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Pharmaceutical Technology Europe
This year marks the 40th anniversary of our sister publication Pharmaceutical Technology, and it is our tradition to reflect on how far the industry has come over the past four decades. The global pharmaceutical market continues to grow, but one thing that stands out is the increasing need to balance cost and value. Despite criticisms on Pharma’s ability and willingness to adapt to change, the industry has made manufacturing improvements to meet market demands for cost efficiency while ensuring that product quality is not compromised.

Anil Kane, executive director, Global Head of Technical & Scientific Affairs at Patheon, notes that the shrinking drug discovery pipeline has led to significant changes in dosage form development and manufacturing strategies. Existing molecules are being evaluated for newer indications in the same or different therapeutic categories, he says. Drug developers are exploring the possibility of combining new drug entities with off-patent drug candidates to produce synergistic effects or other clinical benefits.

Biotech has contributed to the discovery and manufacture of large-molecule drugs and the development of biosimilars, observes Mike Arnold, board chair of the International Society for Pharmaceutical Engineering (ISPE). He adds that medicines are becoming more personalized to the benefit of the patient.

Technology has made a significant impact on the pharmaceutical industry, Jim Agalloco, president of Agalloco & Associates, says. Automation and computerization of systems have reduced manual labour requirements and the potential for mistakes, he says, and data can now be assembled, analyzed, and used in ways not previously possible.

In reviewing the history of contract manufacturing and outsourcing trends, Matthew Moorcroft, vice-president, global marketing for Cambrex, reflects how services and capacities have evolved in response to changing pharma models—from small-scale boutique operations specializing in individual technologies or chemical processes, to the rise of one-stop shops and low-cost providers in India and China.

These are just some of the trends shaping the industry. You can access the complete content of Pharmaceutical Technology’s special anniversary issue at www.PharmTech.com/PT/PharmTech40.
Data Integrity Expectations of EU GMP Inspectors

The author reviews key technological expectations of EU GMP inspectors on the integrity of e-records.

An expectation pertinent to the computer systems performing good manufacturing practices (GMP) regulated-related functions is the integrity of electronic records (e-records). This expectation takes the highest priority in any worldwide health agency GMPs, including the European Medicines Agency (EMA) and its European Union (EU) member states.

E-records comprise raw e-records, derived e-records, and associated metadata. E-records integrity is the foundation of GMPs. The electronic information, properly recorded and managed, is the basis for manufacturers assuring the competent authority of their products' identity, strengths, purity, and safety. Reliable e-records also demonstrate that the production process of the regulated entity and the computer systems adhere to the GMPs, including manufacturing instructions.

Any unintended changes to e-records as the result of a storage, inputs and outputs (I/Os), or processing operation, including malicious intent, unexpected hardware failure, and human error, will compromise the integrity of e-records.

This article provides the key expectations of EU GMP inspectors in the area of data integrity of e-records. These expectations are based on the following EMA sources:

- European Community (EC) Commission Directives 2003/94/EC (1) and 91/412/EEC (2)
- EC GMP Annex 11 Computerized Systems (3)
- Chapter 4 of the EC GMP guide concerning documentation (4)
- EMA Questions and Answers: Good Manufacturing Practices—Data Integrity (5)
- EudraGMDP Database (6)
- Medicines & Healthcare Products Regulatory Agency (MHRA) GxP Data Integrity Definitions and Guidance for Industry (7)
- MHRA GMP Inspection Deficiency Data Trend 2016 (8).

EMA e-records integrity technical requirements

EMA has overall responsibility for regulating human and veterinary medicinal products within the European Commission. In terms of what all EU countries must achieve related with the manufacturing of medicinal products, all EC member states are bound by a single set of directives. Computer systems and e-records associated with GMP-related activities are delineated in the Commission Directive 2003/94/EC.

"When electronic, photographic, or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained." (1)

The veterinary medicinal products GMP requirements can be found in 91/412/EEC (2).

