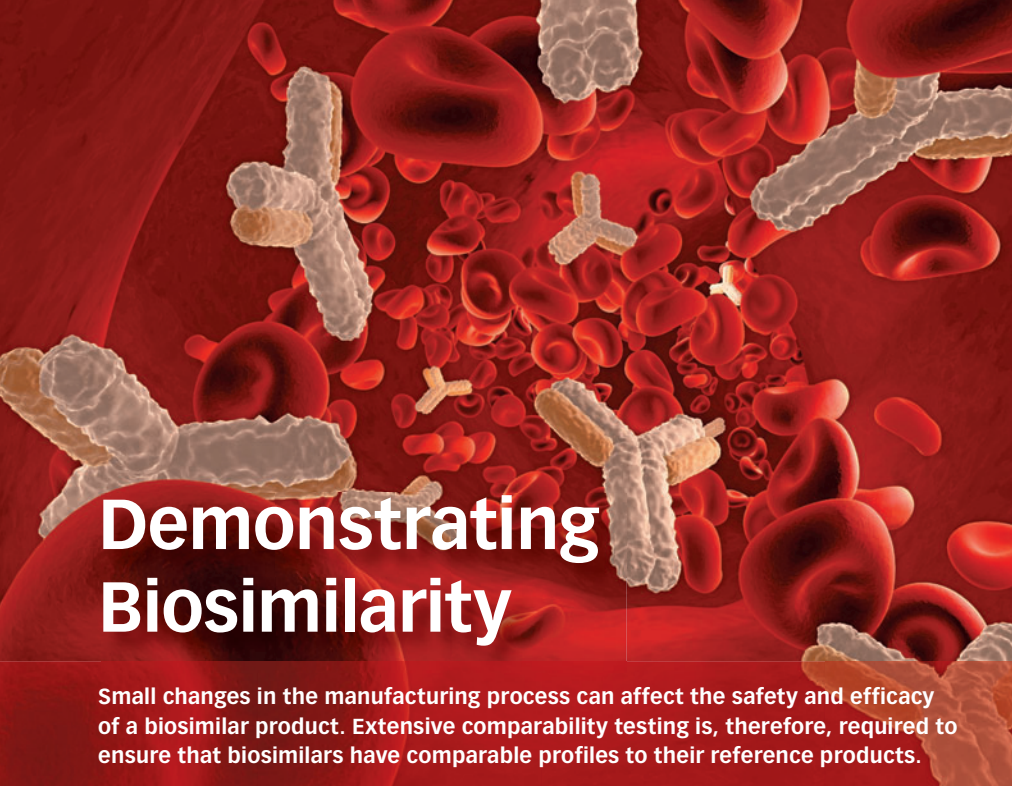
In June 2013, GSK received an offer from South Africa's Aspen Holdings/Aspen Pharmacare for its facility in Notre-Dame de Bondeville, France and the associated thrombosis brands manufactured at the site. GSK is also proceeding with plans, announced in February 2013, to improve the competitiveness of its European pharmaceutical business and restructure its manufacturing and R&D operations. The company is targeting to realise annual savings of at least £1 billion (EUR 1.16 billion) by 2016.

Eli Lilly. In April 2013, Eli Lilly indicated plans to invest an additional \$180 million (EUR 136 million) in its insulin-manufacturing operations in Indianapolis, Indiana. The investment is

in addition to its \$140-million (EUR 106 million) expansion of the its Indianapolis insulin-manufacturing operations. Lilly is proposing other ancillary investments totaling about \$80 million (EUR 61 million), including a \$40-million (EUR 30-million) product-inspection centre. The latest \$180 million (EUR 136 million) proposed investment would add a second insulin cartridge-filling line and increase insulin-active-ingredient manufacturing capacity through productivity enhancements. Eli Lilly is also investing EUR 330 million in a new biopharmaceuticals facility at its Kinsale campus in Cork, Ireland, according to a 27 Feb. 2012 IDA Ireland press release.

Merck & Co. Merck & Co. opened a new \$120-million (EUR 91 million), 75,000-m² pharmaceutical manufacturing facility in Hangzhou, China earlier this year. The facility has capacity of up to 16 high speed lines to package pharmaceutical tablets and sterile products. Annual packaging capacity is more than 300 million packages. The facility builds on other recent investment by Merck in China. In 2011, the company established its Asia R&D headquarters in Beijing and committed to invest more than \$1.5 billion (EUR 1.1 billion) in R&D in China during the next several years.

AstraZeneca. In June 2013, AstraZeneca announced that Cambridge, UK will be the location for the company's new UK-based global R&D centre and corporate headquarters. The new £330-million (EUR 384-million) facility in Cambridge will bring together AstraZeneca's small-molecule and biologics R&D activity. The purpose-built facility, which will be located in the Cambridge Biomedical Campus, is part of the company's previously announced plan to create strategic global R&D centres in the UK, US and Sweden by 2016. The company is also proceeding with further restructuring activity, which entails an estimated global headcount reduction of about 5050 over the 2013-2016 period. AstraZeneca also moved forward with two key production facilities during 2012 in China (Taizhou) and Russia (Vorsino) to supply products to both markets locally. These sites are intended to begin phased commercial production in 2014. **PTE**



Demonstrating Biosimilarity

Small changes in the manufacturing process can affect the safety and efficacy of a biosimilar product. Extensive comparability testing is, therefore, required to ensure that biosimilars have comparable profiles to their reference products.

Alison Armstrong is director of development services at BioReliance.

Biosimilars are biologically derived therapeutics that are designed to be the equivalent, both functionally and structurally, as branded biologics. Because biologics are so sensitive to manufacturing changes, they can be particularly hard to copy. Unlike drugs made from small molecules, any change in the process or the products used to make them increases the possibility that they will be dissimilar from the originator product.

Biosimilars have been available in Europe since the 2006-approval of Omnitrope, Sandoz's version of Pfizer's growth-hormone product Genotropin (somatotropin). Several versions of two other biologics, erythropoietin and filgrastim, are also now available from various companies. While none are yet approved in the United States (US), a legal framework towards biosimilar approval is now in place, and it is only a matter of time before the innovator companies face competition in this market.

The European Union (EU) authorities implemented their guidelines for biosimilars in 2004 as part of an amendment to the community code relating to medicinal products for human use. In Europe, however, the term "biosimilar" is not explicitly defined, and whether a product would be acceptable via the "similar biological medicinal product" approach is dependent on analytical procedures, the manufacturing processes used, and clinical and regulatory experience. The European Medicines Agency (EMA) also demands comparability studies to substantiate the similar nature of the two products in terms of quality, safety and efficacy.

The clinical trials for biosimilars that have been demanded by the EMA ahead of approval have somewhat varied. Products have been approved despite differences in the glycosylation patterns and impurity profiles between the biosimilar and the innovator product. So far, all the biosimilars approved in Europe have been versions of naturally occurring hormones or cytokines, and draft guidelines for monoclonal-antibody products were published in 2011 (1).

FDA established the US framework in March 2010, and there are a number of key differences from the guidelines delineated in Europe. The US guidelines state that the clinically active ingredients in a biosimilar must be highly similar to the reference biologic, with no clinically meaningful differences in terms of safety, purity or potency. It must have the same mechanism of action, be administered in the same way via the same dosage form and have the same strength as the reference product.

With no biosimilars approved in the US to date, the guidelines have yet to be tested in practice for a marketed product. However, the experience gained in Europe during the past seven years may provide pointers. So what does the European experience tell us?

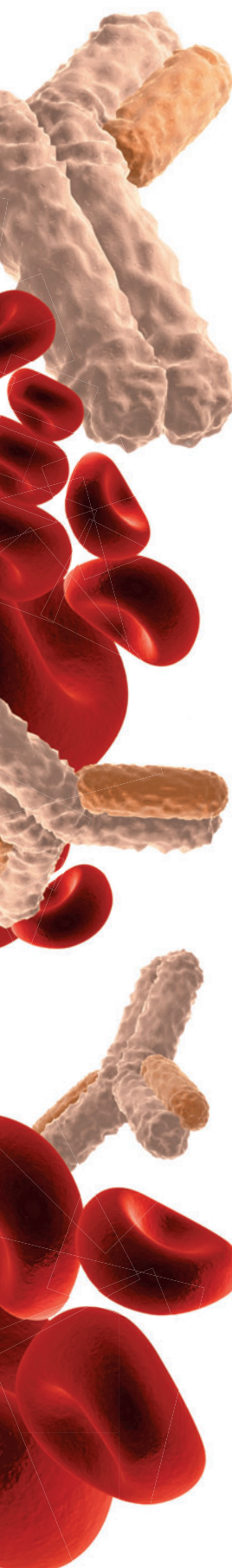
Safe substitution

To confirm the biosimilarity of a potential competitor biologic product to the original reference biologic, analytical studies must be carried out to show that it is indeed highly similar to the reference product. In general, extensive comparative physicochemical and functional studies are required.

Little is generally known about the originator company's manufacturing process as this is proprietary information. Variability in the exact nature of the biologic product is inevitable, thus, its intrinsic similarity to the reference product must be proven.

