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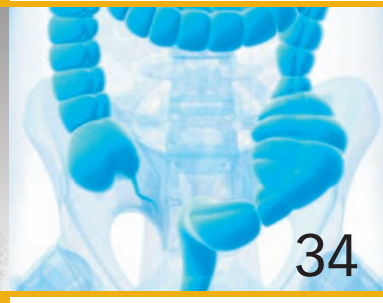

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Associate Publisher
Chris Lawson
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Senior Sales Executive
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CRS Meets in Edinburgh

The Controlled Release Society (CRS) is holding its 42nd Annual Meeting in Edinburgh, Scotland on 26–29 July. We are expecting approximately 1500 attendees at this event, which is spearheaded by strong science and a programme that allows members social time to network.

Although known as CRS, we often use the phrase "delivery science and technology" to describe our field. Technologies can take a drug that has to be orally administered two to six times a day and convert it to an improved dosage form that is taken only once a day. A drug that requires daily injections can also be developed into a formulation that is administered only once a month. These are two examples of the time element of delivery.

Formulations and technologies also allow for spatial delivery. This local delivery can be accomplished as easily as a direct injection into the eye or brain, for example. Alternatively, a drug can be linked to an antibody, delivered systematically, and the antibody then targets cancer cells for the oncology payload. In a recent case of local delivery providing systemic administration, sophisticated device and formulation have allowed the delivery of insulin particles into the lung, where the insulin is absorbed into the bloodstream, eliminating the need for some injections in the treatment of diabetes.

Like other societies, ours has changed, in particular over the past decade. People have become increasingly accustomed to free content. Niche meetings are becoming more prevalent. CRS continues to have a membership that remains engaged, which I attribute to the following reasons:

- We provide an effective forum for and access to strong fundamental delivery science.
- We continue to have luminaries in our field as speakers, collaborators, and mentors.
- We foster dialogue between scientists, both established and emerging.
- We focus on creating networking—scientific or social collisions—be they between academicians and industrialists, scientists and engineers, or amongst people from various countries.
- We nurture our young scientists with special sessions and events planned for our next generation of leaders.

While we embrace newer ways of information exchange, there is still nothing as enjoyable and productive as that face-to-face scientific discussion. We look forward to a multitude of those in Edinburgh, and trust some will be held over a dram of whisky.

Arthur J. Tipton, PhD
President and CEO of
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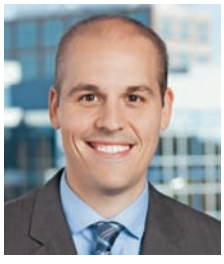
President of CRS

Market Access Outlook for France

With the French pricing and reimbursement policies becoming increasingly stringent, pharmaceutical manufacturers must adapt their drug development and commercial strategies if they want to secure premium pricing for their new products.



Michael J. Kuchenreuther, PhD
is a research analyst for Numerof & Associates.

In France, the pricing and reimbursement landscape is certainly changing. Take for instance the case of Gilead's Hepatitis C blockbuster, Sovaldi. According to clinical trial data, 90% of patients for whom this drug is indicated for are for all intents and purposes cured upon treatment completion. A few years ago, Sovaldi would have likely been awarded a premium price in France, which has traditionally only considered the therapeutic benefit of new drugs to inform pricing decisions. It would have also entered the French market at a high price point relative to other European Union Five markets, including the cost-conscientious United Kingdom.

However, the need for the government to continue providing universal healthcare coverage to an aging population, along with increasing drug prices and shrinking budgets, recently drove the country to introduce pharmacoeconomic analysis as part of its pricing process. Due in part to a more economically focused health technology assessment process, in late 2014, the French government was able to get Sovaldi at the lowest list price in Europe. The government also secured a volume-based tax and performance-based discount in exchange for 100% reimbursement. Based on the limited number of pharmacoeconomic analyses that have been published to date, manufacturers can expect to face tougher negotiations with the pricing committee, with a final price potentially below expectations.

In addition to pricing pressures, manufacturers face other challenges in France including the government's mounting focus on driving the use of generic drugs and biosimilars, which may restrict market growth. This article explores some of the recent developments in the French pharmaceutical market, identifies pricing and reimbursement challenges, and discusses strategies manufacturers should consider for sustainable success.

Healthcare spending regulation in France

As in most other developed markets, budget and cost control have been key issues in France. The country's compulsory and uniform health insurance scheme has faced large deficits over the past 20 years. Economic downturns and the growing healthcare needs of an aging population have only amplified the government's focus on driving down healthcare costs to ensure sustainability.

Successive reforms have led to a decrease in government-sponsored reimbursement rates for select populations and/or types of care, leaving some patients with higher copayments and coinsurance. While more than 90% of the country's population has supplemental health insurance, reimbursement of copayments through private insurers has recently been discontinued for certain types of prescription drugs, doctor visits, and ambulance transport (1, 2).

Decreased reimbursement is just one mechanism through which healthcare spending has been regulated. Other mechanisms include a reduction in the number of acute-care hospital beds, the removal of more than 600 drugs from public reimbursement over the past several years, the monitoring and sanctioning of medical practitioners for prescribing too many drugs, changes to its health technology assessment (HTA) process, and promoting uptake of generic and over-the-counter medicines (3). The French Government shows no sign of slowing down its health reform efforts, as it hopes to make €10 billion in additional cuts over the next three years (3).

The French pharmaceutical market—Overview, key trends, and developments

Pricing and reimbursement in France. Reimbursement for pharmaceuticals is determined primarily at the national level. Following market authorization from the European Medicines Agency (EMA), a drug is assessed by the independent health authority, Haute Autorité de Santé (HAS).

In France, HTAs have traditionally only considered the therapeutic benefit of new drugs to inform pricing and reimbursement decisions. Consequently, the key requirement for obtaining maximum reimbursement and a premium price has historically been innovation. However, since the formal introduction of drug cost-effectiveness evaluation in October 2013, therapeutic benefit remains a prerequisite for optimal market access but is no longer sufficient on its own.

HTAs still begin with determination of a product's "medical benefit" (SMR—Service Médical Rendu)

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based on the following criteria—efficacy and safety; existence or absence of therapeutic alternatives; severity of the disease; treatment type, specifically preventative, curative or symptomatic; and public health impact.

In a separate, but concurrent process, a new product is also measured against a comparator drug to determine the "improvement of medical benefit" (ASMR—Amélioration du Service Médical Rendu). In France, the method for assigning a comparator is less rigidly defined than in other countries. For instance, in Germany, the comparator is defined by the government, while in France, the manufacturer sets the comparator but must provide justification (4). The ASMR rating, from I (superior) to V (inferior), is generally clearly correlated to a relatively narrow range of price premiums or discounts.

Nonetheless, as highlighted above, in late 2013, the Committee for Economic Evaluation and Public Health (CEESP), a separate group under HAS, was mandated to also consider pharmacoeconomic evidence for new technologies that claim a high ASMR (I–III) and that are expected to have sales in excess of €20 million. By the end of 2014, the CEESP had completed 12 economic evaluations, four of which have been made publically available (5). These evaluations include cost-effectiveness/cost-utility analyses, health economic modelling, and sensitivity/scenario analysis, all of which feed directly into the decision-making process of the pricing committee (6).

While guidelines used for economic assessments in other countries such as the UK are descriptive, detailed, and prescriptive, the ones published by HAS are prominently non-exhaustive and non-definitive, leaving researchers with more flexibility to conduct these evaluations (7). One aspect of the pharmacoeconomic evaluation that remains quite unclear is the financial threshold HAS deems to be acceptable when looking at the conclusions of CEESP's analyses. Currently, there is no established threshold in terms of incremental cost per quality-adjusted life year (QALY) or per life-year gained.

Potential future changes to the pricing and reimbursement process. Despite the recent introduction of pharmacoeconomic analyses, innovation and clinical effectiveness remain the sole determinants of product adoption in France. However, as the government continues to explore mechanisms for reducing healthcare expenditures and increasing healthcare value, manufacturers should expect discussions around future changes to the pricing and reimbursement process to continue. For instance, in a recent report, the General Inspectorate of Social Affairs highlights the introduction of economic evaluations into the pricing process and discusses how cost effectiveness analyses could also be considered in national coverage decisions and in defining specific reimbursement rates as seen in other countries like the UK (8). With the commission currently finding it difficult to justify the use of a fixed threshold to refuse a new product, a dramatic shift is unlikely in the near future but remains a possibility over time.

Beyond the role of cost effectiveness analyses, changes to the broader pricing and reimbursement system are also being considered. In 2012, the HAS proposed to replace SMR and ASMR by a single index called the Relative Therapeutic Index (ITR), a new assessment tool which was to place greater emphasis on comparator and clinical endpoint relevance as well as on the validity of studies aimed to demonstrate superiority and non-inferiority (9). While the ITR determination process failed to gain enough traction among policymakers to lead to changes, the government continues to explore new, stricter methods of deciding on reimbursement rates and pricing. In fact, the French Ministry of Health has reportedly commissioned a work group to review current modalities for drug assessments (10).

Use of generic drugs. France has historically been a strong market for branded drugs. In 2008, generic drugs accounted for only 21.7% of the pharmaceutical market in terms of volume. As of 2013, the rate climbed to 30.2%, largely due to measures introduced to stimulate generic prescription by physicians, generic substitution by pharmacists, and generic acceptance by patients (11).

Generic-drug prescribing in France, however, still lags behind other countries. To address this issue, France's health minister, Marisol Touraine, presented a national plan to increase generic prescription by five percentage points by removing "the remaining obstacles to the use of generic drugs for all situations where such use is possible" (12). Specific elements of this plan include a national advertising campaign to boost public confidence, the provision of additional payments to physicians and pharmacists linked to generic-drug prescription, mandates for hospitals to comply with a generic prescribing rate, and interventions to monitor physicians' markings of prescriptions as non-substitutable.

With biologicals representing more than 25% of spending on drugs in France, legislation has also focused on promoting biosimilars as a means of reducing expenditures. In 2014, France became the first European country to formally allow substitution of biosimilars under certain conditions (13). Since 2007, the French market has not necessarily been a leader in biosimilar penetration relative to other EU countries, but volume in terms of sales has consistently increased each year. The recent launch of Celltrion's Remisura, the world's first biosimilar monoclonal antibody indicated for multiple chronic diseases, taken together with looser regulations on how biosimilars can be used, have many feeling optimistic about the cost-savings potential of these follow-on biologics moving forward.

Implications for manufacturers

The French government remains committed to reducing growth in healthcare costs as evidenced by recent legislation and the introduction of cost-effectiveness evaluations in pricing decisions of select new products. While the country's pharmaceutical industry has long been one of the biggest in both Europe and the world, these cost-

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containment and other measures have serious implications for manufacturers and their go-to-market strategy. The market is forecast to grow at a tepid compound annual growth rate (CAGR) of 0.7% from US$46.2 billion in 2014 to US$48.2 billion by 2020 (14).

Some manufacturers may prefer to wait and see if France adopts more stringent pricing and reimbursement policies for new therapeutic products—either through more rigorous clinical effectiveness requirements or through the use of cost-effectiveness analysis to guide coverage decisions—before changing their development and commercial strategies. However, global markets, including France, are already showing clear signs that incremental innovations will be closely scrutinized and that unless there is clearly demonstrated value, new products are unlikely to command premium pricing. Even doing so may not be enough to protect products from additional scrutiny over price and access restrictions, as seen with Sovaldi.

With generic drug use expected to rise and as "generics as standard-of-care" settles in, biopharmaceutical companies will need a higher degree of clinical and economic differentiation to be successful (14). Business models need to shift from being product-centric to patient centric (15). Clinical trials must focus on endpoints that matter to patients, their caregivers and their families, as opposed to surrogate endpoints that are not validated.

The message manufacturers are delivering to key stakeholders also needs to change. Large data packages and exhaustive global value dossiers deliver much-needed evidence but do not make a compelling case in isolation. "What is your technology's benefit to the patient population and other stakeholders in that particular market?" This question needs to be front and center of all discussions. Manufacturers that understand specific pain points can design products or services that address these issues and package those benefits into meaningful value stories.

While product innovation remains the key determinant of coverage in France, innovative pricing mechanisms, such as risk sharing, outcomes-based contracting and managed entry agreements, are becoming more important for optimal pricing. This trend is seen in other countries as well (16). In fact, Celgene recently committed to the French Government on the effectiveness of their multiple myeloma drug Imnovid in exchange for a higher price (17). The agreement required Celgene to build a registry for collecting real-world efficacy and safety data. Discounts and price volume agreements have been used in this market for several years; however, the growing focus on value has created a greater appetite among decision makers for more productive sharing of risk with manufacturers. Here, understanding the economic and clinical value delivered by a given product is crucial in determining whether a risk-based agreement is the right strategy, and if so, how an arrangement should be structured.

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Unravelling the Complexity of EU's ATMP Regulatory Framework

The European Union has a challenging task ahead as it strives to harmonize regulations on advanced therapy medicinal products.

The European Medicines Agency is approving a growing number of advanced therapy medicinal products (ATMP) despite claims that their commercialization is being hampered by increasingly complex regulatory and standards requirements. The creation of ATMPs by a 2007 European Union regulation (1), backed by a specialist committee for advanced therapies (CAT) within EMA, aimed to boost development of medicines derived from progress in cellular and molecular biology.

Over the past few years, there have been signs of a surge in ATMP development.

ATMP development

Initially, the regulation seemed to have little impact on the number of advanced medicines on the market after the start of its implementation in early 2009. By mid-2013, there were only four marketing authorizations from 10 applications in the three ATMP categories of gene therapy, somatic cell therapy, and tissue engineering (2).

Over the past few years, however, there have been signs of a surge in ATMP development. The number of medicine applications recommended by CAT to be classified as advanced therapies rose by 26% in 2014 (3). In late 2014, EMA recommended for EU approval the first advanced therapy medicine containing stem cells. It is also the first drug for the treatment of moderate to severe limbal stem cell deficiency (LSCD), a rare eye condition due to physical or chemical burns to the eyes that can result in blindness.

Complex regulations

At the same time, the quality, safety, and efficacy rules under existing and proposed EMA guidelines on ATMPs have been becoming more complex. One reason is that expanding knowledge about the new therapies has raised new concerns, particularly relating to issues regarding the quality of starting materials and drug substances. The regulators have gradually become more aware of the biological variability and intricacy of ATMPs. This tightening of standards seems to be deterring big pharmaceutical companies rather than small- and medium-sized enterprises (SMEs) from developing advanced therapy products.

In a 2014 report (2) on the application of the 2007 regulation, the European Commission, the Brussels-based EU executive, found that the majority of ATMP research was being done by small companies and entities. Approximately 70% of sponsors of ATMP clinical trials were SMEs or not-for-profit organizations, while large pharmaceutical companies accounted for less than 2%.

The report concluded that because there are "still many unknowns" with advanced therapies, "it is important to put in place adequate controls to prevent detrimental consequences for public health" (2). Nonetheless, it is also acknowledged that "too burdensome requirements" could have adverse consequences for public health because they could prevent the marketing of valid treatments for unmet medical needs.

Data requirements

One onerous requirement is the amount of data needed on starting materials, such as the source and history of cells, and their detailed characterization. In addition, a complete description, including source, characteristics, and testing details, of all materials used during the manufacture of products is needed. Some developers of ATMP products complain about the regulators making demands for data that existing analytical technologies cannot yet provide. There have also been complaints about EMA wanting unnecessary high levels of purity in cell-therapy treatments, especially those comprising mixtures of undifferentiated cells.

Another matter of contention has been EMA's insistence that marketing authorization applicants for tissue-engineered products must demonstrate through pharmacokinetics the longevity or persistence of their medicines. "From the point of view of our members, pharmacokinetics does not include longevity, but resorption, distribution, and excretion of a drug," Matthias Wilken, head of European drug regulatory affairs at the German Pharmaceutical Industry Association (BPI), told *Pharmaceutical Technology Europe*. "The requirement to demonstrate longevity might lead to extensive clinical studies that would be an undue burden to pharmaceutical entrepreneurs," he explained.

Also in some cases with ATMPs, the regulators are seen as taking too much of a "generic" approach to advanced technologies and not making a strong enough distinction with conventional pharmaceuticals. "The assessors and members of EMA scientific committees often come from the field of conventional medicinal products," said Wilken. "Initially, there was a lack of understanding of the peculiarities of ATMPs. But this [understanding] is getting better, as is shown, for example,

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by the fact that EMA, along with the Commission, is currently working on tailoring GMP requirements for ATMPs."

Risk management

The big regulatory differences between ATMPs and chemical-based pharmaceuticals is the greater emphasis needed with biological products on quality issues, mainly because with many of them, there are gaps in knowledge about ways of managing their risks. However, EMA has acknowledged the limitations of applying uniform rules to ATMPs by adopting a risk-based approach that allows the products to be assessed on a case-by-case basis.

The distinct approach needed for ATMPs has been highlighted by the latest EMA guidance (4) on advanced therapies, which covers the quality, preclinical, and clinical aspects of gene therapy. The draft guideline (4) on gene therapy was issued in May 2015 for a period of public consultation ending in August. It replaces a guidance note (5) published in the early phase of gene-therapy development in 2001.

Since the 2007 ATMP regulation was implemented, EMA has had to deal with three applications for gene-therapy authorizations, only one of which has so far been successful. "[From a quality perspective], there were no major changes or inconsistencies in the 2001 guideline that required an immediate revision," an EMA spokesman informed *Pharmaceutical Technology Europe*. "However, some updates were necessary, for example, to reflect novel methodologies for testing and characterization, and also to ensure cross references to new legislation and guidelines that were developed separately."