As noted, EMA’s e-records integrity objectives are:

- E-records will be appropriately stored during the anticipated period of storage.
- E-records stored by computer systems shall be made readily available in legible form.
- E-records shall be provided to the competent authorities at their request.
- E-records shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data.
- There must be a record of any e-records change made, the previous entry, who made the change, and when the change was made. These audit trails shall be maintained.

It is up to the individual countries to decide how the applicable directive is implemented into national law.

EMA GMP inspections comprise an on-site compliance assessment. These EMA GMP assessments are performed by official(s) of the EU competent authorities, or authorities found an equivalent under a mutual recognition agreement.
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Data Integrity

<table>
<thead>
<tr>
<th>Table I: Key definitions of records based on EudraLex (4).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td><strong>Certificates of analysis</strong></td>
</tr>
<tr>
<td>Records that provide a summary of testing results on samples of products or materials together with the evaluation of compliance with a stated specification.</td>
</tr>
<tr>
<td><strong>Records</strong></td>
</tr>
<tr>
<td>Provide evidence of various actions taken to demonstrate compliance with instructions (e.g., activities, events, investigations, and in the case of manufactured batches, a history of each batch of product, including its distribution).</td>
</tr>
<tr>
<td><strong>Raw data</strong></td>
</tr>
<tr>
<td>Records that are used to generate other records. For e-records, regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.</td>
</tr>
<tr>
<td><strong>Reports</strong></td>
</tr>
<tr>
<td>Records that document the conduct of particular exercises, projects, or investigations, together with results, conclusions, and recommendations.</td>
</tr>
</tbody>
</table>

The method used to verify e-records integrity may vary contingent on the technology used by the regulated facility.

**EU e-records integrity guidelines**

There are two key guidelines associated with e-records integrity resulting from Commission Directive 2003/94/EC and 91/412/EEC; one being EMA GMP Annex 11 Computerized Systems and the other, EMA GMP Chapter 4: Documentation (1–4).

EMA GMP Chapter 4 relates to good documentation practices. It provides key definitions of records (see Table I).

Complementing the definitions in Table I, the author recommends the following:

- Records must be written evidence of what has happened and are recorded contemporaneous either by personnel or automated equipment. As an example, automated equipment may measure process parameters.
- In automated environments, the events recorded are contemporaneous and retained in the format in which they were originally generated and considered raw data.

Explicitly, the EMA GMP Chapter 4 establishes that suitable controls to ensure integrity of documents must be established (4).

The key EMA GMP Annex 11 e-records integrity-related clauses are depicted in Table II. The e-records integrity controls listed are the most observed as part of the associated non-compliance report located at the EudraGMDP database (6).

There are many other e-records integrity-related clauses in Annex 11 (9, 10). These clauses are also implemented during the design phase or during the operational and retirement phases as part of procedural controls.

**Expectations of EU GMP inspectors**

Based on a collection of non-compliance reports by EU inspectors (July 2013–February 2017), located at file://OLOPEZ6102/Google%20Drive/Erecs, the following tabulations about e-records integrity-related issues were obtained (Table III).

- Comments such as “integrity and security of analytical data,” as part of the non-compliance reports, do not provide relevant information to assign the deviation to a particular cause. The tabulation of these comments is not part of Table III.
- Deleted, manipulated, or falsified data. Records retained in computer storage must be secured by both physical and logical means against loss, damage, and/or alteration. The main clauses applicable to these e-records actions are Clauses 7.1 and 12.4 of Annex 11 (3). It excludes the issue related to the unauthorized entry to the storage area in Clause 12 of Annex 11.

E-records warehouses security design must make provisions to protect original or true copy e-records and the associated metadata. These e-records cannot be deleted or changed without recording the modification. As an element of the e-records integrity in storage, there must be a record of any modification made that includes the previous entry, who made the change, and when the change was made (5, 11).

The modification of an e-record can be documented by an electronic- or paper-generated audit trail. The paper-based audit trail may be acceptable until an electronic audit trail functionality becomes available. To reduce the risk of losing e-records in the storage and guarantee e-records readiness to the users, periodic back-ups must be performed. The back-up must be stored separate from the primary storage location, and at a frequency based on an analysis of risk to GMP e-records and the capacity of the storage device.