In addition, any impurities related either to the product itself or the process used to manufacture it must be identified, characterised, quantified and compared to those of the reference product as must all the substances deliberately included within the product. The type, nature and extent of any differences between the biosimilar and the reference must be clearly described and discussed in the application for approval.

A number of different factors should be considered when assessing if the two products are indeed highly similar. First, the expression system must be considered, including the identity of the cell line being transfected, the sequence of the transgene, any promoters or other control regions and the overall genetic identity and stability of the cloned gene. Biosafety testing of the cellular substrates including the master cell bank (MCB) and cells at the limit of *in vitro* cell age used for production must also be performed. The gene-copy number, and the gene-sequencing process, whether messenger ribonucleic acid (mRNA) or complementary deoxyribonucleic acid (cDNA) should also be determined in the cellular substrates. Fluorescence *in situ* hybridisation (FISH) analysis and restriction enzyme analysis should also be carried out. This comparison of the MCB and the cells at the limit of *in vitro*



cell age (considered to be the 'worst case scenario' in a bioproduction setting) enables the demonstration of the genetic stability characteristics of the MCB.

Next, the manufacturing process must be studied, including the cell line used, the glycosylation structure and heterogeneity it produces as well as both product expression levels and the expression of endogenous retroviral particles. Also, the viability and productivity of cells, product integrity and degradation products and levels of host-cell protein and DNA must be assessed. The nature of the media is also important, such as whether or not it contains serum, is protein-free or chemically defined. Processing considerations, such as the bioreactor

results can be accurately interpreted for marketing authorisation. It is also important to have careful interpretation of results to ensure continued safety and efficacy in the target populations. Analytical assays, therefore, have an important role in the decision-making process for marketing authorisation of biosimilar products.

Demonstrating equivalence to the materials used in toxicology and early phase clinical trials are required if bridging studies are to be avoided. Yet, demonstrating that two separate manufactured lots are identical is very difficult. The key is to achieve a level of consistency that falls within a set of defined parameters based on testing and characterisation.

Successful and effective comparability studies are key in the development of biosimilars.

format and the downstream process, must also be considered, along with the removal of process- and product-related contaminants, virus inactivation and removal, product formulation and product stability.

Finally, as with all medicinal products, the viral and microbial safety of the biosimilar must be considered. These are assured by three complementary approaches:

- Testing of starting materials for viral and microbial contaminants
- Testing process intermediates at appropriate stages in the manufacturing process for any contaminating viruses, mycoplasma, bacteria and fungi
- Analytical characterisation.

Comparability studies

Small changes in the manufacturing process can alter a product's efficacy and safety. According to the guidelines of the EMA, extensive comparability testing will be required to demonstrate that the biosimilar has a comparable profile in terms of quality, safety and efficacy as the reference product.

Various analytical assays are available to compare physicochemical and biological properties between production batches of a biosimilar in comparison with a reference product. It is important to recognise the limits of existing assays so that the

Prior knowledge of the innovator product (i.e., biochemical, biological and clinical data) is principally held by the regulatory authorities based on historical filing of clinical and toxicology data. The ability to reduce development time for the sponsor of the biosimilar is based on good regulatory interaction at the earliest stage of manufacture. This is important as such additional studies (e.g., bridging studies) can significantly extend development timelines and the cost of biosimilar development. Successful and effective comparability studies are thus key in the development of biosimilars.

Chemical analysis. As with small-molecule generic drugs, the structure of the biosimilar must be analysed but unlike small molecules, it is not so much a black-and-white question of proving that it is exactly the same but rather proving that it is sufficiently close to resulting in no obvious or appreciable functional difference in its biological activity. Analytical characterisation of a biosimilar should include primary, secondary, tertiary and quaternary structural assessment, biological activity and analysis of product impurities. All of these components must be understood and further characterised during comparability studies of the biosimilar with reference to the

innovator drug. Molecular weight is assessed using one or more forms of mass spectrometry, usually matrix-assisted laser desorption/ionisation mass spectrometry (MALDI-MS), electrospray MS or liquid chromatography-mass spectrometry (LC-MS). Techniques such as sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), high-performance liquid chromatography (HPLC) peptide mapping, glycosylation patterns, amino acid determination and carbohydrate content analysis are also used to carry out isoform and impurity studies.

There is no single analytical technique that will demonstrate all required criteria and characteristics of a biosimilar product for the purposes of comparison; therefore, a wide variety of tools are needed for this purpose. Several examples of these techniques are defined below:

- Mass spectrometry can be utilised to show any differences in molecular shift between the biosimilar and innovator product
- Capillary isoelectric focusing (CIEF) can be used to provide data for in-process samples
- Biacore analysis is used to assess receptor binding function
- Peptide mapping is utilised to differentiate enzymes or combinations of enzymes.

Biological analysis. Biologically relevant tests must be used to measure the product's activity and can also be used to glean information about higher order protein structure. In all instances, the results are compared with those of similar analyses for the reference innovator product. It is, however, not expected that the quality attributes of the biosimilar and the reference product will be completely identical. Minor structural differences between the two active substances may potentially be acceptable, but must be justified, as must any variability in post-translational modifications and differences between the impurity profiles. These differences will only be deemed acceptable if they are supported by the comparability exercise for quality attributes in relation to safety and efficacy.

Cell-based potency assays. Potency is a critical quality attribute,

and it is essential to prove the comparability of the biosimilar to that of the reference product in a relevant biological system. A potency assay that measures biological activity is, therefore, required for both lot release and stability testing. Biological potency assays can be *in-vitro* cell-based systems, *in-vivo* tests or enzymatic assays. Several

Potency assays typically measure the biological activity of the product over a range of concentrations.

different cell-based assays are available, including ligand binding assays, cell proliferation, cytotoxicity and cell death studies, activation or inhibition signalling events such as cyclic adenosine monophosphate (cAMP), measuring the cytopathic effect, and reporter gene assays. More than one bioassay may be required, depending on the biologic product's mechanism of action or complexity.

Cell-based assays are increasingly being used to demonstrate the biological activity of a product because of their advantages over *in-vivo* assays. Cell-based assays reduce animal usage while being both faster and cheaper, and they raise the regulatory standard in terms of output. They also provide a demonstration of equivalence of biological function with the original reference product.

Potency assays typically measure the biological activity of the product over a range of concentrations, comparing it to that of a well-characterised reference standard. The resulting dose–response curve may depict either the stimulation or the inhibition of the biological response. This potency is typically expressed as either an EC₅₀ value (half maximal effective concentration) or an IC₅₀ value (half maximal inhibitory concentration).

The inherent variability of biological assay systems and the resolution of such assays (a function of the dilution series, for example) may result in differences in measured potency from one assay to the next. The potency of the biosimilar in the test is thus expressed relative to that of the reference standard in the same assay to account for this. For example,

it might be described as, 92% as potent as the reference standard if its potency is a little lower, or perhaps 109% if it induces higher activity.

Besides showing that the biosimilar induces a similar biological effect, the assay must be sufficiently sensitive to discriminate small differences in biological activity and stability, with a quantitative readout over a range

of treatment concentrations. The cell line is the single most important factor in the development of most potency assays. Ideally, the cells will be of a physiologically relevant origin, but they may also be genetically engineered. Either way, it is vital to use well-characterised cells that respond predictably if the assay is going to be suitable for quality control use.

Once developed, potency assays need to be shown to be fit for the intended purpose, with experimental evidence of operation within acceptable parameters. The stringency and extent of validation required depend on how far down

Even after approval, clinical safety and pharmacovigilance procedures must be put in place.

the development process the product is. For late-stage and commercial products, the assay must be well characterised with all specifications set and justified, and full validation in accordance with ICH Q2(R1) is recommended (2). While this may take several months to complete, it is required for product licensing, and such assays require ongoing maintenance to ensure robust performance, including monitoring trending data and characterisation of key reagents throughout the assay's lifespan. Any changes in reagents should also be qualified, whether these are the internal reference standards or critical reagents such as growth factors, assay plates or detection reagents.

Nonclinical animal studies. Comparative *in-vitro* pharmacology and *in-vivo* studies comprising efficacy testing, pharmacokinetic assessment

and toxicology studies, including toxicokinetics anti-drug antibody and tolerance assessment, should be designed to maximise the information obtained in the comparisons between reference and biosimilar products.