Quality and safety

Also, the format of the sections on quality and manufacturing aspects in the revised guideline has been changed to follow that in the harmonized Common Technical Document (CTD) for marketing authorization application dossiers, according to EMA. "This is expected to be helpful for the small developers of gene-therapy products when compiling their dossiers," said the EMA spokesman. As a result, 40% of the 42-page draft guideline covers quality matters, 30% non-clinical issues, many of which relate to assessing risks linked to quality management, and only 10–15% to clinical development.

A lot of the obligations in the guideline requirements relate to the quality of the components in the vectors or delivery systems of the products. Details of the quality of all starting materials and their sources have to be provided, including virus seed as well as mammalian and bacterial cell banks. All raw materials used during manufacture have to be tested and characterized.

Hospital-based research

Partly due to the detailed EU quality and safety requirements for advanced therapies, companies developing ATMPs are critical of an exemption to EU rules granted to hospitals involved in R&D and the manufacture of the products. Hospital-based research and production in the sector are increasing rather than contracting in Europe. This trend is mainly because some EU states are using these hospitals as ATMS development centres at the core of national regenerative medicine programmes.

The United Kingdom, which is seeking global leadership in the sector, has, for example, a network of cell-therapy centres of excellence based in leading hospitals. "The establishment [of these centres] is essential if we are to build a concentrated critical mass of knowledge, skills, and therapeutic know-how," according to a UK government-commissioned report on regenerative medicine (6).

Under the 2007 EU regulation on ATMPs, member states are allowed to give hospitals exemption from the legislation as long as the hospital's advanced therapies are being provided on a "non-routine basis" to its own individual patients. Some organizations are calling for the "non-routine" provision, which is open to different interpretations, to be extended to cover products only when a fully validated, EU-approved advanced therapy alternative cannot be used.

"While the hospital exemption rule allows the early development and delivery of ATMPs that meet an otherwise unmet clinical need in a patient, the exemption should only be used to deliver a product if there is no licensed alternative, with proven efficacy and safety, available," says Michael Werner, executive director of the US-based Alliance for Regenerative Medicines, a global advocacy group representing stakeholders in the ATMP sector.

Its European arm has been among the leading critics of criteria applied for the exemption, particularly those relating to manufacturing standards. Sceptics about the potential of exempted hospital-based development systems contend that they encourage the avoidance of the strict EU data requirements because the hospitals have to adhere only to national quality and safety standards, although these standards should be consistent with those at the EU level.

Even the European Commission in its report (3) on the impact of the ATMP regulations concedes that the exemption can enable hospital-based centres to have lower development costs than commercial ATMP organizations because of the advantages of being subject to less rigorous standards. A major objective behind the EU's ATMP regulation was the introduction of harmonized standards across Europe. The way the hospital exemption is operating shows that there is still some distance to go before full harmonization is achieved.

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Jill Wechsler is *Pharmaceutical Technology Europe's* Washington editor, tel. +1.301.656.4634, jwechsler@advanstar.com.

Breakthrough Drugs Raise Development and Production Challenges

Manufacturers and the US FDA look for innovative strategies to meet accelerated timeframes.

The United States Food and Drug Administration programme to expedite the development and approval of innovative drugs for serious and life-threatening conditions is a great success, but the abbreviated development timeframe involved raises numerous difficulties for manufacturers seeking to ensure product quality and timely supply. Expert review teams in the Centre for Drug Evaluation and Research (CDER) and the Centre for Biologics Evaluation and Research (CBER) are meeting deadlines and goals for assessing breakthrough designation requests and for expediting reviews of these drugs, but the process is resource intensive and has raised questions about how FDA can keep up with a growing number of candidates.

When the breakthrough programme was established as part of the FDA Safety and Innovation Act of 2012, stakeholders envisioned about two to three designations a year. By the end of May 2015, FDA had received 308 requests for breakthrough status and had granted the designation for 90, approximately 30%. Nearly 15 important new therapies have come to market more quickly as a result, contributing to the recent rise in new drug approvals. FDA acting commissioner Stephen Ostroff pointed out at the annual meeting of the Food & Drug Law Institute (FDLI) in April 2015 that two-thirds of 2014's near-record 51 new molecular entities (NMEs) took advantage of at least one expedited review programme, and many were first-in-class therapies.

Achieving fast approval of a breakthrough therapy creates challenges for manufacturers looking to develop CMC data in roughly half the time, noted Brian Kelley, vice-president for bioprocess development at Genentech. The process, he explained at the April 2015 CMC workshop sponsored by the Drug Information Association (DIA), is resource intensive, and accelerated timelines necessitate new approaches to product and process development to ensure a reliable supply of a quality product at launch. The breakthrough designation "does not mean that sponsors can do less," he said; they just "need to start sooner." This may involve front-loading of crucial product and process characterization activities, and reaching agreement with FDA on which actions for optimizing process and methods can wait until after launch.

High priority for FDA

Expedited quality assessments raise difficulties for FDA as well. New drug applications (NDAs) for breakthrough therapies often contain less manufacturing information than usual, requiring innovative risk-mitigation strategies to ensure product safety. Agency reviewers are agreeing to less stability data at submission, accepting amendments during the review cycle, and increasing postmarketing commitments to cover residual risk, explained Dorota Matecka, acting branch chief in the Office of New Drug Products in CDER's Office of Pharmaceutical Quality (OPQ), at the DIA workshop and again at the ISPE/FDA/PQRI Quality Manufacturing Conference in June 2015. Matecka noted that CDER will schedule CMC-specific meetings during development to advise on these issues, often including CDER upper management and subject matter experts.

Robert Wittoft, pharmacist in OPQ's Office of Process and Facilities (OPF), similarly urged early discussion of residual product quality risks. Manufacturers need to decide dosage form and methods validation strategies much sooner, he said at the CMC workshop, and should "plan for the unexpected," such as facility qualification failures and changes in manufacturing schedules. Effective communication with contract manufacturers is crucial, as is a transparent presentation in the application of design evolution and a rationale for commercial manufacturing process and controls.

John Groskoph, senior director at Pfizer, observed that for most breakthrough therapies, market applications are being filed with FDA after Phase II studies, approximately two years ahead of a traditional NDA that is based on Phase III data. The time reduction presents "significant challenges to the development team," he commented, and may be further complicated if the firm seeks to file simultaneous applications in Europe, Japan, and emerging markets, as well as in the United States.

Japan, for example, has established the SAKIGAKE designation programme for innovative medicines and medical devices that are developed first in Japan and offer "radical improvement" over existing therapies to treat critical diseases, explained Yoshihiro Matsuda of Japan's Pharmaceuticals and Medical Devices Agency (PMDA), at the CMC workshop. He described a greatly accelerated development and approval process for such therapies, combined with stronger postmarketing oversight. The initiative, he noted, requires risk-based assessment strategies and a product quality lifecycle management plan, combined with clear analysis of what can be evaluated during review, and what can be analyzed later after approval.

Groskoph noted that successful launch of a breakthrough drug involves addressing numerous issues: data availability, meaningful and practical specifications, robust manufacturing processes, clinical or commercial site production, site readiness for pre-approval inspection, deferral of Phase III studies to post approval, and the need for comparability protocols to facilitate postapproval changes. Communication with FDA is important throughout the breakthrough development process, he added, to facilitate agreement on strategies for dealing with unexpected production problems.

GLOBE: ZOONAR RF/GETTY IMAGES

For biologics, breakthrough designation may prompt greater focus on the reliability of the Phase I cell line, process and formulation, as shorter pivotal trials may truncate optimization of the Phase III process, added Kelley. A key decision for manufacturers is whether to devote more resources to the project early to front-load process characterization and validation activities, even before gaining the breakthrough designation. Such an approach may involve testing lots before assay validation is completed; filing with broader specifications with the aim of tightening them post-launch; launching from the clinical site and transferring to commercial post-launch; and including a postapproval lifecycle management plan in the application to support deferral of certain activities. But, Kelley commented, "you can't place bets" on potential breakthroughs too frequently without overly straining company resources.

Sustainable programme?

The growth in breakthrough designation requests is prompting FDA and stakeholders to examine options for refining breakthrough criteria so that FDA will be able to manage the programme. The agency is examining past designation decisions and why it turned down certain requests to see if the bar is too low; a goal is to better educate manufacturers on which promising experimental products really qualify for breakthrough status.

FDA "can't sustain a programme where everything is a breakthrough," commented John Jenkins, director of CDER's Office of New Drugs, at an April 2015 workshop on breakthrough therapy designation criteria organized by the Brookings Institution. FDA officials explained that extensive resources are involved in determining designations and in supporting development and accelerated review of breakthrough candidates. Manufacturers acknowledged that designation denials could decrease if sponsors sought breakthrough status only for therapies that offer truly substantial improvements in patient care. And they indicated that additional resources from industry are warranted to support the unexpectedly large breakthrough programme.

While FDA can quickly approve products with clear outstanding value, Jenkins noted that such efforts may be stymied by manufacturing problems and inspection delays. There are situations where the clinical data are good, but where sponsors "have to get manufacturing and facilities in line," he said. Sites for inspections need to be identified early, Jenkins advised, especially for overseas facilities that may raise travel difficulties. Kay Holcombe, senior vice-president of the Biotechnology Industry Organization, urged close examination of ways to prevent approval delays due to difficulties in making a drug according to specifications. "If this is a hurdle at the end," she said, "we need to deal with it more effectively." **PTE**

CDMOs Cautiously Address Expansion

While all market signs are pointing up, memories of past setbacks may discourage CDMOs from expanding capacity.

Jim Miller is president of PharmSource Information Services, Inc., and publisher of *Bio/Pharmaceutical Outsourcing Report*, tel. +1.703.383.4903, Twitter@JimPharmSource, info@pharmsource.com, www.pharmsource.com.

These are high times for contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs). A record flood of external financing is flowing into the bio/pharmaceutical industry. Global bio/pharmaceutical companies are outsourcing more of their development activity, and the United States Food and Drug Adminstration is being especially accommodating. R&D spending is growing, and the clinical development pipeline is really coming to life.

The explosion of development activity is pushing the contract services industry capacity to its limits, particularly for early development. Providers of preclinical research services, such as Charles River Laboratories and Covance, are rushing to reactivate capacity that was mothballed following the financial crisis. CDMOs that were fighting for survival two years ago are now telling clients there is a three- to six-month wait for a production slot.

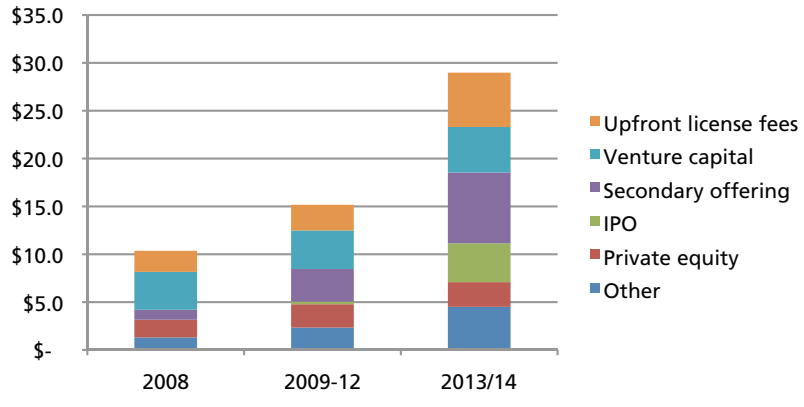
To expand or not to expand

Despite the strong market environment, the decision to expand capacity is not an easy one for CDMO executives, who were burned twice in the past decade. After a period of robust activity in the late 1990s, funding and development activity declined sharply in the early 2000s as a result of the dotcom bust and some major clinical failures. Then just as things were recovering in mid-decade, the global financial crisis once again cut the product development pipeline to a trickle.

New manufacturing and analytical capacity can take a year or more to construct, equip, and validate, and in that time, an upset in industry or macroeconomic conditions can leave CDMOs with a lot of unused capacity that still has to be paid for. So it is not surprising that CDMO executives are careful in committing to new capacity.

Executives' concerns are warranted because the surge in funding that is propelling demand is driven by the skyrocketing valuations of biopharma companies. Valuations of publicly-traded bio/pharma companies (as measured by the Nasdaq Biotech Index) have climbed 300% since 2010, three times faster than the broader stock market (as measured by the S&P 500). Thanks to that surge in equity prices, nearly 60% of the increased external funding flowing into early stage bio/pharma companies has come from initial public offerings (IPOs) and secondary offerings by companies that are already public (see **Figure 1**). But the rapid run-up in bio/pharma stock prices has given rise to increased concern about whether the "biotech bubble" is about to pop.

Figure 1: External financing for early-stage bio/pharmaceutical companies.



Funding stability

PharmSource has been looking closely at the funding issue, and while the possibility of the biopharma bubble bursting is a concern, a disruption in industry funding activity is not likely to be as damaging today as it was in 2008. This optimism is based on several key observations:

Global bio/pharma companies increasingly depend on early-stage companies to feed their own pipelines, so they have a strong interest in supporting them. Partnered or acquired products account for 50% or more of approvals received by global bio/pharma companies in recent years, while upfront payments from partnering deals with global biopharma companies provided 20% of the total funding received by early-stage companies. Investment in partner relationships, including licensing, may exceed 30% of total R&D spending at the global bio/pharmaceutical companies.

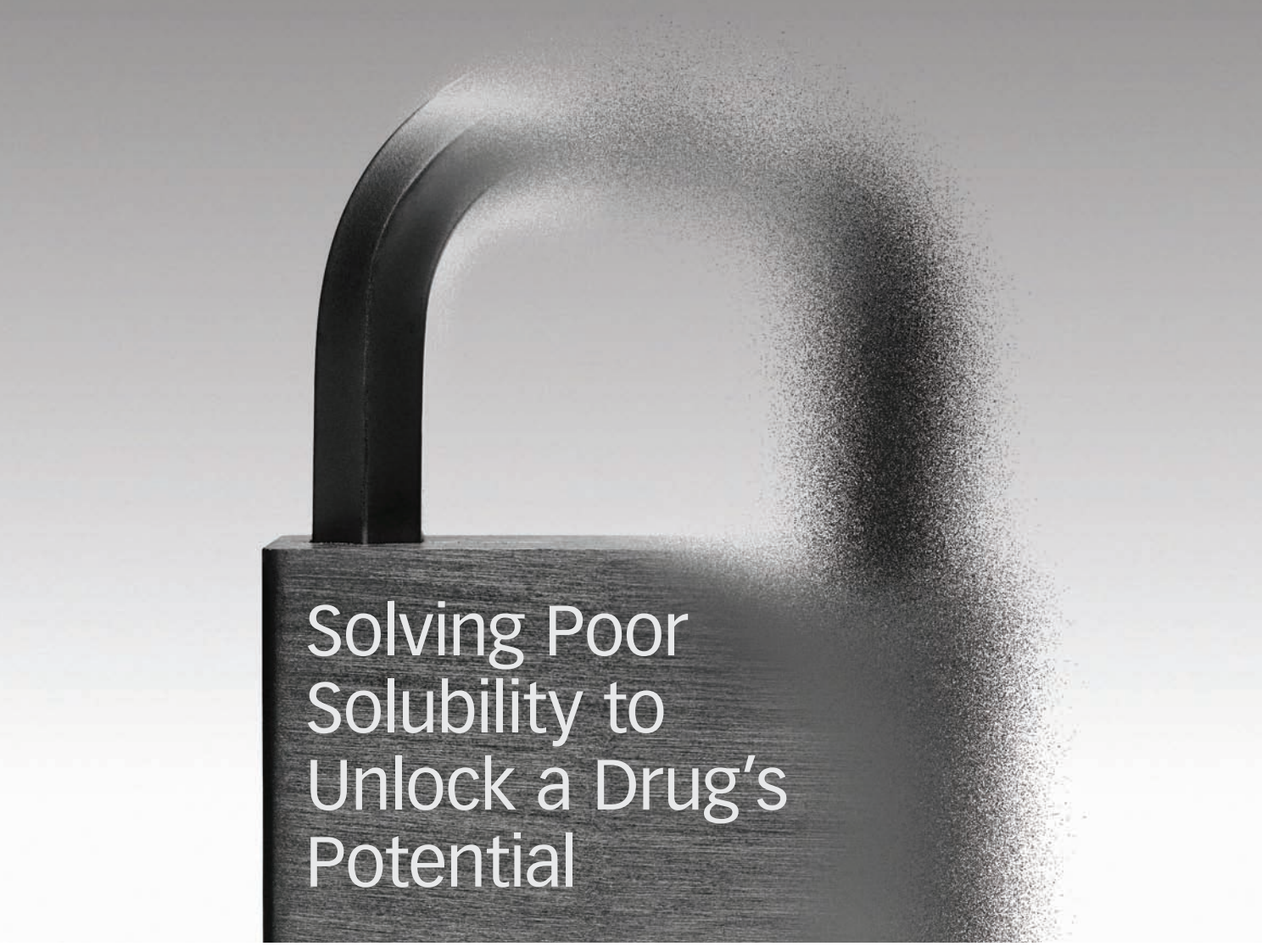
The explosion of development activity is pushing the contract services industry capacity to its limits.