Any rights to alter files must be assigned to personnel independent from those responsible for the record content. Segregation of duties between data lifecycle stages provides safeguards against data integrity failure by reducing the opportunity for an individual to alter, misrepresent, or falsify data without detection (5).

**No logical access controlled to computer systems.** The main Annex 11 clause applicable to this item is 11-12.1 (3). All personnel must be provided with appropriate levels of access and defined responsibilities to carry out their assigned duties. This requirement must be backed up by an authorization policy specifying logical access rights to domains, computers, applications, and e-records. As a function related to security, e-records integrity service maintains information exactly as it was recorded, and is auditable to affirm its reliability. For this reason, controlled access to the short-
Data Integrity

and long-term storage must be implemented.

Security must be instituted at several levels. Procedural controls must govern the physical access to computer systems (physical security). As part of the physical security, it must be considered putting security to devices used to store programmes, such as disks.

The access to individual computer system platforms is controlled by network specific security procedures (network security and database server). Access to these devices should be controlled (logical security). User access controls should be configured and enforced to prohibit unauthorized access and the attributes of the e-records.

Computer systems not properly validated. The main clause applicable to this deviation is 4. As part of the inspection, the validation of the computer system is evaluated. The validation process must take into account the interface between the data acquisition function and the data recording function. These functions must be verified, tested, and periodically verified to check the accuracy of the data. I/Os errors can result in severe production errors and distribution of adulterated or misbranded products. The extent and frequency of I/Os checking will be assessed on an individual basis and should be determined based upon the risk and built in controls. These built-in checks provide the accurate exchange of electronic data to decrease the issues of data integrity while the electronic data are in transit.

The computer system must incorporate validated checks to ensure the completeness of data acquired (4). For systems using automated data capture, the EU inspector should review validation records to ensure correct I/Os and processing of data are implemented and are effective.

Audit trails and the validation records of the associated functionality for computer systems should be verified as well.

Entries not contemporaneous. Contemporaneous e-records should be recorded at the time they were generated. The main clause applicable to this item is 12.4 of Annex 11 (4).

The following observation relates to a contemporaneous type of deviation: “Analysts routinely use the PC administrator privileges to set the controlling time and date settings back to over-write previously collected failing and/or undesirable sample results.”

Conclusion

Manufacturers of human and veterinary medicinal products are required to meet EMA’s expectations.

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on the integrity of the e-records for those computer systems performing GMP-related regulated functions. The occurrences of the non-compliance cause on recent reports have driven EU inspectors to conduct a comprehensive initial evaluation on the integrity of the e-records, including computer systems validation, accuracy of the e-records, physical and logical security, and the traceability of the modification to e-records. Ensuring integrity of e-records as part of a system implementation will ensure a positive inspection outcome.

References
A Question of Quality

Greater transparency and reliability of information are needed in the quality assessments of biosimilars.

The size of the European biosimilars market is accelerating rapidly as government-funded healthcare services increase their support for these medicines in an effort to reduce costs. Sales of biosimilars in Europe has tripled in the past five years (1). In 2015–2016, they soared by approximately 50%, according to figures from QuintilesIMS, the US-based international healthcare services company that has been carrying out studies on the European biosimilars market for the European Commission, the European Union executive (1).

By March 2017, 26 EU-approved biosimilars were available in the European market, 10 years after the European Medicines Agency (EMA), the EU’s centralized licensing body, authorized its first biosimilar. In 2016, Europe accounted for 87% of global sales of biosimilars, underlying its world leadership in the development of the medicines, particularly in the regulatory procedures for establishing comparability between biosimilars and the original products. The biosimilars sector in Europe, which is still in its infancy, has now reached a stage where more information about these regulatory procedures needs to be provided to stakeholders, particularly healthcare professionals, if the strong momentum behind biosimilar sales is to be maintained.

Physicians are not greatly concerned anymore about the safety of biosimilars. In the 10 years since they have been on the European market, the EU’s pharmacovigilance monitoring system has not identified any marked differences in the types of adverse effects between biosimilars and their originals. But prescribers are concerned about the challenges of convincing patients about security of treatments by biosimilars for new therapeutic areas such as autoimmune diseases, oncology, and especially chronic conditions.