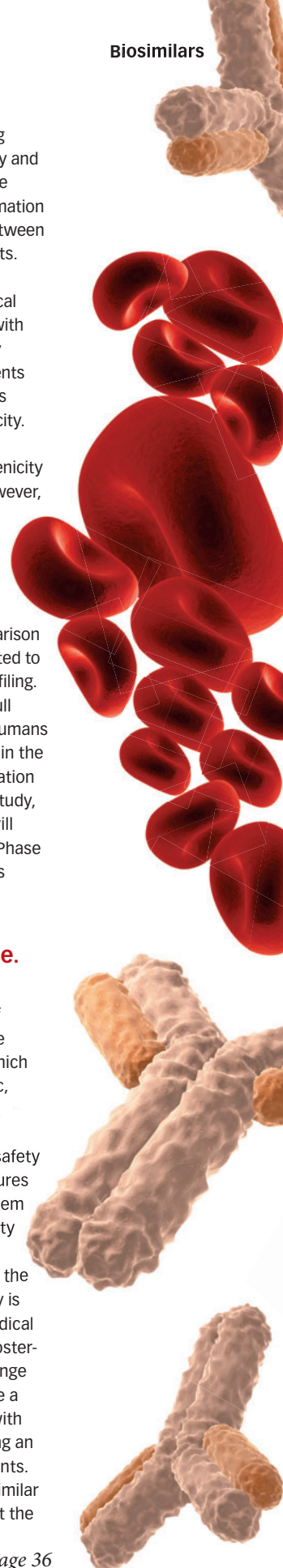
The pharmacodynamics effect and activity relevant to the clinical application must be assessed, with at least one repeat dose toxicity study. Toxicokinetic measurements will include antibody titres, cross reactivity and neutralising capacity. Normal safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies, however, are not required for biosimilars. For biosimilars, the conclusion of nonimportant differences in pharmacological activity, pharmacokinetic behaviour or toxicological tolerance in comparison to the innovator drug are expected to be referenced in the regulatory filing.

Clinical studies. Although full safety and efficacy studies in humans are not required for biosimilars in the EU, a degree of clinical investigation is necessary. A Phase I safety study, usually in healthy volunteers, will have to be performed. Then, a Phase III comparative study in patients

to look at the relative effects of the biosimilar and the reference product must be performed, which should include pharmacokinetic, pharmacodynamics and clinical efficacy assessments.

Even after approval, clinical safety and pharmacovigilance procedures must be put in place. One problem that can occur is immunogenicity (i.e., patients developing an unwanted immune response to the product). While immunogenicity is rare in innovative biological medical products, it can happen. The poster-child case was a packaging change for Eprex (erythropoietin) where a substitute stopper interacted with the product formulation, causing an immunogenic response in patients. Biophysical comparison of biosimilar and innovator drug showed that the

contin. on page 36



Using Tandem LC–MS for Cleaning Validation

The author describes how liquid chromatography–mass spectrometry works and explains some of its advantages and disadvantages.



Geoff Carr, PhD, is director of Analytical Development at Patheon, Mississauga, Ontario, geoff.carr@patheon.com.

Within any pharmaceutical manufacturing facility it is crucial to ensure that following the manufacture of a product, equipment has been thoroughly cleaned to avoid risks of any carryover into the following product. The process by which this is achieved is called cleaning validation, and an approach for conducting such validations is to develop a sequence of operations likely requiring the application of solvents or detergents and rinses. It must be demonstrated that this sequence of operations can remove traces of product residues down to levels that do not present risks to patients who may receive them as carryover components in the next product manufactured on the same equipment train. To collect data, swab samples taken from equipment surfaces or rinsates (i.e., washes that are used for the rinsing out of equipment after they have been treated with detergent) are analysed. Typically, samples of the final washes are taken for analysis.

If a validated cleaning procedure has not been developed, it will be expected that swab or rinsate analyses will be conducted on each occasion to demonstrate effectiveness of the cleaning procedure; this practice is referred to as cleaning verification.

For both cleaning validations and verifications, analytical testing of samples is a crucial step. Typically, analytical procedures that are specific for the APIs that were used for the manufacturing of previous products are applied. It is expected that a separate analytical procedure will be developed and validated for each individual API that is handled in any manufacturing facility. High-performance liquid chromatography (HPLC) is probably the most widely used analytical procedure for this application with ultra-high performance liquid chromatography (UHPLC) gaining increasing popularity, but liquid chromatography–mass spectrometry (LC–MS) also offers potential opportunities.

How LC–MS detection works

For mass detection to work, various analyte components that elute from the chromatographic

column must become ionised. Ionisation may be achieved using electrospray ionisation (ESI). An example of an MS detector (MDS SCIEX, AB Sciex) is depicted in **Figure 1**, and **Figure 2** depicts the layout of the electrospray of an MS detector. As shown in **Figure 2**, the effluent from the HPLC column is directed through a nebuliser that is maintained under a high voltage. The voltage can be selected for either positive or negative polarity depending on the conditions required for the components of interest. The charged droplets are subjected to heat to remove solvent, which creates a charged aerosol that is directed into the MS quadrupole.

Mass-spectrometry detection has almost universal applicability.

A quadrupole system provides the mechanism for discriminating between different components within the sample under test on the basis of M/z values, in which M is the molecular weight and z is the magnitude of charge. For example, the ESI process could lead to single or double-charged species or even higher depending on the chemical structure of the component concerned. By varying the magnetic field within the quadrupole system, species of different M/z values may either be eliminated or directed onto the instrument detector.

The configuration described in **Figure 2** is for a single quadrupole instrument (i.e., LC–MS). An even more discriminating system is provided by a triple quadrupole approach (i.e., LC–MS–MS). In this case, the species that are selected by the first quadrupole (Q1) are directed into a second quadrupole (Q2), which serves to collect the particular M/z species of interest and then direct them into a third quadrupole (Q3). Within Q3, the species are subjected to collisions with other atoms or molecules that are often provided by allowing a small volume of nitrogen into the system. Collisions lead to fragmentations and resulting fragment ions may then be used as a basis of the analysis required.

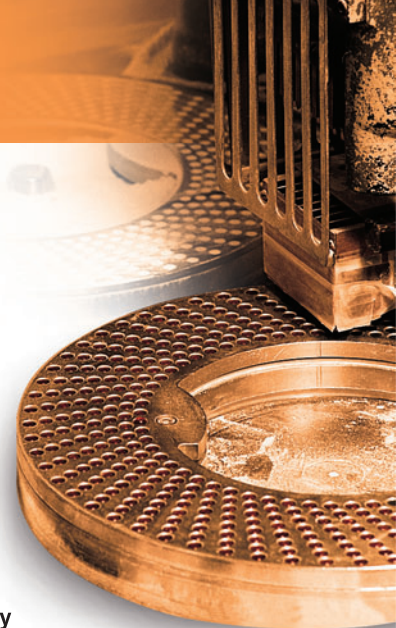
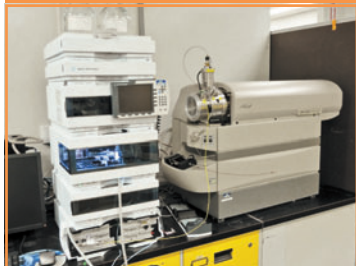


Figure 1: High-performance liquid chromatograph (Agilent 1200) with attached triple quadrupole mass spectrometer (MDS SCIEX).



Advantages and disadvantages of LC-MS

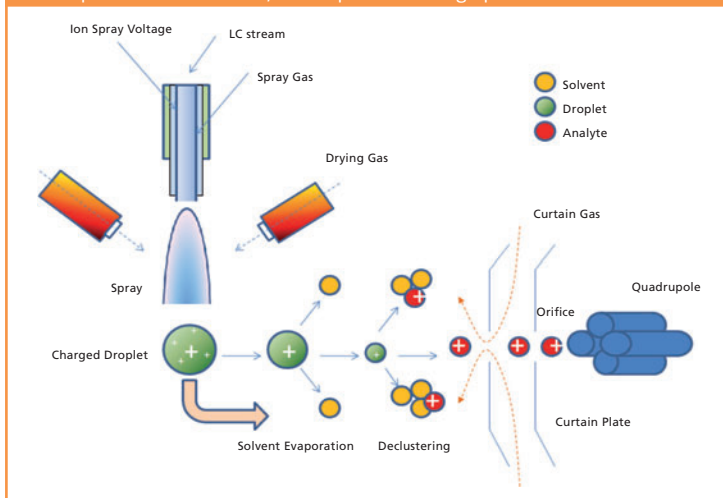
Cost. The price of a typical HPLC system with UV detection is approximately EUR 58,700. The price of a typical triple quadrupole MS detector is approximately EUR 147,000, and the user must still also purchase an HPLC front end for the system. In addition, at least two systems are recommended for any organisation considering the use of the LC-MS approach so that a back-up system is available. Pharmaceutical manufacturing facilities are scheduled to very tight timelines. Any downtimes, such as those due to cleaning following the manufacture of a batch and analytical testing of swabs and release formalities prior to manufacture of the next product, must be kept to a minimum; delays due to breakdowns of analytical equipment cannot be tolerated.

Applicability. HPLC is most often applied using ultraviolet (UV) light absorption detectors, which require that the chemical structures of analytes of interest include a chromophore (i.e., chemical structural features that absorb UV light). For most compounds of pharmaceutical interest, this is frequently the case, but there are exceptions that may require other types of detection. MS detection is appropriate for any analyte, provided that it can be ionised. Since most can be ionised, this approach has almost universal applicability.

Sensitivity. Analysis for cleaning residuals is an example of an application that requires very high sensitivity. LC-MS is capable of providing reliable quantitation of trace components from 100 to 1000 times lower than HPLC with UV detection.