Venture capital is not nearly as volatile as public financing. Venture capital funding for bio/pharma companies stayed fairly consistent through the financial crisis and has risen only gradually in the past several years. Global bio/pharma licensing activity will continue to provide an exit for venture capital investors even if public equity markets shrink.

The early-stage companies have plenty of cash. PharmSource analysis indicates that 70% of the public biopharma companies have more than two year's cash on hand, assuming current levels of spending.

CDMOs, therefore, can expand with the confidence that demand for their services should remain robust for the foreseeable future. Capital for expansion should be readily available given market conditions and a growing willingness on the part of bankers to lend, but the biggest challenge for CDMOs will be getting enough technical and project management staff to meet the growing demand. CDMOs and contract labs are already hiring aggressively, and poaching of staff, fed by rising salaries, has become a big problem. This poaching is especially true for people with the higher-order technical skills needed for prime growth segments such as advanced formulations and analytical services for biopharmaceuticals.

Restrained growth of capacity may not be the worst thing for CDMOs, however. Tight capacity conditions are likely to help CDMOs improve their profitability, just like they have for the airlines. After years of being beaten up on price by clients, especially the global biopharma companies, CDMOs and contract labs finally find themselves with some pricing power and the ability to improve their bottom lines. A healthy and profitable CDMO sector is in the best interest of the bio/pharmaceutical industry



Solving Poor Solubility to Unlock a Drug's Potential

Modern methods and modelling offer a better way to understand solubility issues and solve today's complex formulation challenges.

Adeline Siew, PhD

Poor solubility is an ongoing challenge in pharmaceutical development. A drug must be in solution form for it to be absorbed regardless of the route of administration. The solubility of an API, therefore, plays a crucial role in bioavailability given that drug absorption is a function of solubility and permeability.

Modern drug discovery techniques, with advances in combinatorial chemistry and high throughput screening, continue to fill drug-development pipelines with a high number of poorly soluble new chemical entities (NCEs). "Estimates have varied over the years, but it is reported that 40%–70% of NCEs are poorly water-soluble," observes Sampada Upadhye, PhD, technology platform leader for bioavailability enhancement & OptiMelt, Catalent Pharma Solutions. "There has been a tremendous amount of research going on in the industry to overcome the challenges in bringing poorly soluble drugs to the market."

Improving success rates in drug development

Selecting a suitable drug-delivery approach for these challenging NCEs depends on various parameters, explains Praveen Raheja, associate director, Formulations, at Dr Reddy's CPS, "for example, the drug solubility, chemical composition, melting point, absorption site, physical characteristics, pharmacokinetic behaviour, dose, route of administration, and intended therapeutic concentration, to name a few." An analysis of all these parameters is required to determine the most appropriate method of drug delivery, he says.

According to Marshall Crew, PhD, vice-president, Global PDS Scientific Excellence, Patheon, there are two aspects that must be understood in a comprehensive way before proceeding toward the best solubilization technology—the drug molecule and the target product profile. "The dosage form, dosage, and other requirements for the drug product must be taken into consideration, along with the molecular properties and profile of the API," he says. "Modern pre-formulation approaches begin by understanding the target product attribute space, and leverage modelling to more fully characterize and understand the molecule." Crew explains that this approach enables solubilization formulation scientists to know the starting point and direction

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of the process from the earliest stage to formulation design and optimization.

"Once the drug product requirements have been understood and the API characterized, solubilization technologies can be screened to identify the best fit for the particular drug and desired outcome," Crew adds. After the technology has been identified, the next step is to conduct experiments involving a range of excipient/polymer models in combination with the drug. Crew advocates the use of computational screening, which allows a greater number of options to be explored more efficiently, thereby increasing the likelihood of identifying the best approach.

Dan Dobry, vice-president, Bend Research, a division of Capsugel Dosage Form Solutions, also recommends a mechanistic, model-based approach. "Simple modelling and characterization tools can relate physicochemical aspects of the compound and therapy to potential delivery challenges," he notes. "The models are often not quantitative in early development, but give context to experiments, *in vitro* and *in vivo*, to help shape the problem statement and pair the right delivery technology."

Mastering multiple delivery technologies, from formulation through to scale-up and manufacturing, reduces bias for a particular technology, says Dobry, and allows each technology's sweet spot to be exploited, rather than trying to force fit a technology to a problem statement. He further adds that integrating appropriate enabling technologies into lead selection (instead of using them in a rescue mission during mid-development, when it may already be too late), can streamline the process and help identify the most effective combination of molecule and drug-delivery technology.

Dieter Lubda, PhD, director, Process Chemical Solutions R&D Franchise Formulation, Merck Millipore, finds that conventional solubilization approaches such as physical modifications of APIs, micronization, or nano-milling tend to have limited results. "The formulation of new drugs often needs new technologies and excipients that can induce specific solubility- and bioavailability-enhancing properties," he says. However, Lubda stresses that the interaction of new technologies and the excipients used is a far more complex scenario. Instead of focusing on one technique, it is important to consider how a range of excipients or approaches could work best for the poorly soluble API under development. "This helps increase the success rate of selecting suitable drug-delivery solutions," he asserts.

Tackling solubility challenges

When considering solubility, Dobry says the industry has a range of commercial solutions to choose from, such as size reduction, and the use of lipids or amorphous dispersions. These proven approaches can be selected based on the individual drug's properties and specific problem statement.

Each method, however, has its limitations and may pose new formulation challenges, notes Upadhye. Strategies such as polymorphism, salt formation, co-crystal formation, and the addition of excipients may marginally increase drug solubility, but often have limited success in increasing bioavailability, according to her. In some cases, they can even increase drug toxicity, resulting in negative side effects, she says.

Although particle size reduction may be a safe way to increase drug solubility, it does not alter the solid-state properties of the drug particles, Upadhye observes. In addition, solid dispersions, solid solutions, amorphous generation, and lipid-based formulations each has its own set of challenges that can affect drug stability and drug loading capacity, she adds.

One of the greatest formulation challenges today, according to Dobry, is the fact that poorly soluble compounds often present other problems, such as metabolism or permeability challenges, drug-to-drug interactions in a combination dosage form, or the need to modify pharmacokinetics (e.g., blunting the maximum concentration [Cmax] or extending drug release). "These challenges rapidly increase as the dose increases and desire for dosage form burden comes down," Dobry notes.

According to Stephen Tindal, director, Scientific Affairs, Softgel R&D, Catalent Pharma Solutions, dose is the number one problem. "Unless you can get significant increases in bioavailability, the patient has to take multiple large unit doses whether they're tablets, capsules, or softgels," states Tindal. Another problem is because APIs are not designed with enabling technologies in mind, there can be a suboptimal fit between the API and the dosage form.

"It can be beneficial to not fix the salt form or the polymorph form too early," says Tindal. "For example, if the API salt form has been selected with water solubility in mind, this may not be the ideal form for presentation as a lipid based drug delivery system."

Lubda explains that the first key consideration in formulation development is the route of administration. "The main question here is where the API needs to go in the body and how the drug can best be formulated to reach this targeted location," he continues. "In this challenge, the prerequisite for API bioavailability is to increase its solubility and permeability. These parameters must be optimized to achieve optimal release properties and the desired plasma profile within the required therapeutic window."

"Depending on the properties of the API, we have to assess if the drug can be formulated with standard formulation technologies or whether we need to explore non-conventional approaches," Lubda expands further. "Developing a good formulation is not easy per se. The excipients used could interfere with the drug during the formulation process (e.g., a pH shift during wet granulation) and result in a lower therapeutic effect."

Developing an oral formulation

According to Raheja and Lubda, the main challenges encountered during the development of oral formulations for poorly soluble drugs are:

- ensuring the stability of the formulation during processing and in the gastrointestinal (GI) tract (e.g., avoiding precipitation of the drug in gastric fluids)

- achieving consistent drug release rates
- considering food effects, such as different levels of drug absorption during fed or fasted states
- taking into account the presence of p-glycoprotein and cytochrome P450 (CYP) enzymes.

A common problem, as Raheja highlights, is determining the combination of suitable excipients and the enabling technology that increases solubility, as well as determining the appropriate tool to predict the solubility *in-vivo* so that an *in-vitro in-vivo* correlation (IVIVC) can be established.

Lubda emphasizes the importance of choosing the best excipients for the formulation, adding that process conditions such as heat or moisture during drug development are also crucial. "In the end, it comes down to: How can we cost-effectively formulate APIs with good content uniformity?" he asserts and highlights some key questions that should considered:

- Can we simplify complex formulations (requiring large number of excipients) that can lead to unexpected excipients interactions and limited drug stability?
- How can we influence the recrystallization of amorphous APIs and what are the pH effects on their stability?

Lubda sums up that the ultimate goal is to achieve a robust manufacturing process that takes into account disintegration and dissolution of the oral dosage form, hardness, content uniformity, waste, and productivity with high tableting speed.

According to Crew, developing a customized formulation for poorly soluble drugs requires achieving the best balance of dose, polymer, and API loading to allow the final drug product to have the required stability, manufacturability, and performance. "To accomplish this type of local optimization within a global context, using a modern approach is essential," he notes. Crew recommends a systematic methodology, employing rigorous scientific practices, and then performing extensive *in-silico* simulations. "Fortunately, the computational intensity of this type of exploration and analysis is now feasible," he adds.

Choosing a suitable solubilization strategy

When selecting a solubilization strategy, a number of considerations, such as the physicochemical and physiological properties of the drug, should be taken into account. Lubda lists the following key factors to consider:

- dosage form
- administration route
- mode of action (e.g., oral local or oral systemic for fungal drugs)
- API dose per unit or API load
- physicochemical properties of the API (i.e., pH-dependent solubility, pKa value(s), log P, temperature sensitivity, shear sensitivity, solubility in suitable solvents, known undesirable interactions with excipients, polymorphs, properties of crystalline state vs amorphous state)
- suitability of the manufacturing process for the API
- scalability of the formulation process
- differences in performance during feasibility studies and screenings
- availability of necessary equipment for process and method used
- stability of the final formulation and shelf life
- total cost of ownership
- intellectual property and licensing considerations.

Raheja offers a real-world example. "If a compound has an acidic or basic functional group and the log P is between 1.0 to 3.0, one could explore buffer systems to solubilize it," he says. However, he notes some possible drawbacks—a buffer-based system could result in precipitation in the GI. In such cases, anti-nucleating polymers could be used to overcome this problem. "These agents maintain a high degree of supersaturation and help improve bioavailability," Raheja explains. "Other solubilization techniques such as complexation and solid dispersions can also be considered for compounds with a log P in the range of 1.0 to 3.0. For compounds with a log P of 5, it is better to explore lipid-based systems."

Each solubilization technique has its pros and cons, Upadhye observes, and only a careful consideration of the API's physical, chemical, and thermal properties as well as its mechanical properties, will allow the best solubilization technique to be selected.

While most experts would agree on the list of key factors guiding a solubilization strategy, Dobry stresses the importance of having a framework or model that puts method selection into a broader context that also considers the mechanism of dissolution and absorption, and allows for problem statement definition, risk assessment, and sensitivity analysis. "In this context, it is important to have basic pharmacokinetic data of the crystalline drug in animal models to guide initial model development," he continues. "We find this aspect to be so important that we have developed discovery stage formulation tools to generate pharmacokinetic/pharmacodynamic data in animals, even for poorly-soluble actives."

While the drug molecule plays the key role in the decision, Crew adds that other crucial considerations include the amount of API available at the earliest stage of development and the drug product's goals. "In some instances, the initial assessment and process development can employ one technology, and then, when the formulation design has been completed, another technology can come into play," he says. Crew provides an example: creating an amorphous solid dispersion, for which either spray drying or hot-melt extrusion (HME) might be used. In this case, the API dictates the options available, he explains, and the decision tree includes such factors as:

- the amount of API
- chemical properties
- log P
- melting point
- solubility of API in solvent or polymer
- size of molecule.

These are only some of the factors, but they can only be derived from a thorough characterization of the molecule, Crew points out. Because the amount of API required for early formulation using spray drying is significantly less than what is required for HME, an early feasibility study might be done using that technology, if the API lends itself to

Addressing Formulation Needs With A Different Technology: Say "Hello" to Ion Exchange Resins

ON-DEMAND WEBCAST originally aired Wednesday, June 24, 2015

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Event Overview:

Ion exchange resins have long been in the formulator's toolkit, but only recently has there been an increased interest in their use as excipients. Amie Gehris, technical service manager for Dow Pharma Solutions, will discuss the value and benefits ion exchange resins bring to drug formulation challenges such as taste masking, abuse deterrence, controlled release, and more.

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- Ion exchange resins drug delivery applications and case studies

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- Process and materials engineers and manufacturing experts

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Presenters:

Amie Gehris
Technical Service Manager
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HME (i.e., if its melting point does not exceed 200 °C–225 °C)."

Weighing up the different solubility-enhancement approaches

"Several technologies are available to overcome solubility challenges," states Lubda. "One approach is to influence the surface area of the API particles using micronization, nanonization, co-grinding, or precipitation from supercritical fluids. The other alternative is to increase the solubility with solubilizers (polymers, surfactants, or cyclodextrins), lipid-based formulations (e.g., self-emulsifying or self-micro-emulsifying drug delivery systems [SEDDS/SMEDDS]), polymorphs, salt formation, or co-crystals." He notes that some newer solubilization techniques attempt to address both the surface area and solubility through the formation of liquid and solid dispersions or porous inorganic carriers such as mesoporous silica. "The overall goal is to improve API solubility and achieve a higher dissolution rate, which facilitates faster drug absorption," he says.

According to Lubda, micronization of API is challenging, especially at production scale. "Batch-to-batch homogeneity is poor," he observes, further highlighting the potential stability problems that could occur due to the high energy input, apart from the difficulty in achieving content uniformity in the solid-dosage form. "Surfactants can be seen as a straightforward approach to influence API solubility," he adds. "But because they are not inert excipients, surfactants can interact with APIs and other excipients. Their effects are hard to predict and surfactants potentially have an influence on biological membranes as well as possible side effects." Lubda views porous inorganic carriers (e.g., silica) as well as liquid and solid dispersions as promising technologies to solve solubility challenges.

Poor solubility is clearly a problem that will continue to challenge drug developers. As Crew points out, the number of insoluble molecules continues to rise. "During the decade of the 1970s, only 0.6% of FDA-approved molecules had been solubilized," Crew observes. "The next two decades showed increases, and by the 2000s, this category accounted for more than 10% of approved drugs."

According to Crew, Patheon analyzed the number of drugs approved by FDA between 1970 and 2013, which used diverse solubilization platforms (including lipids, amorphous solid dispersions, nanocrystals, and other alternative technologies). While lipid systems were the most widely used in the 1980s, and continue to be favored today, Crew says that solid dispersions saw a steep increase in the mid-2000s, and continue on a rapid growth rate even today. Findings from Patheon's study show that lipids dominated with a 50% share, solid dispersions took second place with 30%, ahead of the next closest technologies at less than 10%. Catalent's softgel expert Tindal concurs that lipid-based formulations have a historic advantage over solid dispersions, but notes that use of solid dispersions is increasing.

Solid dispersions continue to show broad applicability

Solid dispersions are widely used as a solubilization technique. Kevin O'Donnell, PhD, and William Porter III, PhD, who are both associate research scientists at Dow Pharma & Food Solutions, attribute it to the ability of solid dispersions to drastically improve the solubility of most APIs. "While solid dispersions present their own challenges, they eliminate the issues associated with traditional techniques," O'Donnell observes. "Non-ionizable APIs or those that do not fit in complexing agents can now find success."

"Owing to its simplicity from both manufacturing and process scalability standpoints, solid dispersion has become one of the most active and promising research areas and is therefore of great interest to pharmaceutical companies," comments Upadhye. "The term 'solid dispersion' refers to solid-state mixtures, prepared through the dispersion, typically by solvent evaporation or melt mixing, of one or more active ingredients in an inert carrier matrix. In these dispersions, the drug can be present in a fully crystalline state (in the form of coarse drug particles), in a semi crystalline state, or in fully amorphous state (in the form of a fine particle dispersion, or molecularly distributed within the carrier). Such systems prove to be very effective for enhancing the dissolution rate of low solubility drugs."

Dobry says that the approach is broadly applicable because of its mechanism of stabilization and dissolution, as well as a scalable, precedented process. "The most prominent advantage of solid dispersions is the purely physical change of the active compound (mainly from the crystalline to the amorphous state). If the change is performed in a controlled manner you don't have to deal with concerns about undesired effects from chemical changes of the compound," Lubda adds.

According to O'Donnell, until recently, the number of methods available to a formulator to generate an amorphous solid dispersion was limited. "However, recent growth in the techniques capable of generating an amorphous solid dispersion—such as spray drying, HME, precipitation methods, co-milling, KinetiSol dispersing, cryogenic methods, and others—has created processing flexibility, allowing almost any API to be formulated into a solid dispersion," he notes.

Spray drying and HME are currently the most commonly used methods to produce solid dispersions. "Spray drying is highly effective at generating the amorphous form of an API and can be used for APIs that have low degradation temperatures," Porter observes, adding that selecting the appropriate polymer and solvent will ensure the resulting product is homogenous.

HME, on the other hand, is a versatile process that does not require solvent. "Moreover, because it is a continuous process with narrowly defined output quality attributes, HME represents an ideal manufacturing platform for the implementation of process analytical technology (PAT)," Upadhye says.