Quality attributes

This necessity for greater transparency is being centred on the way the quality attributes of the manufactured biosimilars are compared with those of the original or reference product. Manufacturers are required to establish that their biosimilars have sufficient levels of similarity in order to be authorized. These attributes mainly comprise physicochemical and functional properties such as molecular structure, protein modifications, and biological activity. Because the drugs are biological, there are inevitable differences. But for a drug to be “highly” similar so that it can be licensed as a biosimilar, these differences must not result in inferior levels of safety and efficacy to the reference product.

With biologicals in which the active substance is a protein, the biosimilar and reference product must contain the same protein (i.e., amino acid sequence) and the same three-dimensional structure or folding of the protein. In the finished medicine, certain differences, such as excipients used in formulations and in the administration device, are allowed because they have no effect on safety and efficacy.

Quality assessments

Quality assessments have become such an essential part of the process for approving biosimilars that in most cases once a biosimilar has proved itself to be highly similar on a quality basis to regulators, investigation of clinical studies to establish safety and efficacy has not been required. “By demonstrating biosimilarity [at the quality level], a biosimilar can rely on the safety and efficacy experience gained with the reference medicine,” says an EU guide to biosimilars for healthcare professionals published jointly in May 2017 by EMA and the European Commission (2). “This avoids unnecessary repetition of clinical trials already carried out with the reference medicine,” it adds.

With quality having such a key position in biosimilars’ authorization, healthcare professional organizations have been urging EMA to increase the transparency of the comparability exercise applied to quality data to show high similarity between biosimilars and their reference products. “Given the role of healthcare professionals on the front line of patient care, it is vital that they have access to reliable information on these medicines: what they are and how they are developed, approved, and monitored,” says Professor Guido Rasi, EMA’s executive director.

Biosimilars switching

When selecting biosimilars for patients, prescribers have tended to rely on the basic details in its summary of product characteristics (SmPC), which focuses on safety and efficacy information. A much more suitable communications vehicle on the quality aspects of biosimilars would be a group of documents known as the European Public Assessment Report (EPAR). In addition to the SmPC information, EPAR documents contain assessment reports on the scientific evaluation of the medicine at the time of approval and on major changes, such as the addition of new indications. Crucially, it integrates the whole comparability exercise covering the quality, safety, and efficacy of the biosimilars. By extending EPAR to give more information on quality aspects, EMA could deal, for example, with concerns about lack of appropriate data when prescribers switch patients from one biosimilar to another.

In a joint position paper (3) on biosimilars switching issued in March 2017, the European Federation of Pharmaceutical Industries & Associations (EFPIA), European Biopharmaceutical Enterprises (EBE), and International Federation of Pharmaceutical Manufacturers & Associations...
The agency plans to run the pilot until it has undertaken six studies they should conduct on the quality, analytical, and functional data that they already have available. EMA’s scientific advisors usually do not make suggestions on the assessment of existing data. The agency plans to run the pilot until it has undertaken six scientific advice requests, with a maximum of one scientific advice request being accepted per month.

EMA is also considering ways of gaining greater value from the statistics generated by quality assessments in the development of drugs, particularly biosimilars. Conclusions or inferences could be reached from data rather than using the statistics merely in a descriptive manner to make measurements or to detect patterns. The agency issued in March 2017 a reflection paper (4) on statistical methodology in comparative quality assessment to investigate to what extent the implementation of inferential statistical methods can facilitate comparative evaluations of quality data. The paper highlighted some current difficulties with quality assessments in biosimilars development with some experts being sceptical about what could be achieved with the help of statistics.

“There is no common understanding what kind of statistical data analyses approaches would be considered suitable, if any, for comparison tasks involving quality attributes data,” EMA said in the paper. Furthermore, the effects of quality differences on safety and efficacy can be difficult to measure. “The impact of differences at the quality level on clinical outcome—efficacy/safety/immunogenicity—is often hard to predict or quantify,” the paper said.