Speed. HPLC runtimes are extremely variable depending on the particular method concerned. Run time is the time from the injection of the analytical solution into the chromatograph to the end of the resulting chromatogram. Run times of 5-10 or even 20 min. are not unusual. With LC-MS, typical run times are one to two min. System set-up time is also much reduced for LC-MS, as the same LC column and mobile phase can be applied for many applications. Each analysis will involve a sequence of injections, including those required for system suitability, standard solutions and sample solutions. Chromatograms then need to be processed into analytical reports, and data must be reviewed and

Figure 2: Diagram showing the layout of the electrospray system of a mass-spectrometer detector; LC is liquid chromatograph.



receive laboratory organisation approval. Overall, Patheon has found that laboratory turnaround time for analysis of swabs is about 24 h with HPLC and about 8 h with LC-MS.

Acknowledgements

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All figures are courtesy of the author.

Advancing Peptide Synthesis Through Stapled Peptides

Stapled peptides are a nascent class of peptides that stabilise helical conformations to enable cell permeability, binding to therapeutic targets and modulation of biological pathways.



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As a drug type, peptides offer certain benefits, such as specificity and potency, but they also present challenges, such as poor stability and short half-life. Stapled peptides, small modified helical proteins, are an emerging class of peptides that seek to address these limitations. These alpha-helical peptides have structural and functional properties that enable them to penetrate into the cell, bind to the therapeutic target and modulate biological pathways.

Peptides as drugs

Although peptides have the size and functionality to effectively modulate intracellular protein–protein interactions, they often do not permeate cells and, therefore, are used to modulate extracellular targets such as receptors (1–3). The majority of peptide candidates target extracellular molecules with less than 10% binding to intracellular targets, according to an analysis of the peptide drug pipeline by the Peptide Therapeutics Foundation (1, 4). The most common extracellular targets were G-protein coupled receptors (GPCRs), which include nearly 1000 transmembrane proteins that activate cellular response. During 2000–2008, 60% of peptides entering clinical development targeted GPCRs, and most had agonist activity. Although peptides represent a small portion of total drug candidates, the number of peptide drugs entering clinical development has increased during the past several decades, according to the Peptide Therapeutics Foundation analysis, which excluded insulins (1, 4). The study found that the average number of new peptide candidates entering clinical development in the 1970s was 1.2 per year, which rose to 4.6 per year in the 1980s, 9.7 per year in the 1990s, and 16.8 per year through 2000–2008 (1, 4).

On a commercial level, there are several peptide drugs that have reached blockbuster status. These include: Teva Pharmaceutical's Copaxone (glatiramer acetate), an L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine; AbbVie's Lupron (leuprolide acetate), a synthetic nonapeptide analog of the naturally occurring gonadotropin-releasing hormone (GnRH or luteinising hormone-releasing hormone [LHRH]); AstraZeneca's Zoladex (goserelin acetate),

a decapeptide and GnRH agonist and synthetic analog of a naturally occurring LHRH; Novartis' Sandostatin (octreotide acetate), a cyclic octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin; and Eli Lilly's Byetta (exenatide), a 39-amino-acid peptide amide (1, 4).

Stapled peptides as a solution

Stapled peptides are a nascent class of peptides that use stabilisation technology to enhance potency and cell permeability to address pharmacological limitations of small molecules and existing biologics in intracellular protein–protein interactions. Although small molecules are able to penetrate cells, the large binding surfaces for intracellular protein–protein interactions often make small-molecule modulators ineffective. Peptides and proteins have the size and functionality to effectively modulate intracellular protein–protein interactions, but do not permeate cells and therefore are used to modulate extracellular targets (1, 2, 5). Stapled peptides seek to resolve those problems. Because many undruggable therapeutic targets include those protein–protein interactions in which alpha-helices are required in lock-and-key-type mechanisms, an approach is to design alpha-helical peptides that have structural and functional properties that enable them to penetrate into the cell, bind to the therapeutic target and modulate the biological pathway (1, 2, 5).

A commercial path for stapled peptides

Aileron Therapeutics is one company specialising in developing stapled peptides. Its technology stabilises peptides by "stapling" them with hydrocarbon bonds into an alpha-helix. Once constrained in the alpha-helix structure, the peptides are protected from degradation by proteases. The stabilised alpha-helical peptides can penetrate cells by energy-dependent active transport and typically have a higher affinity to large protein surfaces (1–3, 5).

Aileron was cofounded in 2005 by Gregory L. Verdine, recently named CEO of the genomics company Warp Drive Bio. Verdine, who served as professor of chemistry at Harvard University, director of the Harvard/Dana-Farber Programme in Cancer Chemical Biology, and

executive director of the Chemical Biology Initiative at the Dana–Farber Cancer Institute, is noted for advancing the field of stapled peptides. In 2006, Aileron acquired exclusive rights from Harvard University in Massachusetts and the Dana–Farber Cancer Institute to develop and commercialise a drug-discovery pipeline of stapled peptides. In 2006–2007, Aileron licensed rights from the fine-chemicals and technology firm Materia for catalysts used in olefin metathesis. Materia holds the rights to the olefin metathesis technology

Aileron Therapeutics, which is partnered with Roche for stapled peptides, completed a first-in-human study of its lead stapled peptide drug earlier this year.

developed by Robert H. Grubbs, professor at the California Institute of Technology, who was awarded the Nobel Prize in Chemistry in 2005 with Richard R. Schrock and Yves Chauvin for their work in olefin metathesis using ruthenium-based catalysts. Part of the reaction scope of olefin metathesis is ring-closing metathesis (RCM), which transforms a diene into a cyclic alkene and is used to create macrocycles, including bioactive cyclic peptidomimetics. Grubbs was one of the first to offer research describing RCM to tether residues of helical peptides (1, 5).

Aileron is partnered with Roche for stapled peptides. The companies formed a potential \$1.1-billion (EUR 833 million) drug-development collaboration in 2010 for the discovery, development and commercialisation of stapled-peptide drugs and later expanded the collaboration. The initial programme encompasses up to five programmes with the initial two programmes targeting oncology, and the third programme, launched in late 2011, involving inflammatory diseases. Aileron also is partnered with Novartis and Eli Lilly through the respective venture funds of those companies (1, 5). In May 2013, Aileron announced the completion of the first-in-human study of its lead stapled peptide drug, ALRN-5281, a proprietary, long-acting growth-hormone-releasing hormone agonist for treating orphan endocrine disorders.

Other companies are involved in

stapled peptides. In November 2012, MorphoSys, a company specialising in antibody technology, partnered with the Dutch biopharmaceutical company Lanthio Pharma, which is involved with discovering and developing lantipeptides, a class of stapled peptides with high target selectivity and improved drug-like properties, which the company produces through its proprietary technology LanthioPep. The technology is used to identify peptides that are selective for a specific disease target and to stabilise them in

their optimal structural conformation for receptor binding. LanthioPep is a *Lactococcus lactis* based lanthionine-peptide technology and is used to discover peptide therapeutics with increased resistance to peptidase degradation, high receptor specificity and increased intrinsic activity.

Lanthio Pharma has generated stable, peptidase-resistant lanthionine peptides with specific agonistic activity for a number of GPCR targets, which is a focus area of the company. Many peptide ligands are thought to bind to their GPCR receptors through a “turn motif,” which can be stabilised in Lanthio Pharma’s peptides with a strong thioether bond. Fixing the turn motif in its optimal receptor binding conformation can result in specific agonistic receptor activation, according to the company. The technology also includes a proprietary bacterial display library capability, which allows for the construction of focused or randomised libraries of lanthionine-peptides. These libraries allow for functional screening and production of peptides for further *in vivo* and *in vitro* testing. Therapeutic plasma levels of lantipeptides can potentially be achieved by oral, pulmonary or subcutaneous delivery. Therapeutic products in Lanthio Pharma’s pipeline include a lanthionine-stabilised specific agonist of the AT2 receptor, which has potential in diseases where tissue protection is important, such as fibrosis.

Under the agreement, MorphoSys

and Lanthio Pharma will jointly apply their respective technologies to establish lantipeptide-based libraries. MorphoSys received preferred rights to exclusively license the LanthioPep technology for drug discovery and made an equity investment for a minority stake in Lanthio Pharma. Lanthio Pharma also is partnered with US-based Tarix Pharmaceuticals for Lanthio’s lead compound PanCyte, a lanthionine-stabilised angiotensin-(1-7) agonistic peptide for treating pulmonary indications. The start of clinical development of PanCyte is expected this year, according to company information.

Stapled peptides advance

Scientists are advancing research in stapled peptides in both drug design and peptide synthesis. Researchers at the New York Structural Biology Centre reported on high-resolution nuclear magnetic resonance techniques with dynamic light-scattering to characterise a family of hydrocarbon-stapled peptides with known inhibitory activity against the HIV-1 capsid assembly to evaluate the various factors that modulate activity (1, 6). The researchers reported that helical peptides share a common binding motif but differ in charge, the length and position of the staple. The research showed that the peptides share a propensity to self-associate into organised polymeric structures mediated predominantly by hydrophobic interactions between the olefinic chain and the aromatic side-chains from the peptide. The researchers also detailed the structural significance of the length and position of the staple and of the olefinic bond isomerisation in stabilising the helical conformation of the peptides as potential factors influencing polymerisation (1, 6).

Researchers at the Dana–Farber Cancer Institute, Children’s Hospital in Boston, and Harvard University reported the use of hydrocarbon double-stapling to remedy the proteolytic instability of a lengthy peptide (5, 7). Specifically, the researchers applied the stapled approach to Fuzeon (enfuvirtide), a 36-amino-acid peptide that inhibits human immunodeficiency virus Type 1 (HIV-1) infection by targeting the viral fusion apparatus (5, 7).