For amorphous solid dispersions, a primary challenge is the stability of the amorphous drug, according to O'Donnell. "Improperly formulated systems may recrystallize into more thermodynamically stable and less soluble forms, resulting in dramatic changes in the dissolution, absorption, and therapeutic effect of the API," he points out. "The stability of crystalline formulations is also of great concern if a high-energy polymorph is selected, due to the risk of polymorphic transformations that can have negative effects."

"Another challenge consistently observed is that many poorly soluble drugs require delivering a high dose of the API to the patient," Porter notes. "This issue creates complexity in designing adequately sized dosage forms and can result in adverse drug effects and poor patient compliance." Porter explains that while amorphous solid dispersions may reduce the required dose circumventing this issue, a high drug load lowers the amount of stabilizing polymer present in the formulation, which can result in the aforementioned stability concerns.

Raheja sees great potential in solid dispersions citing a growing number of commercial products and those in development. "In the past decade, a lot of understanding on formulation components, analytical tools, and scale-up challenges have improved," he states. "Our own experience with this technology has brought products into different clinical and commercial stages."

"While simple solid dispersions will continue to be a cornerstone technology for enhanced bioavailability, we need to continue to innovate," says Dobry. "This will include the evolution and combination of the best aspects of multiple technologies, such as combining manufacturability and solid-state stability of amorphous dispersions with rapid dissolution and permeability enhancement of lipid formulations."

Mesoporous silica gains recognition

According to Lubda, the use of silica has been gaining traction since it was first used as a drug carrier in the 1980s. Most research has focused on the use of ordered mesoporous silica. "Materials such as SBA-15 (Santa Barbara Amorphous-15) or MCM-41 (Mobile Composition of Matter-41) are pure silicon dioxide particles with an ordered mesoporous structure but remain on scientific production levels. Silica materials with unordered mesopores are most widely used because their manufacturing process is easily scalable and the pore structures are known to be pressure resistant," he elaborates.

These mesoporous silica particles are inert and have a large internal surface area (potentially exceeding 1000 m^2/g) that provides space for the drug molecule to be absorbed, which is crucial for drug loading capacity, Lubda says. The challenge, however, will be making this surface area accessible to the drug molecule.

Different silica carriers can be used for drug delivery, Lubda explains, but it is important that they are monograph-compliant and have GRAS (generally regarded as safe) status. The underlying solubilization technology is to impregnate an amorphous drug form into the pores, with the help of an organic solvent in a pre-formulation step, and to prevent recrystallization during dissolution in the body, Lubda says. The result after drying and removal of the solvent is an intermediate, in powder form, of silica with the API. In most cases, he notes, such intermediates enhance the solubility (by supersaturation), dissolution rate, and stability of the poorly soluble small molecules. "This solubilization approach is applicable to a broad range of drugs, as the API only needs to be soluble in a volatile organic solvent," says Lubda, adding that the final formulation can easily be compressed into a tablet and the process is scalable.

Recent advances in the field

Given the range of solubilization technologies available, poor solubility does not necessarily prevent a drug from reaching the market anymore, notes Lubda. Research promises to expand the range of technologies available in the future.

"There is an increasing focus on understanding solubility and more importantly, the bioavailability of drugs in general," Lubda remarks. Experts notice the increasing collaboration between pharmaceutical manufacturers and academic research groups to develop more appropriate, better fitting test systems for *in-vitro* and *in-vivo* studies that will help provide deeper insights into drug properties and further the understanding of solubilization strategies. "The ability to model both molecules and excipients separately and then in combination *in silico* allows access to a broader solution space, and also significantly increases the predictability of solubilized outcomes," Crew adds.

Dobry notes that, during the past decade, significant advancements have been made in improving the stability, bio-performance, and manufacturability of NCEs that, in the past, might have been considered too insoluble to proceed into the next drug-development phase. "An important advancement has been in solid-state characterization and stability prediction of amorphous dispersions," Dobry observes. "Five to 10 years ago, this was seen as an Achilles heel. Now, it is one of several important aspects to address in a risk assessment, he says. "Continued innovation will be needed in this area, as molecules and formulations become more complex."

The ability to characterize dissolution mechanisms has been a major achievement, Dobry says, especially since today's formulation problems tend to transcend simple insolubility. "In many cases, there is a need to incorporate enabling technology into the discovery interface," he explains. Integrating quality-by-design principles in development, for example, allows interaction between the process and formulation attributes to be identified, enabling the manufacturing space to be optimized, while allowing performance and stability targets to be met.

As formulations become increasingly complex, new approaches tackle the problems of solubility and bioavailability in different ways. The future promises to bring more solutions to what may once have been viewed as insoluble problems. **PTE**

A Risk-Based Approach to Data Integrity

Heightened regulatory scrutiny of data integrity highlights the need for comprehensive reviews and strategies for managing mission-critical information.

Kurt In Albon, kurt.inalbon@lonza.com, is head of global IT quality, **Daniel Davis, PhD,** is a global GMP compliance specialist, and **James L. Brooks** is a global quality control systems manager, all with Lonza Group Ltd.

The regulatory requirement for data integrity is not new and was stated in United States 21 *Code of Federal Regulations* (*CFR*), Part 11 in 1997 (1). In the area of cGMP, regulatory focus on the integrity of electronic and paper-based data has increased sharply. Systems that formerly were given only superficial reviews have started to come under intense scrutiny. Standalone raw data-generating systems and business processes, as well as interfaced business and production control systems, present a large pool of crucial business information with which data integrity issues can occur.

Reviewing regulatory citations concerning data integrity, including US Food and Drug Administration warning letters and European Medicines Agency statements of GMP non-compliance, invariably leads to the conclusion that the current focus of the regulator lies strongly with systems involved in generation of quality-control data. Numerous early citations were caused by fraudulent behavior; therefore, focus also has been on the few tools that can detect such behaviour after the fact. The primary detection tool is a system's capability to write a detailed audit trail subject to the rules of 21 *CFR* 11. Therefore, some industry approaches to ensuring data integrity will concentrate on these types of systems and their respective audit trails.

Two other important aspects of data integrity include the validated state of a process or a computerized system (ensuring accuracy of generated or recorded data), and the management of critical authorizations (protection of data to avoid integrity breaches during operation).

When implementing measures to establish, maintain, and review data integrity across an organization, the following steps should be followed:

- **Awareness.** It is crucial that employees at all levels understand the importance of data integrity and the influence that they can have on the data with the authorizations assigned for their job roles. This understanding can be achieved with a relatively short, simple training session across an organization. More detailed sessions are required for process, system, and data owners; this training should describe the responsibilities for data within each employee's remit, as well as accountability for and consequences of accidental or intentional integrity breaches.
- **Standardization.** The standardization step should be based on available regulatory guidance, such as definitions (2) from the UK's Medicines & Healthcare products Regulatory Agency (MHRA), to ensure a common understanding of terms and concepts. This step should include, but not be limited to, interpretation of available government regulations and guidelines, internal procedures, terminology and concepts, as well as levels of risk for data.
- **Gap analysis.** A subsequent gap analysis of processes and systems, with emphasis on the existing controls for data integrity and their compliance with regulations, will yield the basis for the next step in the process: the determination of the risk associated with each process or system and the data generated or modified by it. As with any risk assessment, thresholds for mitigating action should be set before assigning criticalities to the individual data elements and their controls. In general, any such risk-based approach should be based on accepted standards, such as ICH Q9, *Quality Risk Management* (3).
- **Risk determination.** The completed risk determination will provide the basis for implementation of new required controls, in addition to existing ones. GMP-compliant businesses often will have data integrity under good control. The determined level of risk should be taken into account when deciding whether to implement technical or procedural controls.

Once implemented, the systems, controls, and data should be reviewed periodically, at a frequency commensurate with the determined risk, type of system, and industry guidance/regulatory requirements. **Table I** indicates the difficulties associated with the different types of systems.

Audit trails

According to agency warning letters, FDA expects that reviews of audit trails are done as part of the release

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Table I: Data integrity challenges in pharmaceutical manufacturing systems.

Review type	System type		
	Quality control lab (data acquisition)	Manufacturing (data acquisition)	Business (data processing)
Validated state	Stable, usually easy to control and maintain (no frequent changes)	Stable, usually easy to control and maintain (for single-product facilities)	Highly variable, frequent changes, numerous interfaces
Audit trails	Limited, usually compact and relatively easy to analyze	Limited, usually easy to analyze (operator logs), critical data in batch records	Extensive, difficult to separate by batch/product, difficult to analyze
Critical authorizations (physical and logical access)	Diversified, difficult to manage centrally, frequent access by diverse people	Limited, easy to manage (exception: package units, skids)	Extensive, difficult to manage and control

of each single batch. Equally, the notion that reviews of audit trails from analytical release tests should be done for each test is widespread. It is obvious, though, that indiscriminate application of such rules will generate a large number of reviews of perfectly accurate audit trails, revealing no untoward activity, and—ultimately—not generating value, ensuring product quality, or improving patient safety.

To perform meaningful audit trail reviews, it is important to ask what the review aims to accomplish. A review to determine whether an audit trail is functioning correctly should be limited to the initial validation phase of a computerized system. Typically, for the systems listed in **Table I**, audit trail functionality is a standard, off-the-shelf feature, possibly configurable to define what activities the end user wants to record in the audit trail. There is no need to re-qualify the correct function of an audit trail on a periodic basis. A proper operational qualification test will establish valid functionality, and requalification should be limited to system tests after major software upgrades. Of course, prior to implementation, an audit trail should demonstrate it is capable of recording events with sufficient granularity. If this is not possible, it will be difficult to perform meaningful and value-adding reviews of the recorded information.

Reviewing an audit trail to establish data integrity requires prior definition of critical items to be reviewed. For this definition to be meaningful, the relationship between the audit trail elements and the critical quality attributes (CQA) being tested by an analytical instrument, or the critical process parameters controlled and measurements recorded by a control system during manufacturing, should be established. There should be a strong relation between the criticality of test results and the frequency and depth of review of associated audit trails. Audit trails for analytical tests that do not have bearing on CQAs do not have to be reviewed to the same degree. To support this practice, a scientifically sound definition of the CQAs is required prior to implementation of the review cycle. Development of analytical methods, manufacturing, or business processes should include the definition of these critical attributes; If these attributes are not defined, it will be difficult to decide at a later time which data integrity breaches are critical in terms of patient safety and which are not.

For a chromatography data system, for example, analysts will require some flexibility to work with the data acquired by the system and the connected instrument to account for changes in system performance. Extensive manipulation, however, can have the effect that results—which were outside of specification during data acquisition—can later be in specification. For such analytical tests, critical entries in the audit trail to be reviewed for high-risk (release) samples must include manual integration events or changes to processing method integration events. In another example, the completion of sample well templates on microtiter plate readers after data acquisition causes a misordering of events, which will only appear in the audit trail. Audit trail entries indicating such deviations from established procedure should be included in the review.

To perform meaningful audit trail reviews, it is important to ask what the review aims to accomplish.

In system audit trails or logs (as opposed to data audit trails), certain patterns of activities should be reviewed. Repeated failed logins, which may indicate fraudulent break-in attempts, are a prime example. Algorithms for detecting such activities that are built into a system should be enabled. A review of the output of such an algorithm replaces the actual physical review of the raw audit trail for these events. Read/write errors to and from data storage, which could indicate a breach of data integrity due to hardware failures, should also be checked.

Events not included in the list of critical items that will not improve patient safety or compliance, or add value, should be excluded from any review by default. This action becomes especially important for the review of audit trails from enterprise resource planning (ERP) software used in the supply chain

Table II: Suggested review frequencies for software by risk class.

Risk class	Good Automated Manufacturing Practices (GAMP 5) Software Category			
	5	4	3	1
High	3 months	6 months	12 months	24 months
Medium	6 months	12 months	24 months	For Cause
Low	24 months	36 months	For cause	For cause

and materials management. When configured accordingly, these systems can generate large amounts of audit-trail data with normal daily transactions. Business process steps executed automatically by the system, such as the promotion of a document from one status to the next after an electronic signature by the user to release a document for production, can generate many audit trial entries. In a company with hundreds of system users, this activity may result in hundreds of megabytes of audit trail information to review. A restrictive filtering process is needed to eliminate all non-critical events and focus the review on the critical entries. On these types of business systems, a clear definition of the critical entries is the only way to perform a meaningful review in support of data integrity.

For all types of reviews and for all types of systems, the actual detection of a data integrity breach should cause process deviations to be raised followed by subsequent corrective and preventive action.

Critical authorizations

As shown in **Table I**, data acquisition systems in manufacturing may require the lowest amount of effort to control access security, because these systems typically are physically separated from other systems (non-networked) and, in many cases, are only accessible using physical access controls (badges, keys).

Access to laboratory systems and processes will be highly varied, with stand-alone instruments and linked instrument computers. For each instrument, the requirements for data integrity apply, whether the system complies with 21 *CFR* Part 11 or the test results are printed and the electronic information is discarded. Commonly, access to data and instruments is based on what the drug manufacturer considers to be critical authorizations; these permissions warrant periodic review. As with the audit trail events, critical authorizations must be defined prior to launching the review cycle to generate consistent and useful reviews. Notably, the review of critical authorizations will not include analysis for fraudulent access attempts, but only the status and history of authorization levels and issued permissions.

System administrator permissions for all systems, regardless of the area in which they are used, should be reviewed periodically. System administrations can act outside enforced business process and have direct access to database tables via management tools that may not include input validation or other data-integrity protection safeguards. It is crucial to control these authorizations to a high degree to avoid intentional or accidental data corruption.

Super-user permissions, which may be needed to change recipes on process control systems or test methods on laboratory systems, also should be considered critical, because activities of these users may cause incorrect data further along the management process.

Authorizations needed to create records in the system or to initiate the generation or acquisition of information need not necessarily be classed as critical authorizations, and as such would not be included in the periodic review (except for business reasons, such as license retirement, etc.)

Validated state

A properly validated computer system or business process will support the maintenance of data integrity. It is therefore crucial that the baseline validation is kept up-to-date to show that all changes have been tested in accordance with assigned risk criteria. Often, the primary aim of a review of the validated state of a system is to show that it still complies with regulations for computerized systems, such as 21 *CFR* Part 11 or EU GMP Annex 11 (4). For systems subject to few or even no changes, there may not be added value in reviewing this documentation periodically. Unless there is a degradation of performance of the system due to its nature or mode of action, a review of the validated state at an appropriate frequency will confirm the state of control and compliance required by regulations.

In particular, business systems such as large-scale ERP or document management systems are often subject to frequent changes in configuration and functionality. For these types of systems, a periodic review—including all change control records, service tickets, and documentation changes—will be extensive. Determination of the cumulative effect of changes is also difficult and not always entirely accurate under these circumstances. It is, therefore, necessary during collection of information for the review to only select changes and modifications that may have a potential impact on data integrity for the area of patient safety and product quality. For a cGMP determination of data integrity, human capital

information, or financial data integrity may not be applicable and can be excluded from review. Tickets and change requests in these areas can be omitted during such an assessment. It has proven useful to tag change requests as GMP-relevant or business-relevant during an impact assessment by the quality unit as part of the regular change control process. Such a tag will allow easy filtering during review of the validated state. The same principle should be applied to business process deviations or help-desk tickets.

For all types of reviews and for all types of systems, the actual detection of a data integrity breach should cause process deviations to be raised followed by subsequent corrective and preventive action. This action can include, if warranted, an increase in the frequency of the particular review cycle. **Table II** offers guidance for review frequencies, based on the Good Automated Manufacturing Practices (GAMP 5) software categories of a system (5) and an arbitrary scale of risk (high/medium/low). The scale should to be determined according to the proximity of the system to the regulated product and by the potential impact a data integrity breach would have on patient safety and product quality.

Conclusion

The number of computerized data acquisition and processing systems in the pharmaceutical industry is growing quickly and with it the number of records generated that are inextricably linked with the regulated products manufactured by the industry. The situation is complicated by the integration of systems, interfaces between the systems, and conversions, calculations, and compression of information that may take place during transmission. The knowledge generated from these data and information is directly used in the manufacture of drugs. Data integrity and its practical maintenance are therefore crucial to the safety of patients and the quality of healthcare products. By using a risk-based approach and the presented principles, it is possible to generate meaningful reviews and proof of data integrity.

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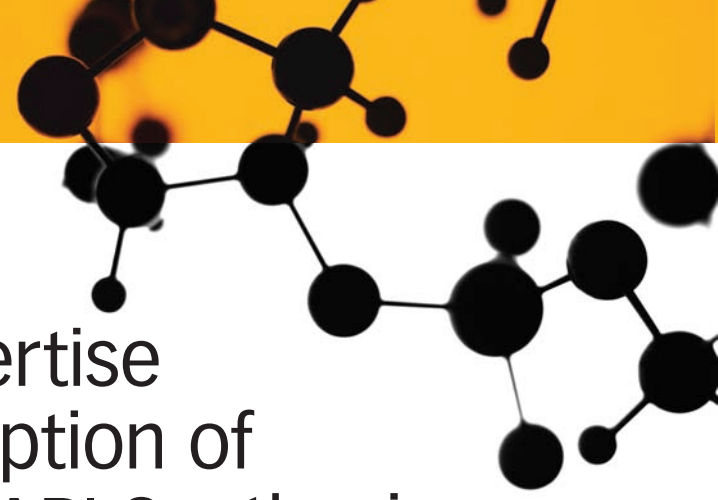

Lack of Expertise Hinders Adoption of Continuous API Synthesis

Authorities and early adopters look to speed up the use of continuous API manufacturing.