Some of the concerns about quality data stem from the limitations of data sources when biosimilars have been produced in small commercial batch quantities over a relatively short period. “At first sight, it might seem straightforward to apply inferential statistical methods for comparing data from quality attributes,” the paper continues. “But often severe limitations exist regarding practical applicability, given the specific circumstances relating to sampling and data collection. Hence, the question of whether the desired conclusion of similarity of products could indeed be inferred from often limited information from sample data remains difficult to answer on many occasions.”

**Biosimilars prescribing**

Meanwhile, physicians in some parts of Europe are coming under growing pressure to prescribe more biosimilars as governments step up their efforts to drive down medicine prices by introducing tendering schemes for mass supplies of biologicals, including both originals and biosimilars. They are also offering incentives for doctors to prescribe lower-cost biosimilars through “gain sharing” projects under which at least some of the money saved is channeled into local healthcare budgets. Nonetheless, the biosimilars market in areas of Europe remains fragmented. Levels of prescribing are high in Scandinavia but relatively low in Western European countries such as France and Spain and, despite recent rises in the availability of certain biosimilars, in Eastern Europe (5).

There are also huge contrasts in individual countries. In Italy, for example, uptake of biosimilars has reached close to 75% in the north but is as low as 10% in the south (6). Caution among healthcare professionals has been a major factor behind these differences. It remains an open question as to how much greater transparency and reliability in information on quality will help to change their attitude to biosimilars.

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Contract Manufacturing Through the Years

How has the bio/pharmaceutical contract manufacturing industry evolved and changed over the years and what does the future hold?

Contract development and manufacturing organizations (CDMOs) have long played a part in the bio/pharmaceutical industry’s growth, but it is only in the past 20 years that they have become a critical element in bio/pharmaceutical company operations. Prior to 1996, there were three primary participants in the CDMO industry: global bio/pharma companies that provided manufacturing services to each other; fine chemical companies providing intermediates; and a small number of dedicated service providers offering specialized capabilities. It was quite common in this period for the major bio/pharma companies to manufacture products or intermediates for companies of similar stature, especially when it could be done without enabling competition.

During this time, the generic API business was still dominated by European companies, and custom manufacturing was a small piece of the business as the global bio/pharma companies had large internal laboratories and manufacturing facilities for process development and commercial production. There wasn’t a biologics contract manufacturing sector, and early entrants such as Amgen and Genentech had to build their own facilities.

Dedicated contract drug-product manufacturers were rare prior to 1996. Those that existed generally offered specialized capabilities: Ben Venue Laboratories was the principal provider of lyophilized injectable product manufacture; Vetter offered bulk syringe filling; and Custom Pharmaceuticals, the forerunner of Patheon, manufactured primarily over-the-counter (OTC) products.

The modern CDMO industry emerges

The CDMO industry really took off in the late 1990s. Starting in 1996, Custom Pharmaceuticals became Patheon and began acquiring facilities in Europe from global bio/pharma companies. Lonza, already a major player in the contract small-molecule API manufacturing business, acquired Celltech and began establishing its position as a leader in contract biologics manufacturing. Cardinal Health, looking to diversify beyond its core wholesale distribution business, acquired R.P. Scherer, the first piece of what became today’s Catalent. In Europe, a number of new drug product CDMOs were established with private equity backing including Nextpharma, Haupt, and Famar.

Three factors contributed to the industry’s launch during the 1996–2007 period. The first was the shedding of excess capacity by global bio/pharmaceutical companies as older products went off patent and as the establishment of the European Union and North American Free Trade Agreement enabled freer cross-border trade of bio/pharmaceuticals. Facilities were usually sold to CDMOs, many of which were formed for the specific facility being sold, at a nominal price and with contracts for legacy products. That enabled the bio/pharmaceutical companies to rid themselves of the assets without negative publicity and costly labour settlements.

A second factor was the explosion of early stage bio/pharma companies, thanks to the maturity of biotechnology and the availability of external funding. Emerging bio/pharma companies rode the coattails of Internet companies to gain access to venture capital and the market for initial public offerings (IPOs). Those early stage companies were unable or unwilling to establish their own manufacturing operations and became core customers of the emerging CDMO industry.