The researchers noted that enfuvirtide is used as a salvage treatment option because of poor *in vivo* stability and poor oral bioavailability. To address the proteolytic shortcomings of long peptides as therapeutics, the researchers studied the biophysical, biological and pharmacological impact of inserting all-hydrocarbon staples into the drug (5, 7). The researchers found that the peptide double-stapling created protease resistance and improved pharmacokinetic

Researchers at Duke University recently reported on the use of a new method, protease-operated depots, as a way to deliver peptide-based drugs.

properties, including oral absorption. The hydrocarbon staples created a “proteolytic shield” by reinforcing the overall alpha-helical structure, which slowed the kinetics of proteolysis and also created a complete blockade of peptide cleavage at the constrained sites in the immediate vicinity of the staple (5, 7). The researchers noted the potential of double-stapling to other lengthy peptide-based drugs.

But for all their promise, some researchers point to limited benefits of stapled peptides. Earlier this year, researchers from the Walter and Eliza Hall Institute of Medical Research in Australia, the University of Melbourne and Roche’s Genentech reported on a study involving stapled peptides, specifically for stabilized BimBH3 peptides (BimSAHB), which had reduced affinity for their targets, the pro-survival Bcl-2 proteins (8, 9). The researchers attributed the loss in affinity to disruption of a network of stabilising intramolecular interactions present in the bound state of the native peptide. They suggested that altering the network may compromise binding affinity, as in the case of the BimBH3 stapled peptide in their study. They also said that cells exposed to these peptides do not readily undergo apoptosis, which indicates that BimSAHB is not inherently cell permeable (8, 9).

Peptide drug delivery

Drug-delivery solutions can also overcome the challenges in the drug

mechanism of peptide. Researchers at Duke University in North America recently reported on a new method to overcome the challenge of peptide drug delivery, namely a short half-life, which requires multiple and frequent injections and an undesirable peak-and-valley pharmacokinetic profile, which can cause undesirable side-effects (10).

One method to solve this problem involves loading peptide drugs into polymer microspheres that are injected under the skin and slowly degrade and release the peptide drug. Microsphere-

release technology has proven useful, but has many issues related to its manufacture and ease of patient use, the researchers noted in a 29 Jan. 2013 Duke University press release. “We wanted to know if we could create a system that does what the polymer microspheres do, but gets rid of the microspheres and is more patient friendly,” said Ashutosh Chilkoti, Theo Pilkington Professor of Biomedical Engineering at Duke’s Pratt School of Engineering, in the release.

The new approach involves making a fusion protein that consists of multiple copies of a peptide drug fused to a polymer that makes the fusion protein sensitive to body heat. The fusion molecule is a liquid in a syringe but transforms into a jelly when injected under the skin. Enzymes in the skin attack the depot and liberate copies of the peptide, which provides a constant and controllable release of the drug over time, according to the university release.

The researchers developed a new and entirely genetically encoded peptide delivery system—protease-operated depots (PODs)—to provide sustained and tunable release of a peptide drug from an injectable subcutaneous depot (10). They showed proof-of-concept of the PODs by fusion of protease-cleavable oligomers of glucagon-like peptide-1 (GLP-1), a Type-2 diabetes drug, and a thermally responsive, depot-forming elastin-like polypeptide that undergoes a thermally triggered inverse phase transition

below body temperature, thereby forming an injectable depot (10). They constructed synthetic genes for GLP-1 PODs and demonstrated their high-yield expression in *Escherichia coli* and purification by a nonchromatographic scheme that the researchers had previously developed (10).

“Remarkably, a single injection of the GLP-1 POD was able to reduce blood glucose levels in mice for up to five days, which is 120 times longer than an injection of the peptide alone,” Chilkoti said in the Duke press release. “For a patient with Type 2 diabetes, it would be much more desirable to inject such a drug once a week or once a month rather than once or twice a day. Additionally, this approach avoids the peaks and valleys of drug concentrations that these patients often experience,” Chilkoti said.

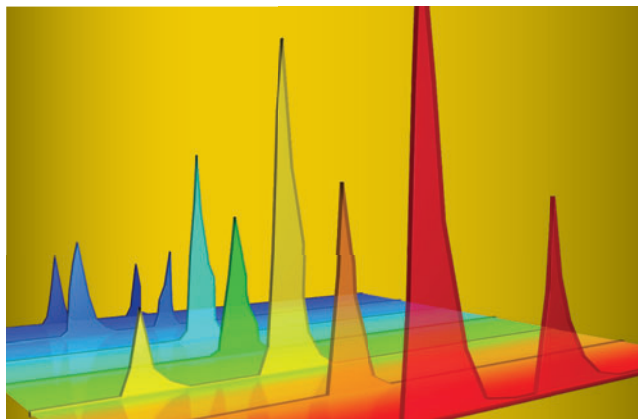
Unlike peptide-loaded microspheres, PODs are also easy to manufacture because the peptide drug and the heat-sensitive polymer are all made of amino acids, so that they are expressed as one long stretch of amino acids in bacteria, according to the Duke University release. “Our experiments demonstrate that this new delivery system provides the first entirely genetically encoded alternative to existing peptide drug encapsulation approaches for sustained delivery of peptide drugs,” Chilkoti said in the release.

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Alternative Solvents for Extractables and Leachables Evaluation

Jennifer M. Roark, Mai N. Jacques, Erica J. Tullo, Andrew T. Blakinger, and Thomas C. Lehman



Extractables and leachables evaluation of packaging components and components of bioprocessing systems is a crucial regulatory requirement. Solvents used for evaluation of process components may include surfactants that can interfere with chromatographic detection and contaminate the chromatographic system. The authors examine alternative solvents that provide extraction equivalence and do not interfere chromatographically.

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Since the FDA *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics* was issued in May of 1999 (1), extractables and leachables evaluation of final packaging components has become an increasing priority of FDA. The regulation on equipment construction (applicable to bioprocessing system components) as per *CFR* Part 211.65 states: "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (1, 2). Every new drug application is expected to include some form of extractables profiling and leachables evaluation for the components at highest risk and in closest contact with the drug. In addition to final container-closure systems, components associated with the bioprocessing system of biologics are considered at risk for leachables. Shelf life, storage temperature and conditions of real-time use of a component under evaluation with the process stream, drug substance, or a final drug product are all key factors in designing appropriate extractables studies, simulation studies and ultimately leachables studies (3).

To demonstrate that a container-closure system or a bioprocessing component is suitable for its intended use, the components typically undergo an initial extractables screening. The design of the extraction experiment should appropriately exaggerate the conditions of real-time use without breaking down or degrading the polymeric component under testing. Although strong polar and strong nonpolar solvents, such as 100% isopropanol (IPA) and 100% hexanes, are commonly used for highly aggressive reflux or soxhlet extractions of final container-closure systems that typically contain the final drug product for extended periods of time, these solvents are not always appropriate for the components of bioprocessing systems, such as bioprocess bags, filters, tubing, O-rings, diaphragms and gaskets (3, 4).

For bioprocessing components, initial extractables screening involves filling or immersing the component in a variety of model solvents that more closely represent the formulation and exaggerate the conditions of real-time use. The components are incubated in the solvent for a predetermined length of time at an elevated temperature, such as 40–60 °C for several days, weeks, or even months. This type of extraction is recommended over an aggressive reflux extraction because exposure of the