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

Despite a few significant investments in continuous manufacturing facilities by pharmaceutical companies, including Vertex Pharmaceuticals, Johnson & Johnson, GlaxoSmithKline, and Novartis (1), the adoption of flow chemistry for commercial production of APIs generally remains in the early stages. The US Food and Drug Administration (FDA) has encouraged the adoption of continuous manufacturing since 2004, but specific guidelines are lacking from the agency and other regulators around the globe. Both former FDA Commissioner Margaret Hamburg (1) and Center for Drug Evaluation and Research Director Janet Woodcock (2) recently have been more vocal about the issue, particularly in relation to the proposed 21st Century Cures Act. This legislation requires FDA to support the development and implementation of continuous manufacturing for drugs and biologicals as one of several approaches to speeding up drug development and commercialization (3). In addition to a lack of comprehensive regulatory guidance, however, a dearth of industry personnel with expertise in flow chemistry is a hindrance to rapid adoption of continuous technologies.

Early adopters and fast followers drive change

"While the industry as a whole is in the early stages of adopting flow chemistry for small-molecule API manufacturing, the early adopters and fast followers not only recognize that flow chemistry is the future of manufacturing, but also believe that they can implement it effectively," asserts Tim Jamison, professor of chemistry and incoming department head at the Massachusetts Institute of Technology (MIT) and CEO of Snapdragon Chemistry, a new company dedicated to catalyzing the adoption of continuous flow synthesis. "Ultimately, when these companies realize the many benefits of flow chemistry, including reduced operating costs, footprint, and capital expenditures combined with improved process efficiencies, control, and product quality, investors likely will modify their expectations and demand this increased value from the industry as a whole. The rest of the industry will then have to scramble to catch up, and the early adopters and fast followers should reap the rewards of their forward-thinking actions. At that point, the entire industry—out of necessity to remain competitive—likely would shift its view on flow technology," he explains.

Most large pharmaceutical companies, according to Peter Poechlauer, innovation manager with Patheon, have at least installed advocate groups with a mission to showcase successful applications of flow processes. Dominique Roberge, head of chemical technologies with Lonza Pharma & Biotech agrees that flow chemistry has become an accepted technology for small-molecule manufacturing, largely for the development of new chemical reactions that have not been feasible in batch operations, to reduce the cost of goods, and to decrease capital expenditures (CAPEX) via process intensification. "These projects are significantly more focused and give a better understanding of what is achievable via flow chemistry. As a result, we have moved past focusing on feasibility studies only and are now evaluating projects that are more mature for tech transfer and scale-up," he notes.

"The decision to develop a certain step as a flow process is, however, opportunistic and may be motivated by the speed provided in early development, the need for smooth scale-up of hazardous reactions, and/or the savings in investment for a new drug whose future is still uncertain," Poechlauer observes. In addition, he notes that these criteria apply to single steps of multi-step pharmaceutical syntheses, and therefore hybrid approaches that combine continuous and batch operations are most common; few companies have developed end-to-end continuous syntheses of pharmaceuticals that combine drug-substance manufacturing and drug-product formulation.

"Continuous flow manufacturing occupies a similar position to where a technology like spray drying was 10–15 years ago. It shows great promise but the 'mainstream' commercial viability within the pharmaceutical industry has yet to mature," says Patrick Kaiser, a principal scientist in the process development business of SAFC. He believes that,

Controlling the Physical Properties and Performance of Semi-solid Formulations through Excipient Selection

ON-DEMAND WEBCAST Originally aired June 10, 2015

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EVENT OVERVIEW:

Semi-solid formulations are in a non-equilibrium state composed of numerous possible microstructures including API polymorphs, surfactant phases, crystalline lipophiles, polymer networks and lipophile-surfactant gel or liquid crystalline phases. The selection of excipients in topical semisolid formulations can determine the structure of microscopic phases that form during processing. The influence of these phases on the formulation physical properties can be observed when measuring viscosity and observing microstructure. Exemplary data will demonstrate how specific excipients were used to modify formulation performance, correct formulations that showed aqueous phase separation or weeping and improve stability.

Key Learning Objectives:

- Participants will be introduced to some simple case studies where the choice of excipients and their quantity had a specific influence on semisolid product quality and performance.
- Participants will learn basic methods for observing or characterizing the influence of excipients on semisolid behaviors.
- Participants will see how BASF oleochemical-based excipients and/or polymers have been employed to solve common formulation problems and to tailor formulations to meet design criteria.

Who Should Attend:

- Dermatological and Topical Product Development Scientists
- Formulators
- Analytical Chemists who work with topical products
- Pharmaceutical Scientists
- Raw Material QA and QC Specialists

For questions contact Sara Barschdorf at sbarschdorf@advanstar.com

Presenter:

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Global Development and Technical Marketing Manager, Skin Delivery
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like spray drying, a clear commercial pathway and, more importantly, a clear regulatory pathway will drive more entrants as developers embrace the technology's promise. Even so, Kaiser expects there will be limitations to its full embrace, because certain systems lend themselves to be more relevant to continuous processing, while others make less sense to perform via continuous means, and this dissonance complicates the pathway forward. "The reality is that CMOs must embrace such disruptive technologies moving forward to ensure long-term competitiveness in the marketplace," he concludes.

Expanding toolbox

A positive indication for the future of flow chemistry is its increasing use for different types of reactions and downstream separation/purification operations. With respect to chemical reactions, using flow processes allows better control of yield and selectivity, which have a direct influence on purification and separation steps, according to Roberge. "The best approach is to develop new processes that can and will lead to a significant improvement in the synthetic route, but will typically not work in a traditional batch process," he comments. His examples include various oxidation reactions (with molecular oxygen or hydrogen peroxide), azide chemistry, and high-temperature/pressure reactions developed via microwave chemistry.

Jamison adds that the use of flow chemistry for photochemical and electrochemical reactions is also exciting, because these reaction classes are typically difficult to carry out and control and also challenging to translate from laboratory scale to pilot or manufacturing scale, but afford significant opportunities to access completely novel chemical scaffolds and greatly streamline current synthetic routes. "By using flow chemistry to gain better control, predictability, and scalability for these reaction classes, chemists can increase their utilization, which will ultimately result in significant advances and broader adoption in the pharma industry," Jamison states.

Integration of chemical synthesis reactions in flow with an increasing diversity of work-up operations in flow, such as continuous extraction, membrane processes, and the crystallization and separation of solids, is also an important development, according to Poechlauer. He further notes that the application of parallel, analytical instruments with sufficiently short response times have been developed, allowing efficient control of these processes.

The development of a complete toolbox of flow reactors that can be used for all types of reaction rates and phases (e.g., liquid-liquid, solid-liquid, etc.) is also necessary for the broad application of flow chemistry to be achieved, according to Roberge. To address some of this need, Lonza has developed the pulsating coil reactor for liquid-liquid phase reactions and an efficient de-plugging system based on ultrasound technology. "Ultimately, true innovation in this field will come from a few key players in the market who have the variety of experience and infrastructure to optimize multiple reaction platforms," asserts Roberge.

Shortage of expertise

In fact, the inadequate supply of scientific talent and expertise necessary to implement continuous flow technology at scale is perhaps the largest factor hindering more rapid adoption of flow chemistry for small-molecule API synthesis, according to Jamison. "It's not as simple as asking current chemists to start working with continuous flow technology. That is like asking a saxophonist to play oboe. While both instruments are woodwinds, a saxophone uses one reed, while the oboe uses two. Thus, saxophonists can certainly become oboists, but it is not automatic; there will be a learning curve in most, if not all cases. Currently, flow chemistry is generally not in most university chemistry curricula. Thus, there will continue to be a lack of expertise in this area until this situation is changed," he explains. "In the long run, industry demand will accelerate such changes; as the industry requires more expertise in this area, education/training standards will shift to meet this demand. This shift will not occur immediately, however, and there will likely be a short- to mid-term lack of human resource supply," Jamison says.

Rhony Aufdenblatten, manager of small-molecule business development with Lonza Pharma & Biotech, agrees that flow chemistry remains a specialized technology, because it requires specific technical know-how that can only be developed over years of manufacturing different chemical products. "The key challenge for any small-molecule development program is management of scale-up of the lab process for industrialization. Moving this type of scale-up into a new platform like flow chemistry can only be handled by the few players who have experience working with a variety of chemistries and processes," he observes.

Poechlauer is not convinced that continuous processing is "experts only" territory any longer, but he also believes that this perception certainly affects decisions regarding adoption of the technology. As a result, he does believe that CMOs with a proven track record in continuous processing may be favored as demand for this capability increases.

Regulatory and infrastructure issues

Two other factors that are influencing the rate of adoption of flow chemistry for API synthesis include a lack of clear regulatory guidelines and the existing batch-based manufacturing infrastructure. Although FDA representatives recently made a number of public comments in support of continuous manufacturing in the pharmaceutical industry, from a regulatory standpoint, there remains a need to develop clear, harmonized guidelines accepted across the various regulatory authorities that will facilitate the development of continuous manufacturing routes in a manner that guarantees a consistent way to monitor/regulate their output, according to Jamison. In addition, while there are a growing number of flow processes being filed with auditors despite this lack of clarity, Poechlauer notes that there is little experience with respect to the auditing of continuous process steps.

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04 Investment in R&D and related facilities is very active and establishment of plants according to the international standards is increasing.

[1] The changing dynamics of pharma outsourcing in Asia, PwC.

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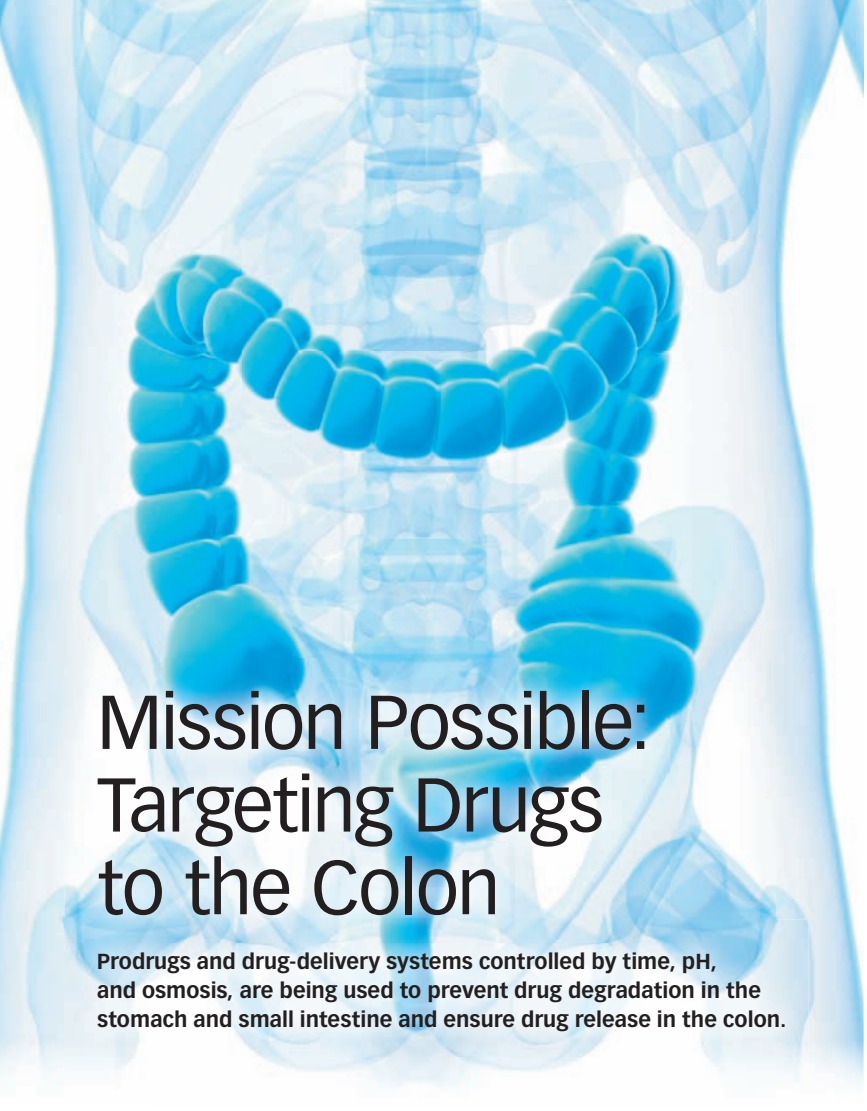

Mission Possible: Targeting Drugs to the Colon

Prodrugs and drug-delivery systems controlled by time, pH, and osmosis, are being used to prevent drug degradation in the stomach and small intestine and ensure drug release in the colon.

Adeline Siew, PhD

Oral formulations, which are still the most widely used dosage forms, can be designed to release the drug at specific sites of the gastrointestinal (GI) tract. Today, the colon is becoming a more attractive target, not only for treating diseases of the colon such as Crohn's disease, ulcerative colitis, and colorectal cancer, but also for GI therapies in general. For example, colon targeting can be used to systemically deliver proteins and peptides that are susceptible to enzymatic degradation in the stomach or small intestine. This approach has been found to provide safe and effective therapy with proven bioavailability enhancement as well as a lower incidence of drug toxicity and unwanted side effects.

Colon-specific drug delivery exploits the differences in anatomical and physiological features of the upper and lower segments of the gut. Research has shown that the colon is more responsive to absorption enhancers, protease inhibitors, and bioadhesive and biodegrable polymers compared with other regions of the gut (1). The challenge, however, comes in ensuring that the drugs are intact when they eventually reach the colon, which is often a problem with traditional oral dosage forms. A number of different approaches are being used to target drug release in the colon. This article will summarize key trends, including the use of prodrugs, pH- and time-dependent systems, as well as newer approaches based on osmotic-controlled drug delivery.

Prodrugs. The prodrug strategy exploits the presence of the colonic microflora, which is in the order of 1011–1012 colony-forming unit (CFU) per mL in the colon, compared with 103–104 CFU/mL in the stomach and small intestine (2). To form the pharmacologically inactive prodrug, the parent drug is attached to a chemical group, and enzymatic degradation by the bacteria in the colon then frees the active drug molecule. Linkages such as azo, amide, glucuronide, and glycosidic bonds are often used in prodrug formation for colon-specific drug delivery. Ruiz et al. reported on the development of a double prodrug system for colon targeting of benzenesulfonamide cyclo-oxygenase-2 (COX-2) inhibitors (3). The prodrug was first activated by azoreductases followed by cyclization to release the active drug. According to the researchers, the prodrug demonstrated good stability in human intestinal extracts and was only activated under specific conditions of the colon, hence achieving targeted drug release.

pH- and time-dependent drug-delivery systems. In this approach, drug release is triggered by a change in pH as the dosage form passes through the gut. It is generally accepted that the pH of the GI tract progressively increases from the stomach (pH 1–2 in fasted state and pH 4 during digestion) to the small intestine (pH 6–8). The important thing is for the formulation to remain intact until it reaches the colon. Such formulations typically incorporate polymer coatings that are insoluble in an acidic environment but become soluble as the pH increases. Commonly used pH-sensitive polymers include Eudragit L and S, polyvinyl acetate phthalate, hydroxyl propyl methyl cellulose phthalate, and cellulose acetate, to name a few.

Time-dependent systems take a different approach by delaying drug release after a specific period of time. Taking into account gastric emptying and intestinal transit times, swellable systems that incorporate different combinations of hydrophilic and hydrophobic polymers as the coating material are used to adjust the time lag. Recent approaches often combine both pH- and time-dependent systems to achieve more targeted drug delivery to the colon. Ofokansi and Kenechukwu, for example, prepared ibuprofen tablets using Eudragit EL 100 and chitosan to form interpolyelectrolyte complexes (4). The formulation showed pH-dependent swelling properties and prolonged drug release *in vitro* (4). The electrostatic interaction between the carbonyl (-CO-) group of Eudragit RL 100 and the amino (-NH3+) group of chitosan was thought to prevent drug release in the stomach and small intestine, facilitating colon-targeted drug delivery.

Osmotic-controlled drug delivery. Osmotic systems are commonly used for controlled-release purposes but the concept can be applied in colon drug delivery as well. The system consists of the drug, an osmotic agent, and a semi-permeable

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membrane with an orifice for drug release. An additional enteric coating is applied on top of the membrane to prevent drug release in the stomach and upper GI tract. As the dosage form enters the small intestine, the increase in pH causes the enteric coating to dissolve, exposing the semi-permeable membrane. Water enters the drug core and the expanding volume forces the drug out the osmotic system through the orifice.

A number of research groups are working on the development of innovative osmotic tablets for the treatment of inflammatory bowel disease. Chaudhary et al., for example, developed microporous bilayer osmotic tablets of dicyclomine hydrochloride and diclofenac potassium for colon targeting (5). The bilayer coating consisted of a microporous semipermeable membrane and an enteric polymer. The tablets showed acid resistance and time release in *in-vitro* dissolution studies, demonstrating the potential for colon-specific drug delivery to treat irritable bowel syndrome.

Nath et al. incorporated Sterculia gum, which is a polysaccharide, into osmotic tablets for colon-specific drug delivery of azathioprine (6). Sterculia gum is digested by the colonic enterobacteria and swelling of the polysaccharide forces the drug out of the tablet core. To ensure that drug release does not occur in the upper GI regions, a double-layer coating of chitosan/Eudragit RLPO (ammonio-methacrylate copolymer) and enteric polymers is used to impart acid- and intestinal-resistant properties to the tablet.