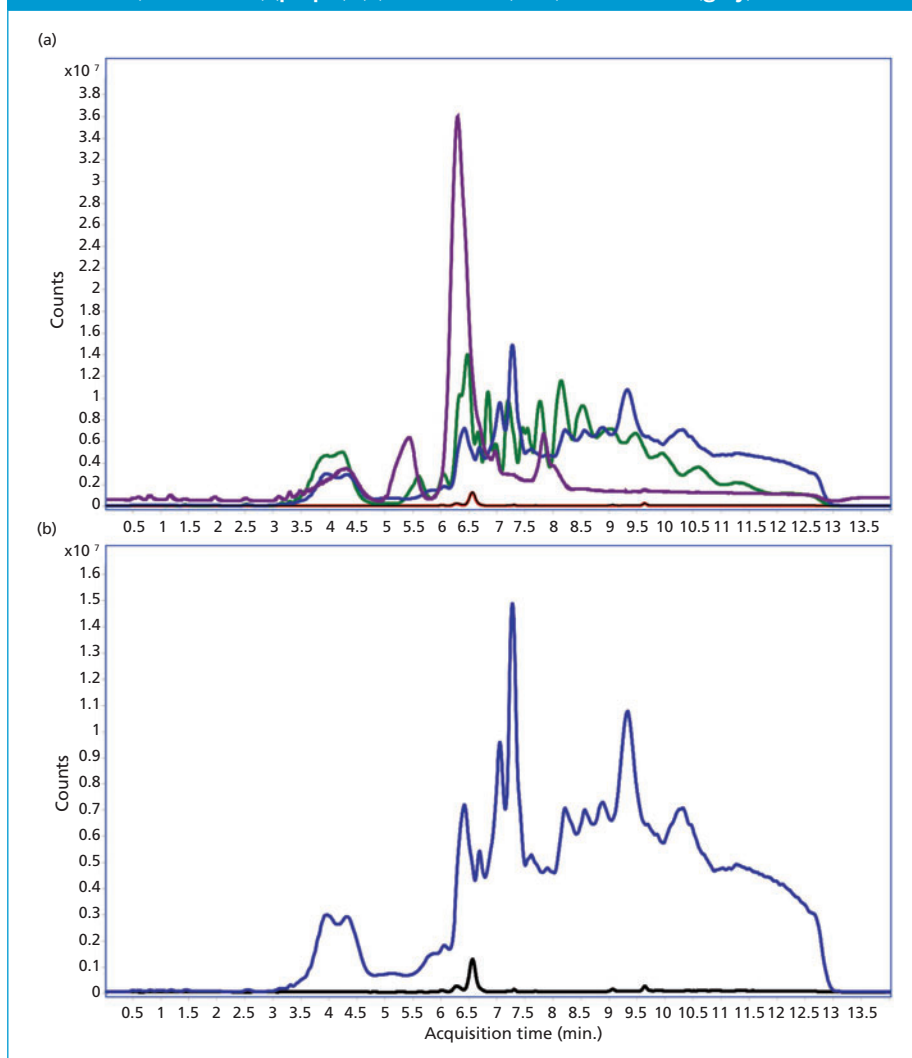
formulation to bioprocessing components is usually very short, and the temperatures of real-time use are typically at or below 25 °C. Reflux extraction of bioprocessing components using strong polar or nonpolar solvents is commonly not recommended unless the real-time exposure of the formulation to the component is long or at temperatures greater than 25 °C and the component is compatible with the solvent (3, 4).

Many extractables studies have instead used model solvents that are comprised of the same excipients that are present in the process buffers, drug substances, or final drug-product formulations. These excipients often include surfactants, which are common ingredients in the formulations of biologics and are regarded as essential components of the model solvents to be used to generate extractables profiles. Surfactants, however, pose major chromatographic interferences when screening for nonvolatile organic compounds by high-performance liquid chromatography–mass spectrometry (HPLC–MS). The detection of extractable compounds may be masked by co-eluting surfactant peaks. In addition, high concentrations of these surfactants are problematic, as they can contaminate the HPLC–MS system. Dilution is not always a viable solution because sensitivity can be greatly affected. Therefore, alternative solvents that provide extraction equivalence and do not interfere chromatographically were examined.

Materials and methods

Polytetrafluoroethylene (PTFE)-lined polypropylene (PP) caps were extracted with 25 mL of each of the following surfactants: 1% nonionic, octylphenol ethoxylate surfactant (Triton X-100, Dow Chemical); 0.1% polysorbate 80 (PS 80); and 0.1% polysorbate 20 (PS 20). The same caps were also extracted with the following two alternative solvents: 60% IPA and 15% ethylene glycol monobutyl ether (EGMB). The caps were submerged in each solvent at 40 °C at ambient relative humidity for seven days. The resulting extracts were tested by gradient HPLC using a time-of-flight (TOF) LC–MS (Agilent

Figure 1: Liquid chromatography–mass spectrometry (LC–MS) time-of-flight (TOF) multimode positive total ion chromatograms (visual representation). (a): 60% isopropanol (IPA) and 15% ethylene glycol monobutyl ether (EGMB) (gray/red), 0.1% polysorbate (PS) 20 (green), 0.1% PS 80 (blue) and 1% octylphenol ethoxylate surfactant (Triton X-100) (purple). (b): 0.1% PS 80 (blue) and 60% IPA (gray).



6500 series) equipped with a multimode source (electrospray and atmospheric pressure chemical ionisation) using positive ionisation. Data were acquired using scan mode with a range of 80 to 1500 m/z and then by extracting ions that corresponded to the compounds of interest.

The PP caps were chosen for this experiment due to the presence of known additives that could be easily tracked during extractables screening. Compounds previously observed through extractables studies that were targeted in this experiment include a di-*tert*-butyl(phenyl)phosphite (Irgafos 168, BASF); a phosphate oxidative degradant of Irgafos 168; ethylene bis(heptadecanamide); pentaerythritol tetrakis 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionate (Irganox 1010, BASF); and erucamide. Determination of extraction efficiency equivalence was made by comparing the responses for each of the targeted extractables observed in each solvent.

Figure 2: Results for the seven-day extraction study on polypropylene (PP) caps showing extractables of common PP additives using five different types of extraction solvents; IPA is isopropanol, EGMB is ethylene glycol monobutyl ether, Triton X-100 (Dow Chemical) is a nonionic octylphenol ethoxylate surfactant, Irgafos 168 (BASF) is di-*tert*-butyl(phenyl) phosphite, Irganox 1010 (BASF) is 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionate.

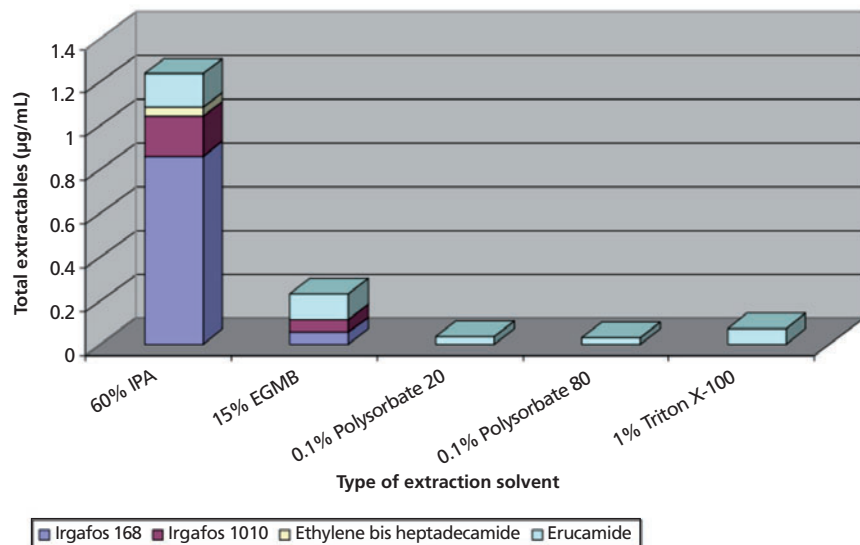
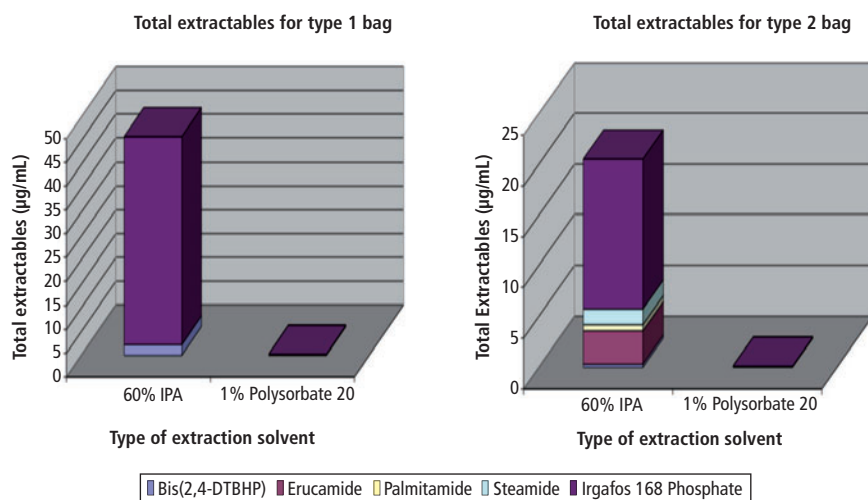


Figure 3: Comparison of extractables of common polymer additives using 60% isopropanol (IPA) and 1% polysorbate 20 extraction solvents in two types of polymeric bioprocessing bags; DTBHP is bis(2,4-di-*tert*-butyl) hydrogen phosphate, Irgafos 168 phosphate is a common degradant of di-*tert*-butyl(phenyl) phosphite (Irgafos 168, BASF).



Results and discussion

Figure 1a presents a visual representation overlay of LC–MS total ion chromatograms (TIC) of all the solvents used for the extraction study. The total ion chromatograms of the 60% IPA and 15% EGMB are similar; therefore, they cannot be distin-

guished in the figure but are shown as the gray/red line. **Figure 1b** presents a visual representation of just the overlay of 0.1% PS 80 and 60% IPA to show that any potential extractables would be masked by the PS 80 interference. Interferences are also observed with 0.1% PS 20 and 1% Triton X-100 as shown in **Figure 1**.

Figure 2 presents the concentration results in µg/mL of each extractable compound detected versus the type of solvent. Concentrations were estimated based upon the average of the responses of the reserpine system suitability standards. As **Figure 2** indicates, not all of the compounds of interest were extracted in each of the solvents. Irgafos 168 and Irganox 1010 were extracted in both 60% IPA and 15% EGMB while ethylene bis(heptadecanamide) was only extracted in the 60% IPA solvent. Irgafos 168, Irganox 1010 and ethylene bis(heptadecanamide) were not extracted in the 0.1% PS 20, 0.1% PS 80 and 1% Triton X-100 solvents. Erucamide was extracted in all solvents. Irgafos 168 phosphate results were not presented because concentrations were similar to the blank concentrations.

Based on the study results, 60% IPA was shown to be the worst-case model solvent for the extraction study because it extracted all of the compounds of interest except for Irgafos 168 phosphate. Not only did the 60% IPA extract the same compounds as the surfactants, it also extracted additional compounds that the surfactants did not extract. These results were comparable to findings from a related study (5) performed

in 2011 in which two types of bioprocessing bag films were submerged for seven days at 40 °C/ambient relative humidity in various types and strengths of solvents, as shown in **Figure 3**. Compounds that were targeted in the related study included bis(2,4-di-*tert*-butyl)hydrogen phosphate, erucamide,

palmitamide, stearamide and Irgafos 168 phosphate. The study also showed that 60% IPA had a greater extraction efficiency compared to the other solvents evaluated including 1% PS 20. Due to carryover issues associated with the 1% PS solutions, 0.1% PS solutions were used to perform the study using PP caps.

In addition to having greater extraction efficiency, as demonstrated in two separate studies using two different types of material, 60% IPA was also shown to eliminate interferences observed in the sample chromatography of surfactants. The use of extraction solvents that do not pose significant chromatographic interferences is critical so that potential extractable compounds are not missed during the extractables screening. In this case, erucamide was extracted in all of the solvents and was tracked using extracted ion analysis based upon the total ion chromatogram of the 60% IPA solvent. To perform extracted ion analysis, the ion of interest must be known. If only the total ion chromatograms of the surfactant solvents were used to screen for potential extractable compounds, and IPA was not used as one of the extraction solvents, erucamide would have been missed in the chromatograms of the surfactants. Erucamide elutes at approximately 7.7 minutes in **Figure 1**.

Conclusion

When comparing extraction efficiency between the various solvents for extractable screening studies, it is recommended

that IPA be used as a worst-case solvent in cases for which surfactants are of interest. In addition, the ions from the mass spectra of compounds detected in the IPA extraction solvent can then be used to perform extracted ion analysis on the extracts that contain surfactants. Use of an alternate solvent such as IPA ensures that potential extractable compounds are not missed in the surfactant extractions during initial extractables screening.

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Join the discussion

What issues are you having with extractables and leachables evaluation?

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BIOSIMILARS – *contin. from page 27*

two products were not structurally identical. Small differences were found in the hydrodynamic structure, the degree of alpha helicity and the stability of these products (3). Thus, despite the rarity of such occurrences, it remains important to test for immunogenicity using state-of-the-art methods.

There are a number of methods that may be selected to perform immunogenicity testing. A double antigen bridging assay has been the preferred method because once it is optimised, it can be applied to immunogenicity testing in any host species. Alternate methods also include application of enzyme-linked immunosorbent assay (ELISA) techniques, immunohistochemistry, electrochemiluminescence and also application of surface plasmon resonance. These techniques must be validated and be sufficiently sensitive to detect low titre and low affinity antibodies. The latest draft guidance on biosimilars issued by FDA in February 2012, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" states that, at the very least,

two separate immunogenicity studies (using methods such as those previously described) should be conducted to compare a biosimilar to its reference product (4).

Conclusion

The EMA Committee for Medicinal Products for Human Use (CHMP) have issued a number of guidelines relevant to biosimilars that detail the requirements for market approval. The EMA guidelines cover a range of issues including manufacturing, measurement and comparability, chemical and biological analysis and clinical trial requirements. In addition to the pharmaceutical, chemical and biological data normally required for a generic-drug application, application for market approval of biosimilar products require additional toxicological and other nonclinical and clinical data.

The key is to demonstrate that the biosimilar product is similar to the reference product in terms of quality, safety and efficacy. Products are dealt with on a case-by-case basis. The 2009 Biologics Price

Competition and Innovation (BPCI) Act directed the US FDA to develop a regulatory framework in support of developing biosimilars and also defined the pathway to achieve drug approval. This pathway is based on a risk-based approach using what the agency has termed "totality of evidence." Working with a partner who has experience with the regulators for both innovator and biosimilar products will help to build this body of evidence.

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Bioprocessing Advances in Vaccine Manufacture

Advances in techniques and single-use systems are revolutionizing vaccine manufacturing.

The vaccine industry, particularly, in major Western markets, continues to be dominated by a few major, long-established players that primarily manufacture aging, long-marketed, non-recombinant (nongenetically engineered) vaccines. The industry, however, will be changing in the coming years and this change may come rather rapidly. According to BioPlan's recently released analysis of 10-year industry trends (1), a confluence of technological advances in bioprocessing is making vaccine manufacture cheaper, faster, and simpler. These advances include:

- Single-use systems (SUS)/disposable bioprocessing systems
- Modular/transportable bioprocessing facilities
- Novel expression systems/improved cell lines
- New purification technologies.

As these technologies advance and are increasingly adopted for commercial-scale manufacturing, the industry will see an evolution in vaccine manufacture. Significant improvements are now commonly being reported as companies develop, adopt, and adapt bioprocessing technologies to vaccine manufacture.

Single use adoption

BioPlan's 10th Annual Report documents increasing adoption of these technologies and their impact on biopharmaceutical manufacturers. Survey data show that bioprocessing at pre-commercial scales, such as manufacture for clinical trials, is now thoroughly dominated by SUS (i.e., disposables) use. This increase included 78% of those surveyed reporting current use of SUS bioreactors and 92% using SUS filter cartridges at some level in bioprocessing (see **Figure 1**).

SUS have moved into large-scale vaccines manufacture more slowly, partly due to the demands for large-scale equipment. In the BioPlan study, vendors were asked if they provide sufficiently scalable single-use disposables and techniques. Overall, 53% of the industry considers scale to be a significant adoption restriction. And vaccines manufacturers place inability to scale up SUS devices high on the list of concerns. SUS involve one-time use

of bioprocessing equipment composed of plastics, not traditional stainless steel. SUS allow flexible manufacture when, and at the scale needed, with substantial reductions in costs and time, including presterilised equipment. In contrast, stainless-steel bioreactor-anchored facilities require costly and complex infrastructure, which further includes complex piping, including steam used for sterilising stainless-steel equipment so it may be reused, which adds weeks to batch turnaround time.

With advancing SUS technology, better plastics and new designs are being developed using SUS (vs. stainless steel) for their application in precommercial R&D, clinical-trial-material supply, and commercial manufacture.

Currently, SUS bioreactors top out at 2000 L, with many engineering challenges (e.g., weight) when larger. Where this does not provide sufficient manufacturing capacity, multiple parallel SUS process lines can be implemented. With advancing SUS technology, better plastics and new designs are being developed using SUS (vs. stainless steel) for their application in precommercial R&D, clinical-trial-material supply, and commercial manufacture. This use of SUS is projected to result in the market (primarily US and EU) for SUS equipment at a commercial scale growing 1000% in five years to \$1.5 billion/year (2).

Going modular

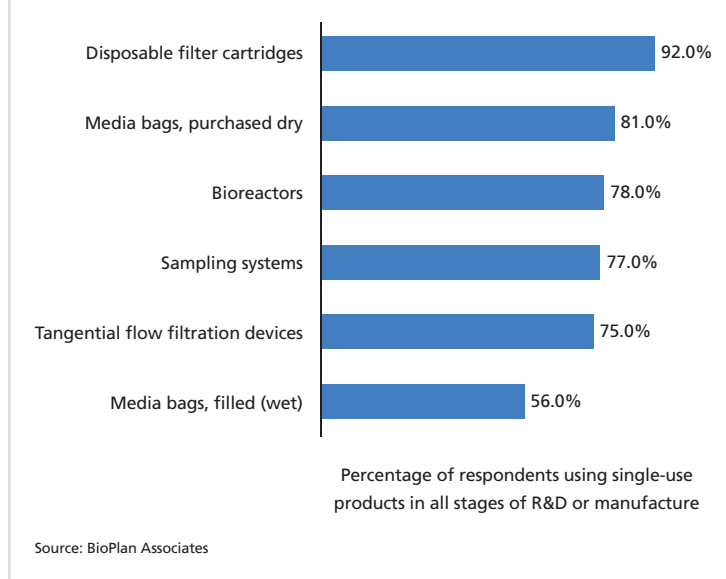
Going modular is the next advancement in bioprocessing hardware. It is closely related to the adoption of SUS technologies and involves housing SUS bioprocessing equipment within their own cleanroom cabinets—whether portable prefabricated trailers or equipment sealed within dedicated isolator cabinets—with these increasingly designed for plug-



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Figure 1: Selected single-use applications in biomanufacturing.

and-play simplicity. Bioprocessing facilities that formerly required years for planning and construction can be brought on line in a matter of months or even weeks. SUS have become common in less than a decade, in as short as 5 or 10 years; however, we may comparably be talking about industry widespread

Going modular is the next advancement in bioprocessing hardware.

adoption of flexible bioprocessing modules and plug-and-play factories. Vaccines are expected to be one of the first product sectors affected by this trend. Modular technology will accelerate worldwide proliferation of vaccine manufacturing, including transfer of bioprocessing to lesser-developed countries. Even easier than with SUS process lines, modular systems allow whole plants to be essentially cloned, potentially allowing cGMP manufacture in many developing countries. Many foreign countries are and can be expected to demand local vaccine manufacture, particularly once modular facilities become commonplace, and equipment vendors plan to actively pursue this market.