In short, the colon offers an alternative drug-delivery approach for acid-labile drugs such as proteins and peptides, drugs that degrade in the stomach and small intestine or undergo extensive first pass metabolism, as well as for topical treatment of inflammatory diseases of the colon. While progress is being made in achieving more specific targeting of drugs to the colon, the complexity of these drug delivery systems will require validated dissolution methods and establishing *in-vitro/in-vivo* correlation.

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The International Conference on Harmonization (ICH) may be an effective body for achieving international guidelines. The organization may in fact be making continuous flow manufacturing a focus issue over the next year to 18 months.

The impact of existing batch plants is less straightforward. For companies with unused batch capacity, Aufdenblatten notes that additional motivation for further investment into large-scale flow chemistry will be needed to overcome the additional CAPEX for flow infrastructure. "Typically, a gain in yield of 2–3% will not be sufficient; reduced cost of goods, safer processes, and breakthroughs in process platforms must also be considered," he explains. Jamison points out, though, that existing infrastructure is in various stages of maturity, and new capacity (whether batch or continuous) could be established naturally, with continuous plants being built in place of new batch plants, as appropriate. "In addition," he says, "continuous manufacturing plants could have a 10- to 100-fold smaller footprint than a batch plant of comparable output. Therefore, the CAPEX investment is smaller, which might sway the economic analysis to favour the business case of mothballing a significant number of existing batch-mode plants."

The mentality of the process development function must also be considered, according to Kaiser. The use of flow chemistry earlier in development requires both the innovator and CMO to be open to using continuous systems as an option in their process development efforts. Doing so potentially requires developing an initial batch process backed up by a second-generation flow process, perhaps simultaneously if the drug is on an accelerated approval pathway, which is not a small shift in today's "fast-fail" drug development business. "Development companies are generally averse to investing too much in the manufacturing process until there is good clinical data to show manufacturing on a larger scale is necessary. Unfortunately, waiting too long to develop a continuous process also complicates a company's regulatory strategy and potentially a challenge with different impurity profiles from different manufacturing processes," he comments. The best strategy to combat this challenge, according to Kaiser, is to have experienced flow chemistry experts recognize where continuous systems provide the greatest opportunity for results early on in the process development effort.

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Beyond the Blink: Using *In-Situ* Gelling to Optimize Opthalmic Drug Delivery

Delivery systems that allow drugs to be administered as liquids, but form gel within the eye, promise to improve efficacy and patient compliance.

Jigar N. Shah, Rakesh K. Patel, Hiral J. Shah, and Tehal A. Mehta

Conventional ophthalmic solutions frequently show poor bioavailability and a weak therapeutic response because they are often eliminated before they can reach the cornea, when patients blink or their eyes tear. Use of *in-situ* gel forming solutions may help improve performance and patient compliance. These solutions are delivered as eye drops, but undergo a sol-gel transition in the conjunctival sac (cul de sac). This article describes how an ion-activated *in-situ* gelling system was designed to deliver an ophthalmic formulation of the antibacterial agent, Levofloxacin.

The delivery system uses gellan gum, a novel ophthalmic vehicle that gels in the presence of mono or divalent cations in the lacrimal fluid. This gum was used alone and combined with sodium alginate as a gelling agent and hydroxypropyl methylcellulose (HPMC) Methocel F4M as a viscosity enhancer. A 3^2 full factorial design approach was used, with two polymers: Gelrite and HPMC, as independent variables. Gelling strength, bioadhesion force, rheological behaviour, and *in-vitro* drug release after 10 h were selected as dependent variables. Both *in-vitro* release studies and rheological profile studies indicated that the combined Gelrite–HPMC solution retained the drug better than the gellan gum alone or a combination of gellan gum–alginate–HPMC. The developed formulations were therapeutically efficacious and provide sustained release of the drug over a 12-h period *in vitro*. These results demonstrate that the Gelrite–HPMC Methocel F4M mixture can be used as an *in-situ* gelling vehicle to enhance ophthalmic bioavailability and patient compliance.

Jigar N. Shah, PhD,* is assistant professor at Nirma University's Institute of Pharmacy's Department of Pharmaceutics in Ahmedabad, Gujarat, India. He can be reached at jigar.shah@nirmauni.ac.in or jigsh12@gmail.com.
Rakesh Patel, PhD, is professor at S.K. Patel College of Pharmaceutical Education & Research, Ganpat University, Kherva, Gujarat, India.
Hiral J. Shah, PhD, professor, J. Arihant School of Pharmacy & Bioresearch Institute, Adalaj, Gandhinagar, Gujarat, India.
Tejal A. Mehta, PhD, is professor, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India.

*To whom all correspondence should be addressed.
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Opthalmic drug delivery systems, such as eye drops, ointments, and soft gel capsules, are typically used to treat diseases of the eye. However, the eye's protective mechanisms often reduce their therapeutic effect. When a drug solution is dropped into the eye, there is typically a 10-fold reduction in the drug concentration within 4–20 min, due to the effective tear drainage and blinking action (1). The cornea's limited permeability contributes to the low absorption of ocular drugs. Due to tear drainage, most of the administered dose passes via the nasolacrimal duct into the gastrointestinal tract, leading to side effects (2). Rapid elimination of both the solutions and the suspended solid administered often results in blurred vision, poor patient acceptance, and short duration of the therapeutic effect, making more frequent dosing necessary (3). New preparations have been developed to prolong the contact time on the ocular surface and slow down drug elimination (4, 5). Ocular inserts (5) and collagen shields (6) can also be used, but they pose challenges.

These delivery challenges can be overcome by using *in-situ* gel-forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel–sol) and pseudoplastic behaviour. Such formulations minimize interference with blinking (7).

Changes to the gel phase (8) can increase pre-corneal residence time and enhance ocular bioavailability. Three types of systems have been used: pH-triggered systems including cellulose acetate hydrogen phthalate latex (9, 10) and carbopol (11–15); temperature-dependent systems including pluronics (7, 16–20), tetronics (21, 22), and polymethacrylates (23); and ion-activated systems including Gelrite (24–26), gellan (27–28), and sodium alginate (29).

The authors used an ion-activated *in-situ* gelling system to deliver Levofloxacin, a fourth-

Table I: Composition of prepared *in-situ* gelling systems.

Batch	Gellan (%w/v)	SA (%w/v)*	HPMC (%w/v)	Gelling capacity	Drug content (%)
LV	0.2	-	-	+	97.23±1.27
LV1	0.3	-	-	++	98.35±1.09
LV2	0.3	0.27	-	+++	99.38±0.94
LV3	0.3	0.29	0.5	+++	98.17±1.12
LV4	0.3	-	0.5	+++	99.47±0.89
LV5	0.4	-	-	+++	99.25±0.79
LV6	0.4	0.27	-	+++	99.52±0.95
LV7	0.4	0.29	0.5	+++	98.93±0.67
LV8	0.4	-	0.5	+++	99.42±1.13

+ gels slowly and dissolves; ++ gelation immediate and remains for a few hours; +++ gelation immediate and remains for an extended period.
*Amount of Sodium alginate was adjusted (equivalent to 0.25% w/v)

generation fluoroquinolone anti-infective agent, which can be used to treat conditions including acute and subacute conjunctivitis, bacterial keratitis, and keratoconjunctivitis. The goal was to demonstrate prolonged action and show antibacterial activity against gram-positive and gram-negative bacteria directly at the site of infection without loss of dosage. The combination of Gelrite (gellan gum) and hydroxypropyl methylcellulose (HPMC) (Methocel F4M) was used to prepare the gelling system, which was used with and without sodium alginate to prepare Levofloxacin eye drops (0.5% w/v). These drops would undergo gelation when instilled into the cul-de-sac of the eye, and provide controlled release of the drug in treatment of ocular infections.

Materials and methods.

Materials. Levofloxacin was obtained from Zydus Healthcare, Gelrite from CP Kelco, and HPMC (Methocel F4M) was provided by Colorcon Asia Pvt. Ltd. All other reagents, chemicals, and solvents were of analytical grade.

Methods. *Method of preparation.* Gelrite-based *in-situ* gelling systems were prepared by dissolving gellan, alone and combined with sodium alginate and/or HPMC in hot phosphate buffer (pH 7.4, 70˚C), by continuous stirring at 40-45 ˚C for 24 h, as shown in **Table 1**. Then the weighed quantities of levofloxacin (0.5% w/v), mannitol, and preservatives, such as methyl paraben and propyl paraben, were added to the solution and stirred until dissolved. The solutions were then transferred into previously sterilized amber-colored glass vials, capped, and sealed with aluminum caps. The formulations were sterilized by terminal autoclaving at 121 ˚C, 15 PSI for 20 min. The sterilized formulations were stored in a refrigerator at 4–8 ˚C until use.

Experimental design

A 3^2 full factorial approach was taken to design the gelling system. Two factors were selected, and a total of nine experimental trials were performed using all possible combinations. The concentrations of Gelrite (cation-sensitive *in-situ* gelling polymer) as X_1 (0.3, 0.4, and 0.5%, m/V) and HPMC (viscosity imparting agent) as X_2 (0.3, 0.5, and 0.7%, m/V) were selected as independent variables.

Gel strength (GS in s), bioadhesion force (BF in N), viscosity (VI) in Pa.s, and cumulative percent drug release after 10 h (CR10) were selected as dependent variables. The design is shown in **Table II**. **Equation 1** summarizes the experimental design, using two independent variables and three levels (low, medium, and high) of each variable:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_{11} + b_{22}X_{22} + b_{12}X_1X_2 \quad \text{(Eq 1)}$$

where Y is the dependent variable, b_0 is the mean response of the nine runs, and b_i is the estimated coefficient for factor X_i.

The main effects (X_1 and X_2) represent the average result of changing a factor at a time. The interaction term (X_{12}) shows how the response changes when the factors are simultaneously changed. Polynomial terms (X_{11} and X_{22}) are included to investigate nonlinearity.

Statistical analysis and two-way analysis of variance (ANOVA) were used to evaluate the significance of each factor to the response at different levels. Three-dimensional response surface plots and two-dimensional contour plots of the data were generated using Design Expert software (Version 8).

Evaluation of formulation

The following were used to evaluate the formulation.

Gelation studies were carried out in a vial containing the gelation solution and simulated tear fluid (STF) solution, composed of 0.670 g of sodium chloride, 0.200 g of sodium bicarbonate, 0.008 g of calcium chloride dehydrate, and purified water, quantum satis to 100 g.

The preparation was carefully taken into the vial using a micropipette, and 2 mL of gelation solution (STF) was added slowly. Gelation was assessed by visual examination (26).

Rheological studies. Viscosities of sample solutions were measured in a Brookfield synchrolectric viscometer (LVDVI

Table II: Composition and results of 3^2 full factorial design batches.

Batch Code	Variable levels		Actual Units		GS (s)	BF x 10^5(N)	VI x 10 (Pa.s)	CP10 (%)
	Gelrite X_1	HPMC F4M X_2	X_1 (% m/V)	X_2 (% m/V)				
LF1	-1	-1	0.3	0.3	105 ±1.12	1955±26.09	1200	99.56
LF2	-1	0	0.3	0.5	108±2.02	1922±78.01	1556	96.45
LF3	-1	+1	0.3	0.7	117±2.68	2020±78.01	1867	90.15
LF4	0	-1	0.4	0.3	111±0.68	2740±78.01	1339	94.86
LF5	0	0	0.4	0.5	116±1.13	2969±26.09	1794	90.59
LF6	0	+1	0.4	0.7	125±2.02	3132±128.1	2121	87.66
LF7	+1	-1	0.5	0.3	118±2.68	4603±128.1	1534	88.43
LF8	+1	0	0.5	0.5	122±3.04	4701±26.09	1984	75.15
LF9	+1	+1	0.5	0.7	134±0.97	4832±26.09	2429	68.39
LF10*	-0.5	0.5	0.35	0.6	112±1.53	2800±78.01	1850	92.62
LF11*	0.5	-0.5	0.45	0.4	113±1.02	3400±128.1	1550	87.60

GS is gel strength; BF is bioadhesion force; VI is viscosity; CP10 is cumulative percentage drug release after 10 h.
* indicates check point batch

prime) at different angular velocities at a temperature of 37±1˚C. The angular velocity was increased from 0.5 to 100 rpm with 6 s between two speeds. The sequence of the angular velocity was reversed. The average of two readings was used to calculate viscosity. Evaluations were conducted in triplicate (26).

Drug content uniformity. Vials containing the formulation were shaken for 2–3 min, and the preparation was transferred aseptically to sterile volumetric flasks. The final volume was made up with phosphate buffer pH 7.4. The concentration of Levofloxacin present was determined at 287 nm using UV spectrophotometry (26).

***In-vitro* drug release studies.** The studies were carried out using a Franz diffusion cell, with STF (pH 7.4) as dissolution medium. The cell consists of glass donor and receptor compartments, separated by a dialysis membrane. The optimized formulation was placed in the donor compartment, and freshly prepared STF was placed in the receptor compartment. The whole assembly was placed in a temperature-controlled shaker water bath maintained at 37 ˚C ± 0.5 ˚C. A sample (1 mL) was withdrawn at predetermined time intervals up to 24 h and the same volume of fresh medium was replaced. The withdrawn samples were analyzed by UV spectrophotometer at 287 nm.

Bioadhesive strength measurement. Freshly excised goat conjuctival membrane was used to measure bioadhesive strength. The membrane was placed in an aerated saline solution at 4 ˚C until used. It was tied to the lower side of the hanging polytetrafluoroethylene (PTFE) cylinder using thread, and the cylinder was fixed beneath of left pan of a pan balance. The formulation was placed into a sterile petri plate that was kept on the platform beneath the left pan. The two sides of the pan balance were balanced by keeping a 2-g weight on the right pan.

The 2-g weight was then removed, lowering the left pan and allowing the membrane to come in contact with the formulation. The membrane was kept in contact with the formulation for 5 min. Weight was slowly added to the right pan slowly, in increments of 0.5 g, until the formulation detached from the membrane surface. The excess weight on the right pan was taken as the measure of the bioadhesive strength. The force of adhesion was then calculated using the following formula (13).

Force of adhesion = Bioadhesive strength x 9.81 / 1000.

Infrared spectroscopy and DSC studies. Infrared (IR) spectroscopy and differential scanning calorimetry (DSC) were then used to analyze the pure drug, gellan, HPMC, physical mixture of drug-gellan-HPMC, and optimized formulation. Resulting spectra were then compared with reference spectra.

Antimicrobial efficacy studies. The solution's antimicrobial efficacy was determined using agar diffusion and commercial Levofloxacin eyedrops as a control. The sterilized solutions were poured into cups bored into sterile agar nutrient seeded with test organisms (*Pseudomonas aeruginosa* and *Staphylococcus aureus)*. After allowing diffusion of the solutions for two hours, the plates were incubated at 37 ˚C for 24 h, and the zone of inhibition (ZOI) was measured around each cup and compared with control's ZOI. The entire process, except for the incubation, was carried out under laminar flow units in an aseptic area (Class 10,000). Each solution was tested three times. Both positive and negative controls were maintained throughout the study (26).

***In-vivo* ocular irritation and stability studies.** *In-vivo* ocular irritation studies were performed using the Draize

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

Presenters:

Steven DeBruyn
Medical Director Early Phase
SGS Life Science Services

Rabia Hidi
Director Biomarkers &
Biopharmaceutical Testing
SGS Life Science Services

Moderator:

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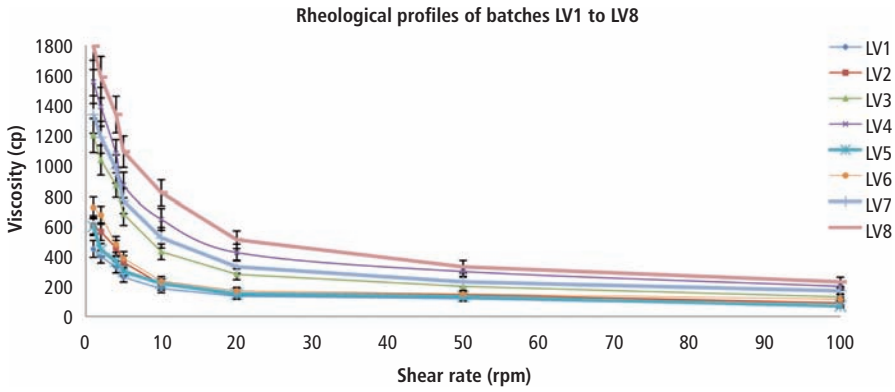
Figure 1: Rheological profiles of the formulations LV1-LV8.



technique (30) and guidelines set by the Organization for Economic Cooperation and Development (OECD) (31). Six albino rabbits, each weighing 2–3 kg, were used for this study. The sterile formulation was administered to the test rabbits twice a day for 21 days and the rabbits were observed periodically.

International Council for Harmonization (ICH) guidelines were used to determine the optimized formulation's stability. The gel was stored in a stability chamber at ambient humidity between 2 ˚C to 8 ˚C, ambient temperature at 40 ˚C ±0.5 ˚C for six months. The samples were withdrawn at regular intervals and analyzed. The logarithms of percent drug remaining were calculated and plotted against time in days. The degradation rate constant was calculated using the equation: slope = k/2.303, where k is a degradation rate constant. The shelf life of the developed formulation was calculated using the Arrhenius plot.

Results and discussion

Composition of various batches of the prepared *in-situ* gelling formulations are shown in **Table 1**. In the batch containing gellan alone, the concentration of gellan was kept at a maximum of 0.4% (w/v). Higher concentration beyond 0.4% caused gelation upon cooling to 40 ˚C.

In the combination batches, the concentration of gellan was varied and the concentration of sodium alginate was kept at approximately 0.25% (by compensating the concentration difference due to reduction in viscosity after autoclaving for sodium alginate) to give a maximum of 0.65% polymer concentration, because an increase beyond this concentration resulted in gelation during formulation.

To maintain the proper pseudoplastic behaviour of formulation, HPMC was used with gellan alone and with combination of gellan and sodium alginate. The drug content and gelling capacity of the formulations were found to be satisfactory as mentioned in **Table I**, and the formulations were liquid at both room temperature and when refrigerated. Viscosity and gelling capacity (speed and extent of gelation) are the most important criteria for any *in-situ* gelling system.

All batches exhibited pseudoplastic behaviour, as showed in **Figure 1**. All batches showed low viscosity at high shear rate and high viscosity at low shear rate. Autoclave process had not affected the viscosity of the formulations, except for those containing sodium alginate where viscosity was reduced around 8–15%. Therefore, the concentration of sodium alginate was adjusted to compensate (25). All measurements were taken three times and showed good reproducibility.

Figure 2 shows the cumulative percentage of Levofloxacin released versus time profiles for batches LV1 to LV8. These results suggested that Levofloxacin was sustainably released from formulation LV8, when the content of gellan gum was 0.4% and 0.5% of HPMC Methocel F4M (**Table I**). A similar release pattern is reported for pilocarpine (32) from alginate systems, wherein an inverse relationship between drug release and polymer concentration was observed.

Experimental design

Based on studies of response variables, the polynomial relationships are expressed in **Equations 2 to 5.**

GS (gel strength)	= 115.33 + 7.33*X1 + 7X2	(Eq. 2)
BF (bioadhesion force)	= 3069.44 + 989.83*X1 + 314.33*X2 + 116*X1^2	(Eq. 3)
VI (viscosity)	= 1771.11 + 220.66*X1 + 390.66*X2 + 57 X1*X2	(Eq. 4)
CR10 (cumulative percentage drug release after 10 hs)	= 90.51 – 9.03*X1 – 6.1*X2	(Eq. 5)

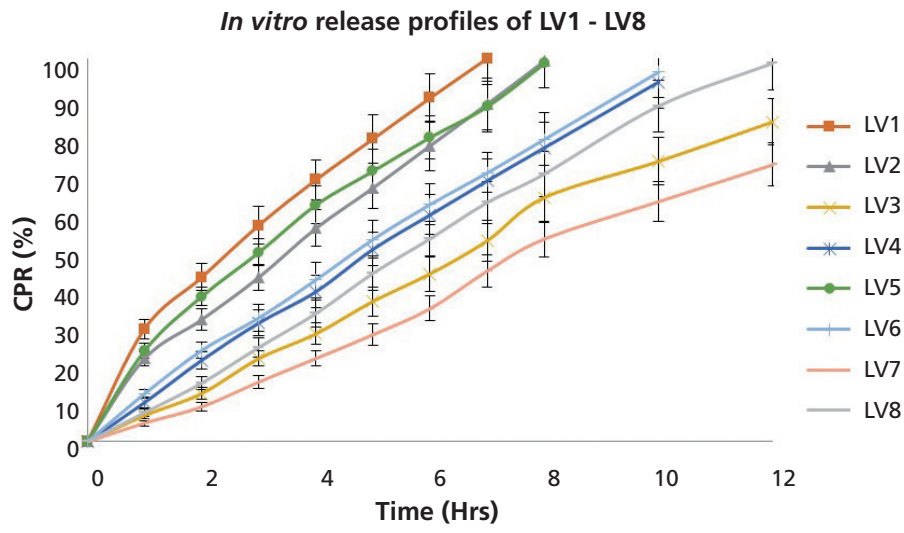
All the polynomial equations were found to be statistically significant ($P < 0.05$) and in good agreement with results. From **Equation 2**, it can be concluded that both gellan gum and HPMC significantly affect the gelling strength (25, 13). Formulation batches LF1 and LF2 showed poor gelation strength, which might be due to the minimum amount of gellan and/or HPMC.

The results are shown in **Table II**. The studies showed that, in the presence of HPMC, as the amount of gellan increased, gel strength increased as well; this effect must be due to the additional effect of concentration of polymer. **Figure 3(a)** shows the response surface plot illustrating the effect of gellan gum and HPMC on the gelling strength.

Studies confirmed that both polymers significantly affect the gelling strength.

From Equation 3, it can be concluded that both polymers have a predominant effect on bioadhesive force. The formulation contained gellan gum, which is a mucoadhesive agent. Studies show that polymers with charge can serve as good mucoadhesive agents. It has also been reported that polyanion polymers are more effective bioadhesives than polycations or nonionic polymers (33, 34). This polymer adheres to the mucin of the eye, which leads to prolonged retention of the formulation inside an eye (13). **Figure 3(b)** depicts the response surface plot, showing the influence of both polymers on bioadhesion force. The studies confirmed that, as the concentration of gellan gum or HPMC is increased, bioadhesion also increases.

Figure 2: *In-vitro* release profile of prepared gelling systems of Levofloxacin LV1 – LV8.



Equation 4 shows that HPMC has a predominant effect on viscosity compared to gellan gum. Normally, water-soluble polymers such as HPMC produce two effects:

- Lowering surface tension and improving mixing with the precorneal tear film
- Increasing viscosity and prolonging contact time, thereby resisting drainage of drug from eye (13).

Gellan gum can significantly increase viscosity of the formulation upon exposure to lachrymal fluid. So, by optimizing the concentration of HPMC viscosity-enhancing agent, one can decrease the amount of gellan gum in the preparation to improve patient compliance. **Figure 3(c)** shows the response-surface plot of effect of gellan gum and HPMC on viscosity. From **Equation 5**, gellan gum and HPMC are inversely related to the amount of drug released.

The results of *in-vitro* release studies show that the formulations retain drug for the duration of the study (12 h). The movement of the eyelid and eyeball provide shearing action for faster dissolution of gels in the cul-de-sac. **Figure 3(d)** depicts the response-surface plot, showing the influence of both polymers on drug release after 10 h respectively. Checkpoint batches LF10 and LF11 were prepared (**Table II**) to validate the evolved model. The actual values of GS, BF, VI, and CR10 of batches LF10 and LF11 are given in **Table III**. Checkpoint batches were found in good agreement with the actual values. Results of ANOVA are shown in **Table IV**.

Release of an optimized batch fitted to a Higuchian matrix equation showed a high R-squared value (0.99), least SSR value, and F value {21} as compared to other batches. Thus, it can be concluded that release of drug was based on a Higuchian-matrix, diffusion-controlled mechanism.

Bioadhesive strength and thermogram results

The bioadhesive strength measurement of designed batches is shown in **Table II**. Differential scanning calorimetry (DSC) thermograms showed characteristic peaks of Levofloxacin at 230.50˚C and 111.55˚C, gellan gum at 266.11˚C, and HPMC at 288.55˚C and 79.79 ˚C (**Figure 4**).

The peak of Levofloxacin was found to be reduced in intensity in physical mixture of drug, gelling agent, and polymer (**Figure 4e**) and could not be seen in optimized formulations of DSC thermogram (**Figure 4c**), indicating the entrapment of drug in the *in-situ* matrix gel system of gellan gum and HPMC.

The optimized formulation (LF5) showed antimicrobial activity when tested microbiologically by the cup-plate technique. Clear ZOIs were obtained in the case of the optimized formulation and marketed eye drops.

The diameters of the ZOIs produced by the optimized formulation against both test organisms were either on par or higher than those produced by marketed eye drops as shown in **Table V**. The antimicrobial effect of levofloxacin gel formulation is probably due to its rapid initial release into the viscous solution and followed by formation of a drug reservoir that attributed to the slow and prolonged diffusion from the polymeric solution due to its higher viscosity (26).

Ocular irritation studies (35) indicated that the formulation is well tolerated by rabbit eyes (36). No ocular damage or abnormal clinical signs were observed (37).

The optimized formulation of Levofloxacin was kept for stability studies at refrigeration temperature (4 ˚C), ambient temperature (25 ˚C), and elevated temperature (40 ˚C) for a

Figure 3. Response surface plot for effects of the amount of Gelrite and HPMC Methocel F4M on (a) gel strength; (b) bioadhesive force; (c) viscosity; (d) cumulative percentage drug release after 10 h.

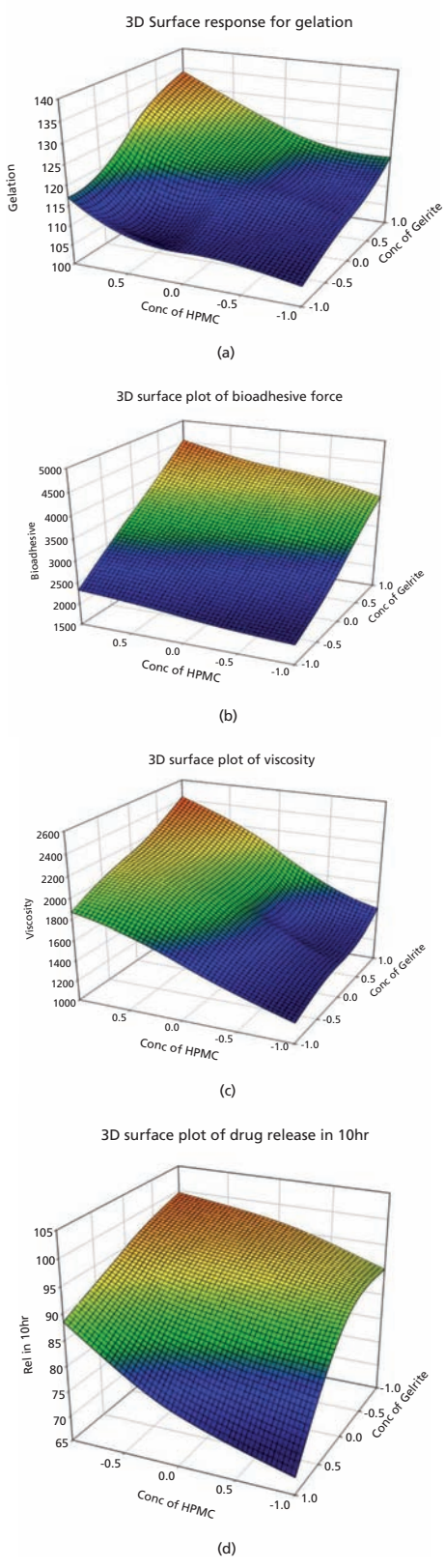


Table III: Comparison of the actual value with predicted values of checkpoint batches.

Batch code	GS (s)	BFx10^5 N	VI x 10 (Pa.s)	CP10 (%)
Actual values				
LF10	112	2800	1850	92.62
LF11	113	3400	1550	87.60
Predicted values				
LF10	115.66	2874.9	1815	91.67
LF11	116	3235.04	1645	88.74

GS is gel strength; BF is bioadhesion force; VI is viscosity; CP10 is cumulative percentage drug release after 10 h.

Table IV: Analysis of variance for dependent variables of the 3^2 full factorial design.

Source	F-value	R^2	P
Gel strength (GS)	287.4	0.998	0.00032
Bioadhesion Force (BF)	1301.908	0.999	0.000033
Viscosity (VI)	559.04	0.999	0.00012
CP10 (%)	17.65	0.970	0.0196

F is Fischer's ratio, p is significance level, CP10 is cumulative percentage drug release after 10h.

Table V: Antimicrobial efficacy of optimized formulation.

Concentration (µg/ml)	Zone of Inhibition (cm) (% efficiency)	
	STD	LF5
	S. aureus	
1	1.4	1.5 (107)
10	2.0	2.4 (120)
100	3.2	3.9 (121.88)
	P. aeruginosa	
1	1.4	1.6 (114.3)
10	2.2	2.5 (113.63)
100	3.8	4.4 (115.8)

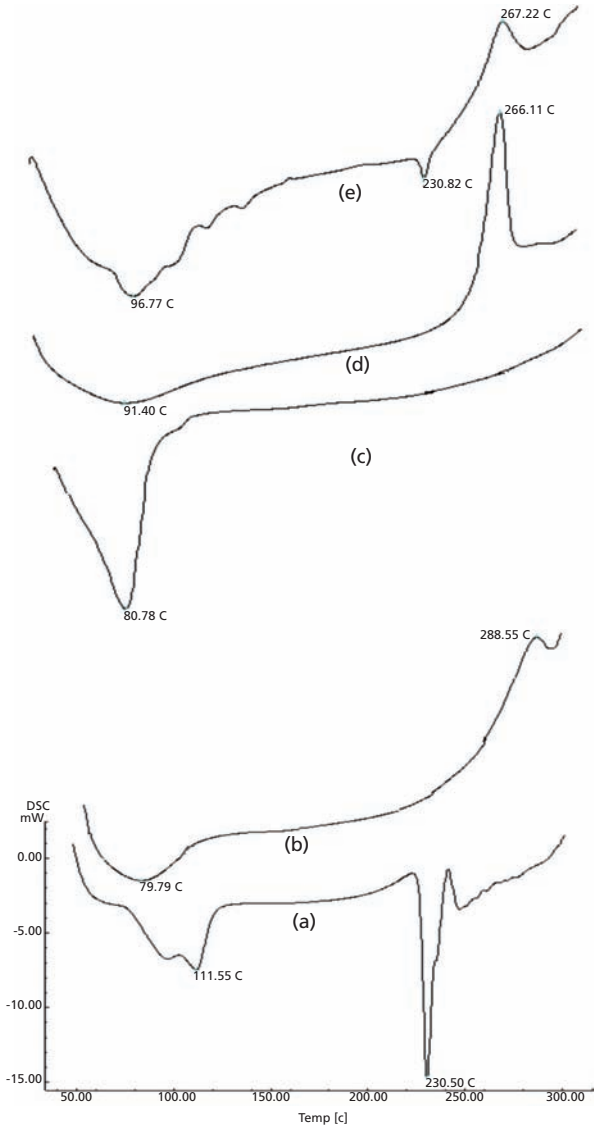
STD = standard (commercial eye drops of levofloxacin); LF5 = optimized formulation from design shown in Table II. Values in parenthesis indicate the percent efficiency; percent efficiency was calculated by (ZOI of test/ZOI of standard) x 100.

period of six months. Samples were withdrawn at regular time intervals and were evaluated for appearance, gelation studies, drug content, and *in-vitro* drug release.

Stability studies

The formulation was found to be sterile at the end of six months. The drug degraded to a negligible extent and the degradation rate constant for optimized formulation was very low (1.12 x 10^{-4}). Because the overall degradation is <5%, a tentative shelf life of two years may be estimated the formulation (13).

Figure 4: Differential Scanning Colorimetry thermogram of (a) Pure Levofloxacin; (b) HPMC Methocel F4M; (c) Optimized formulation LF5; (d) Gellan gum; (e) Physical mixture of Levofloxacin, gellan gum and HPMC Methocel F4M.



Conclusion

An ion-activated *in-situ* gel formulation of Levofloxacin was successfully formulated using gellan gum in combination with HPMC. The formulation underwent gelation in the conjunctival sac (cul-de-sac), allowing for sustained drug release over a 12-h period without any adverse effect to the ocular tissues.

Stability data confirmed that the formulation is stable for a six-month period in given storage conditions. This new formulation can enhance bioavailability through its sustained drug release, higher viscosity, longer pre-corneal residence time, and better miscibility with the lacrimal fluid. These benefits promise to improve patient acceptance and compliance.

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Testing the Stability of Biologics

Biologics exhibit greater variability in stability testing than do small-molecule drugs, and maintaining a stable test environment is crucial.

Ashley Roberts

A number of factors can influence drug stability, especially with highly-complex biomolecules. The increased risk of instability requires more stringent practices to maintain the stability of the drug product throughout its shelf life. In addition, measures need to be taken to minimize exposure to environmental factors that can affect the integrity and efficacy of a product.

Kerry Bradford, analytical projects manager, and Ashleigh Wake, biopharmaceutical services leader, both at Intertek; Kim Cheung, senior director of quality at Genzyme; and Niall Dinwoodie, global coordinator of analytical testing, biologics testing solutions at Charles River, spoke with *Pharmaceutical Technology Europe* about the challenges in maintaining a stable environment for biologics, how to determine shelf life, the effects of upstream processing techniques on the end product, and biologics versus small-molecule drugs and the importance of stability testing.

Securing cGMP requirements

PTE: What standard methods are used to ensure cGMP requirements during stability testing?

Dinwoodie (Charles River): The standard test methods for stability testing are, on the whole, traditional quality control techniques for biologics. They include size exclusion; ion exchange and reversed phase high-performace liquid chromatography; sodium dodecyl sulfate polyacrylamide gel electrophoresis or capillary electrophoresis; potency assays; and physicochemical measurements such as appearance, pH, and particle size. Of these, particle-size measurements are gaining increasing focus, but the first test to fail is still often appearance.

Maintaining a stable environment

PTE: What are some of the challenges of maintaining a stable environment throughout testing?

Bradford and Wake (Intertek): The main challenge here is the need for constant monitoring. Modern stability chambers are able to maintain conditions within the International Conference on Harmonization tolerances with little input, however, excursions caused by mechanical failure need to be quickly identified in order to prevent them from exceeding 24 hours. This requires a 24/7 alarm system to monitor all chambers and a dedicated team of staff to respond to emergencies and fix any breakdowns.