Companies developing modular systems for vaccine manufacture include G-Con, which is working

with partners, including Sartorius Stedim Biotech and GE/Xcellerex. For example, Project GreenVax, a private-public consortium, is currently constructing an influenza vaccine manufacturing facility (to be operated by G-Con, developer of the modular units being used) in Texas for manufacture of recombinant tobacco plant-expressed influenza vaccines, with a projected final scale capacity of 100 million doses per month [1.2 billion doses/year], according to company projections and production costs of pennies/dose compared with conventional dollars/dose for conventional egg-culture manufacturing. The Project GreenVax influenza vaccine-manufacturing facility, subsidized by biodefense funding, uses single-use equipment, housed within plug-and-play-type modular trailers, using tobacco plant expression technology. Medicago and other companies are also developing vaccines using tobacco-plant expression.

Expression systems

Improved versions of currently-predominate expression systems (i.e., genetically-engineered cell lines such as Chinese hamster ovary [CHO], yeast, and *E. coli*) for recombinant protein expression are further making vaccine manufacture easier and cost-effective and reducing the

scale and investment required to manufacture products. The BioPlan annual survey of bioprocessing professionals and other studies show a rather consistent doubling of mammalian-cell protein expression and product yield about every five years, with yields now typically in the upper 2-3 g/L (bioreactor volume) range. Newer expression systems coming on line promise even higher yields and/or cost-effectiveness, with yields of more than 30 g/L being reported. These upcoming systems include plants (both laboratory-grown and field-grown), such as from iBio (Newark, DE); transgenic animals; PER.C6 and other novel high-yield human-cell lines; and various bacteria other than the usual *E. coli*. Using the same manufacturing systems and culture media, these new systems produce the same amount of product at commensurately lower cost and often much faster. This higher yield has led to US biodefense programs providing R&D support for diverse vaccine-expression systems.

Thus, the same equipment can essentially be used to manufacture twice as much product as what was possible only about five years ago. These improvements, however, come amidst intense regulation as major changes in products' bioprocessing are only implemented for new bioprocesses/products as they are developed with established processes rarely undergoing major changes. Upcoming new bioreactor technologies will further increase vaccine-manufacturing flexibility and reduce costs. This includes perfusion. Capillary hollow-fiber perfusion bioreactors being developed by FiberCell Systems, for example, are expected to comparably produce up to 1000 x (based on bioreactor size) the output from conventional bioreactor (e.g., a 50-L desktop perfusion bioreactor matching the overall output of a 5000-L bioreactor).

Purification technologies

Novel purification technologies are also in development. These improvements are much needed, as advances in upstream manufacturing (everything through product formation in the bioreactor)

causing capacity constraints and problems, because later downstream processing, primarily purification, have not advanced as rapidly as expression systems, and other upstream technologies have. The BioPlan study shows that many facilities are considering upgrading (i.e., adopting, new purification technologies). This trend includes 54% considering high-capacity

The BioPlan study shows that many facilities are considering upgrading.

chromatography resins; 44%, single-use filters; 38%, automated buffer dilution systems; and 35%, single-use tangential flow filtration. Other advances being adapted for large-scale use include simulated moving bed chromatography systems and membrane filters, which are starting to replace chromatography columns. Cast-in-place "monolithic" chromatography media, rather than labor-intensive packing of

columns, are yet another example of improvements approaching adoption for commercial-scale manufacture.

Looking ahead

Further practical advances and synergies can be expected when these technological advances are combined, thereby resulting in simpler, cheaper, and transportable vaccine manufacturing. A number of other vaccines currently in the development pipeline are being manufactured in SUS, are being developed for manufacturing using modular units, are using novel, higher-yield expression systems, and/or are adopting newer purification technologies. Besides federal biodefense programs funding, many of these efforts are

independently funded or also being funded by PATH and other vaccine development-oriented philanthropic organisations.

The confluence and combination of ongoing bioprocessing technological advances will increasingly enable manufacture of vaccines quicker, simpler, and at significantly-reduced costs, often just pennies/dose, with many future vaccines likely to be sold at prices that are comparable or even below current manufacturing costs.

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Regulatory Inspections Get Serious



Siegfried Schmitt of PAREXEL explains how regulatory agencies are getting serious about inspections.

Q. Are inspections getting tougher?

A. Many reviews of regulatory inspection activities focus on the top 10 citations/findings, which say a lot about the areas of concern, but little about how these inspections are conducted or whether or not inspections are getting tougher. Several agencies publish their inspection standard operating procedures (SOPs) or how they inspect (1, 2). This gives the industry a good idea how the inspection will be conducted and what areas will be looked at. The industry has studied these documents and learned from inspections over the years. Consequently, one should assume that all is well under control, but is it?

US FDA inspections

Feedback from both inspected companies and consulting firms points to a significant change in the focus of FDA inspections of foreign drug establishments and the expected response by the inspectors. This change has caught many companies by surprise. The following examples clarify the observed change:

- A multinational European manufacturer had been inspected regularly and apart from the occasional observation on form FDA-483 did not have any issues of note. During the most recent inspection by FDA, the same common areas, such as deviation management and the associated corrective and preventive action (CAPA) process were scrutinised. There was no lenience when it came to incomplete or ambiguous records for root cause analysis or delayed completion of CAPA. The argument “but we have always done it this way” only contributed to FDA’s issuance of a warning letter.
- A large Asian company with a good history of compliance received a series of FDA-483 observations to which they responded in the same manner as for previous inspections. However, where it had been sufficient in the past to describe CAPA actions specific to the findings, FDA dismissed their response as not addressing the totality of the findings in a holistic and encompassing way. Where FDA now states that they consider the integrity of the quality system compromised, a review of the entire system is expected. Any response that falls short of this expectation can have serious consequences, such as an import ban.
- Another company learned that implementation of International Conference on Harmonisation (ICH) Q7, Q8, Q9, Q10 and Q11 guidelines is now also expected by FDA. FDA inspectors were no longer satisfied with

being presented the odd risk assessment, rather than a company-wide approach to quality risk management.

Other regulatory agencies

Though the given examples resulted from US FDA inspections, there is no reason to believe other agencies do not or will not apply a similarly tough approach. In these and similar cases, the issue was that companies either failed to maintain their quality management system in a state of compliance with the applicable regulations and guidances, or that their attitude to resolving identified issues was neither holistic nor investigative enough. This is a clear sign that there just is no room and time for complacency and failure to keep up with the developments in regulatory expectations. Just because inspectors sometimes provide industry with some leeway during inspections does not give them any right to flaunt the regulations and compromise compliance. Compliance really is an attitude, one that has to be understood, embraced and implemented by everyone in the organisation, including top management.

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Ad Index

COMPANY	PAGE
Catalent Pharma Solutions	44
CPhI.....	12
Lab Innovations	17
ILMAC	5
Natoli Engineering	23
Pfizer CentreSource.....	43
Shimadzu Europe	2
SIGNTRADE	29
Starna Scientific.....	11
Veltek Associates Inc.....	7

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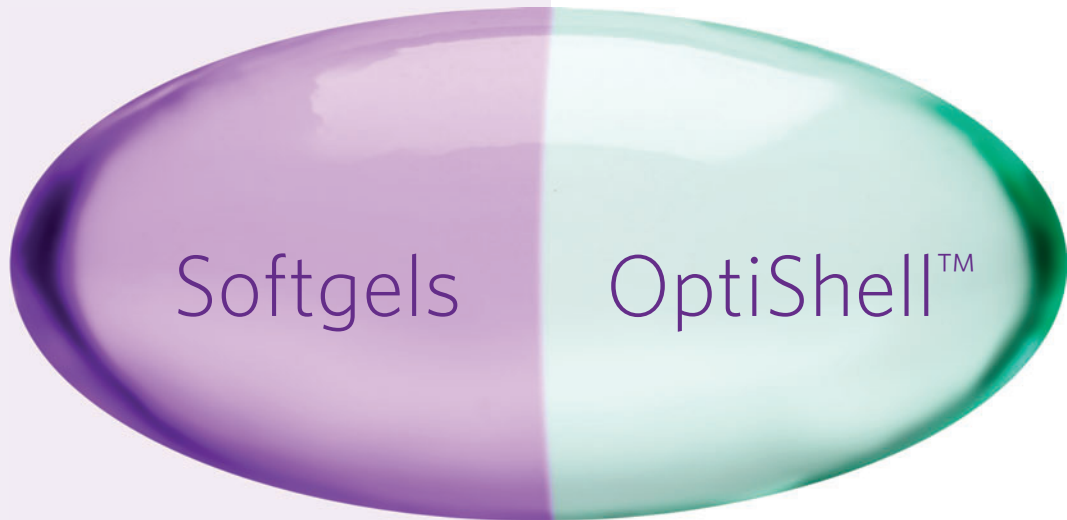
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