Cheung (Genzyme): The biggest challenge is controlling the condition of shipments, from stability chambers to testing locations and storage at these locations. Tracking chain of custody for stability samples, and maintaining sufficient back-up chambers and capacity ensures stability studies are not impacted by equipment malfunction or physical capacity constraints.

Dinwoodie (Charles River): Biologics present a number of challenges in ensuring a stable environment and comparability of results across time points. The glass transition point for highly concentrated protein products can occur within the normal operating range of some freezers. While this is relevant to real storage on the market, it can lead to a sudden change that has no reflection on the period of storage. Also, for frozen storage, consistency in thawing approaches are vital for data comparison between time points.

Accelerated vs. real-time

PTE: What are some of the advantages associated with accelerated stability tests vs. real-time stability tests?

Bradford and Wake (Intertek): According to the Arrhenius equation, samples undergo the same degradation after 32 days at 25 °C as after one year at 5 °C. There are obvious cost benefits to accelerated time periods, particularly to quickly eliminate poor candidates when at the early stages of development of either a new drug substance, drug product, or package. The accelerated tests can also be used to submit early data to regulatory authorities; however, accelerated storage data must always be backed up with real-time data in the long term.

Cheung (Genzyme): Accelerated tests can demonstrate comparability for material associated with process changes in a shorter period of time (e.g., six months) than long-term real-time studies. The tests can assess whether a degradation profile for an attribute is expected to be linear or non-

Trends in Quality Agreements & Communications: A CMO Perspective

On-Demand Webcast Originally aired June 23, 2015

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EVENT OVERVIEW:

Outsourcing of all phases of pharmaceutical/biological development and manufacturing continues to rise. As drug development pipelines shift toward those requiring more complex and specialized capabilities, quality agreements and communication planning to avoid non-compliance and the costly ramifications are becoming more important. This webcast will review the FDA draft guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements and provide insights from the contract manufacturing organization (CMO) perspective into the integrated responsibilities and relationship of the contract provider and the drug sponsor.

Key Learning Objectives

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- Understand how heightened enforcement actions changing the traditional relationship between the CMO and drug sponsor.
- Learn how strong CMO partners can help their pharmaceutical/biotechnology partners avoid delays to market, specifically for drug development pipelines requiring more complex and specialized CMO capabilities (e.g., biologics, biosimilars, cytotoxics).

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linear. When temperature excursions happen during transport, there is a specific procedure that is followed to determine whether the product can be used or whether it must be discarded. The accelerated data are leveraged within that procedure in which we've documented the allowable excursion temperatures and times during processing, shipping, and handling, and the data are used to respond to physicians'/patients' questions about mishandling.

Dinwoodie (Charles River): Accelerated tests are commonly used to confirm that the test methods being applied to the product indicate stability. The methods are qualified early on in a stability programme to ensure that the real-time data reflect the true stability of the product.

PTE: What are some of the challenges or disadvantages associated with using accelerated stability tests for the determination of kinetic degradation?

Bradford and Wake (Intertek): While use of accelerated stability tests in conjunction with Arrhenius calculations is a good predictor of degradation rates for straightforward reaction kinetics, it does not account for physical changes in the sample, or more complex systems such as emulsions and suspensions. For example, elevated temperatures may promote slight solubility of a suspended drug particle, leading to significant degradation that would not occur in the equivalent room-temperature sample.

Dinwoodie (Charles River): Complex molecules such as biologics rarely, if ever, obey the Arrhenius equation. There are different pathways for degradation to occur, both chemically and structurally, so no single degradation rate can be determined. The accelerated conditions will also influence the degradation observed and may lead to steps being missed or inappropriate molecules being targeted as the indication of degradation.

Stability testing and biologics

PTE: What factors are involved in determining shelf life?

Bradford and Wake (Intertek): Understanding the potential degradation pathways of any biologic is key to gaining a true shelf life. Achieving this understanding is definitely complicated by the structural diversity of biologics. Regardless, if we are working on an antibody, peptide, or oligonucleotide, our general approach is the same, and in many ways, weighted before any sample is placed on stability. During early stage development, the material will be stressed under extreme conditions of pH, temperature (60 °C is high), light, and oxidative conditions, as well as physical forces such as prolonged agitation, orientation of storage, and freeze-thaw. The potential pathways of degradation are then evaluated using various analytical techniques such as circular dichroism (for higher order), Fourier-transform infrared, nuclear magnetic resonance, mass spectrometry, chromatography, and electrophoresis.

The use of orthogonal approaches is, where possible, always applied in response to the complexity of analytics. The final stability programme is then designed based on the results observed and the potential degradation pathways elucidated. Stability storage is then initiated accordingly, remembering that chemical/structural integrity is not enough. All biologic evaluations of potency upon storage should also be documented. A simple box-ticking/checklist approach does not work for biologics, as what works for one will not necessarily work for another.

PTE: Do upstream processing techniques have an effect on the stability of end products?

Bradford and Wake (Intertek): The short answer is yes. However, this is dependent on the drug and the downstream process. A lot of this is covered with assessment of the drug product as well as substance.

Cheung (Genzyme): For biologics, yes. For example, hold times of upstream materials can impact critical quality attributes and ultimately affect the stability of drug substances and drug products. Therefore, stability studies are executed on all intermediate production materials held longer than 24 hours.

PTE: How does stability testing of biologics and small-molecule drugs compare?

Bradford and Wake (Intertek): Issues associated with instability are potentially more significant and perhaps more likely to be observed with biologics than their small-molecule counterparts. Biologics are inherently unstable, and this can manifest in many ways, but what differentiates them the most is their tendency toward aggregation, a phenomenon that is both frequently observed and yet difficult to control. Aggregation can present considerable detrimental effects to the safety as well as efficacy of a molecule. Formulations are optimized to reduce or at least slow down the process of aggregation, but often, aggregation is the predominant change to the molecule observed on storage.

Cheung (Genzyme): Both stability testing for large-molecule and small-molecule drugs are important to ensure that a product maintains specifications throughout its shelf-life. For small-molecules, critical quality attributes and degradation products may be better understood for each product and shelf-life specifications for the degradation products can be set based on toxicology studies. In my experience, there is more lot-to-lot consistency for stability testing of small-molecules, so interpretation of results is straight forward. Also, in my experience with biologics, stability testing encompasses many more product attributes and the degradation profiles may be inconsistent from product-to-product and/or lot-to-lot, making understanding identified trends and interpreting results more difficult. Test methods may be more variable, again making it difficult to interpret results.

Dinwoodie (Charles River): There is less predictability for biologics. Similar formulations of different proteins can behave in a different manner and have quite different shelf-lives, and the concentration often has a greater effect than it does for small-molecule drugs. The industry has seen many examples where process changes have led to changes in the stability of products that could not have been predicted. The use of committed stability tests for biologics is vital. PTE

Ensuring Correct Tablet Count

Electronic counters are flexible and allow quick changeover between products.

Packaging of solid-dosage drugs generally occurs by counting rather than by weight or volume. Slat fillers remain commonplace, especially for large batches. Demand is continuing to grow, however, for electronic counters, which are now approaching slat-filler speeds and tend to be more flexible.

"Flexibility to handle a wide range of products is critical now," reports Darren Meister, vice-president of sales at IMA North America (Safe Division). This need for flexibility also generates demand for counters that are easier to clean and faster to change over. "Cleaning and changeover are responsible for a lot of downtime right now," explains Meister.

Consistency is needed too. Programmed settings ensure a product/count runs the same way each time. Integrated quality control is another wish-list entry. There is a focus on quality assurance to ensure correct count and eliminate any broken or rogue doses.

Today's counters

Today's electronic counters share several attributes: flexibility, tool-less changeover, easy cleanability, and faster speeds. The RX-12 Enhanced solid-dose counter from BellatRx can be specified in single, twin, or quad configurations to achieve speeds up to 240 bottles/min (bpm). The flexible system handles solid doses from 2–40 mm and containers from 1–4 in. Other features include simplified product flow and tool-less changeover (1).

The Countec DMC-60T Multi-channel electronic counter, equipped with a 12-track counting tray and twin filling nozzles, is handled in the United States by Key International and counts up to 6000 tablets per minute. The DMC series of counters have programmable logic controllers, touch-screen operator interfaces, and infrared and LED optical sensors with dust-sensing windows. The sensors detect each dose on multiple planes so data can be analyzed from each object that passes. "The machine collects data about the wholeness of the tablet or capsule and checks if multiple doses are falling past at the same time," explains Jonathan Braido, marketing manager at Key International. Dark-time adjustability helps detect broken or double tablets. "If the Countec machine identifies a broken tablet, it will trace the dose to a bottle, then reject the bottle," reports Braido. The flexible Countec unit handles metal, glass, or plastic containers up to 120 mm in diameter. Large access areas, tool-less disassembly, quick-release connectors for product-contact parts, perforated stainless-steel product feeding trays for dust and chip collection, and dust-collection ports expedite cleaning and changeover. "It will usually take about an hour to fully clean the machine," says Braido. Changeover to a different container (same product) involves a few minutes to change container funnels and make a few tool-less adjustments.

IMA's SwiftPharm 2 (SP 2) counter is a second-generation, high-speed machine. Dust-immune electrostatic field sensors replace the photoeyes or optics used by competing systems. The electrostatic field sensors not only ensure accurate counting, but also increase uptime because there's no need to stop the line mid-run to clean the sensor when handling extremely dusty products. In operation, the falling product disturbs the field. Measuring this disturbance allows the detection of overlapping product as well as the differing mass of broken pieces so bottles containing fragments can be rejected. In addition, an optional dual-sensor configuration provides a redundant count. Both sensors must agree each dose is correct and properly counted. IMA also equips its counters with machine-vision systems built by Antares Vision. Cameras mounted over the trays detect broken and chipped doses as well as rogue product. Tool-less disassembly means one operator can remove all product-contact parts, clean the machine, and install another set of product-contact parts so the counter can run while the first set of product-contact parts is being cleaned. This changeover requires as little as 30 minutes. When changeover only involves a different container size (product remains the same), changeover time can drop to less than five minutes.

The next generation CFS-622*4 tablet counter from NJM Packaging offers cleanability, quality control, and onboard inspection. The CFS-622*4 tablet counter can be equipped with a CountSafe inspection system from Optel Vision plus an automated rejection system. The system features a two-axis linear robot that can be adapted and integrated to Cremer electronic counters. The tool-less ejector rejects defects: wrong shape, wrong colour, wrong size, broken product, or rogue. Different alarm levels make it possible to stop the line if a rogue product is detected, but simply reject the fragment, if a broken solid dose is located. The vacuum-reject arm captures any flawed solid-dose product before it falls into a container and deposits it into a closed bin. Virtually all other inspection systems reject filled containers with a flawed solid dose, resulting in considerable rework or waste. A preseparator collector and HEPA filter prevent the escape of any substance or dust.

The intermittent-motion Cremer CFS-622*4 tablet counter consists of four modules. It relies on a feedscrew for container transport and reaches speeds up to 200 bpm. A continuous-motion model, the Cremer CFI-622 tablet counter, can be configured with up to 10 modules, handles containers with starwheels, and reaches speeds up to 400 bpm.

Hallie Forcinio is *Pharmaceutical Technology Europe*'s Packaging Forum editor, editorhal@cs.com.

Figure 1: NJM Packaging's TFE (tablet-free entrapment) conveyor design minimizes line clearance time. Photo is courtesy of NJM Packaging.

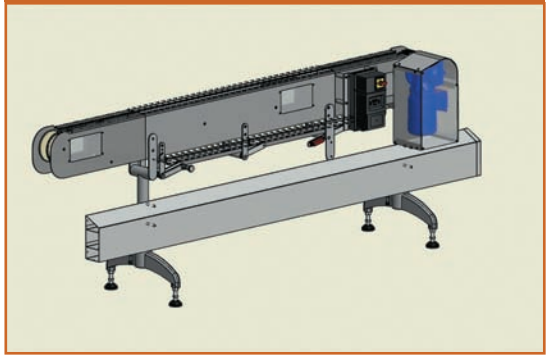

Figure 2: Monoblock machines, such as IMA's Uniline system, combine multiple functions on one base to enhance flexibility and reduce floor space requirements. Photo is courtesy of IMA.

A servo-motor-driven mechanical vibration system eliminates the mechanical springs used in other vibratory systems. The result is a stable and controlled movement of the solid dose, which provides the consistent action needed for a camera inspection and efficient counting accuracy. "Proper separation and delivery of the product into the container are key to having an accurate count," explains Mark Laroche, vice-president of sales at NJM Packaging.

In addition, a patented system, which relies on linear servo technology, feeds tablets out of the hopper. Changeover to a new bottle (same product) takes 10–15 min. Cleaning in preparation for filling another product can be accomplished in as little as 20–25 min, depending on standard operating procedures. Product-contact parts can be removed without tools, leaving a simple-to-clean frame.

To further reduce line clearance time, NJM Packaging offers the TFE (tablet-free entrapment) conveyor (see **Figure 1**). Generally installed after the counter, it eliminates the time-consuming task of disassembling or removing the conveyor chain between runs to check for trapped products. The TFE conveyor chain drops down for tablet recovery, and integral windows and lights help operators see any trapped tablets inside the conveyor.

Monoblock systems also are available and offer a high level of flexibility. IMA's four-in-one Uniline machine integrates desiccant dispensing, solid-dose counting, cottoning, and capping on a single base (see **Figure 2**). Changeover occurs with the push of a button.

Uhlmann's Integrated Bottle Center can integrate counting and capping with desiccant feeding, cottoning, and induction sealing, plus inspection systems such as cameras and metal detectors. Options include the IBC 120 model (capable of speeds of 150 bpm) and the faster IBC 240 machine (240 bpm). The IBC 120 model handles a slightly broader container range with volumes from 30–1500 cc, diameters from 25–125 mm, and heights from 45–200 mm (2).

Romaco also supplies integrated systems with Romaco Bosspak RTC Series or VTC Series counters as the centerpiece (3). The RTC counters feature rotary continuous-motion container filling and tool-less changeover. Positive tablet/capsule separation and vibration-free stream filling help ensure products enter the container singly and maximize count accuracy. A range of models offer one, two, four, or 12 counting stations and speeds from 15–200 bpm (4).

At the opposite end of the solid-dose counting spectrum, there are smaller units for quality control (QC) counts, stock checks, and short runs. Kirby Lester's latest standalone tablet counter, the KL1 model, features a reduced footprint, fast counting speed, and interchangeable product-contact parts. Sharp Packaging Solutions purchased seven units plus product-contact parts for each product it runs to perform hourly QC checks on all bottling lines and small quantity bottle filling. Return on investment is expected within 10 months (5). Patented optic sensing technology "sees" doses falling past the batch sensors to count up to 15 doses/sec. After completing the count, the tablets/capsules are emptied from the KL1's clear tray into a waiting bottle or vial. Cleaning takes approximately 60 seconds. The entire pill path is removable for cleaning with soap and water or alcohol and a lint-free cloth.

Another small unit designed to confirm counts, the Countec DMC-CQ2 tablet verification counting machine from Key International, "can replace a visual count inspection and ensure quality of the tablets or capsules," reports Braido. Suitable for quality checks on the packing line or in the lab, the counter handles tablets or capsules of any shape or size and counts up to 9999. An easy-to-use touchscreen with a built-in printer supports QC and data management. An adjustable container platform accommodates different bottle heights and diameters.

Selecting a counter

Selecting the best counter for an application involves many considerations. First and foremost, "Understand what you want to accomplish," advises Laroche of NJM Packaging.

Braido notes that other questions to be asked include: What products are to be handled (e.g., tablets or capsules)? Is the product coated or uncoated? Dusty or not dusty? How big are the batches to be handled? How many counted tablets and/or bottles/minute are needed for your production line?

"If the machine is changing over three times a day, an electronic counter is better suited," says Meister of IMA Pharma. "If one product runs all day, a slat counter might make the most sense."

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105 ◯ Engineering/Facilities/Construction
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"Machines also should be user-friendly for operating, cleaning, and changeover," says Braido. Other considerations include bottle sizes, cost and labour requirements, room size, and changeover complexity and related downtime. Many pharmaceutical manufacturers and contract packagers specify a counter with dedicated product-contact parts. "They need a solution where they can swap out the entire 'pill path' to eliminate any chance of cross-contamination between counting runs of different medications," explains Mike Stotz, senior marketing manager at Kirby Lester. "They want to change these parts out quickly, clean them easily, and store them for specific NDC [National Drug Code] batches."

Specifications also must consider integration with upstream and downstream equipment and communication between machines so stop and restart signals can be sent when problems arise and are cleared. It's also important to plan sufficient accumulation between machines to prevent downtime for minor faults. "You don't want the counter to stop because it's waiting for bottles, nor do you want containers backing up into the filler due to a downstream slowdown or stoppage," says Meister.

Finally, is onboard inspection needed? "Inspection of tablets has been a number one wish-list item for a long time," reports Laroche. However, onboard inspection can slow production speeds, and small, acceptable variations have been known to cause false rejects.

What's next?

New technologies will be able to count and fill even faster and more efficiently. "Future counting machines will be easier to operate, which leads to less user error and will provide better data management capabilities," says Braido.

Meister predicts we'll see more counters equipped with inspection systems. "There's always the push for more quality," he explains.

Laroche agrees. "Inspection is what customers are requesting. It will take a while, but once we start seeing integrated inspection systems, it will become a requirement."

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