The third factor boosting the CDMO industry was the success of clinical research organizations (CROs). Companies such as Quintiles, Covance, and PPD established themselves as key suppliers of data management, site monitoring, and laboratory services in the late 1990s to both established and emerging bio/pharma companies. Their success validated outsourcing as an effective alternative to in-house capacity for critical development activities, and the relationships with CROs enabled bio/pharma companies to develop critical experience and practices for establishing and managing contract services relationships.

Bouncing back from the financial crisis

The years immediately following the global financial crisis and flood of patent expirations were difficult for the CDMO industry. Emerging bio/pharma companies, one of their core customer groups, suffered a large drop in funding, while mergers among the global bio/pharma companies slowed new drug development. Some CDMOs went out of business while others had to downsize and restructure their operations in order to survive.

The financial crisis created an opening for an important group of players in the CDMO industry—private equity firms. Low valuations and low interest rates combined to provide savvy investors the opportunity to get into an industry whose long-term prospects looked very attractive. The private equity firms brought new capital and financial expertise to the industry, along with the concept of the “roll-up” (i.e., making an initial acquisition in the industry and then build out its capabilities and scope with additional acquisitions). Most importantly, however, the private equity firms were able to recruit top-tier people to run those CMOs, former senior executives from leading bio/pharmaceutical companies as well as experienced operating managers.

External funding for emerging bio/pharma companies began to flow again in 2013, and the CDMO market was ready. Since 2013, CDMO development services revenues have grown at 10–15% annually, as have the revenues of API manufacturers.

The future
The CDMO industry has established itself as a critical part of the global bio/pharma industry. In the United States, drug product is contract manufactured for nearly 50% of all new drug application (NDA) approvals, and drug substance is contract manufactured for more than 50% of all small-molecule NDA products. It can truly be said that the CDMO industry has enabled the rapid expansion of the emerging bio/pharma company sector as 80% of drugs approved for those companies are manufactured by CDMOs. The same can be said for mid-size companies as at least 60% of drugs approved for those companies are made by CDMOs.

Still, the CDMO industry is very much in transition. Four developments in particular bear close watching.

One is the state of external funding available to emerging bio/pharma companies. The early stage bio/pharma sector has buoyed CDMO industry performance thanks to its dependence on CDMOs for pretty much all of its development and manufacturing requirements. However, their funding has historically been quite cyclical and anything that disrupts investor confidence will dent the flow of new funding to emerging bio/pharma and that could hit the CDMO industry hard.

A second development to watch is how the industry has bifurcated into two major segments as it has matured: innovation-driven CDMOs that offer the most sophisticated capabilities and get the lion’s share of high-value new product approvals; and capacity-driven CDMOs that have standard, undifferentiated capabilities and depend on older products and generic drugs to fill capacity. The innovation-driven segment includes less than 10% of the CDMOs in the industry but account for approximately 35% of industry revenues; they have the most advanced technologies, deepest development capabilities and most global regulatory and compliance experience. That gives them the most pricing power and makes them the most desirable strategic partners.

The capacity-driven CDMOs, by contrast, are forced to compete on price and are at risk as the generic-drug business becomes more commoditized. Their margins make it difficult for them to invest in capabilities and compete with the innovation-driven CDMOs. The capacity-driven segment is ripe for consolidation, especially in Europe where labour laws and government procurement practices have kept otherwise-unsustainable operations afloat. We expect to see a shakeout of capacity-driven CDMOs in coming years.

The third development worth watching is how the CDMO industry addresses the global bio/pharma companies (i.e., the 25 largest companies by revenues).

Global bio/pharma companies have made more than $125 billion in capital expenditures for new plant and equipment in the past six years, much of it to support their biologics pipelines. Outsourcing of manufacturing by global bio/pharma companies has actually declined in the past 10 years as they have built up their internal capacity for the new generation of drugs. Thanks to the wide profit margins on new drugs, global bio/pharma companies are far more able to invest in new capacity than CDMOs.

How to address the global bio/pharma sector is a critical strategic issue for CDMOs: with the small and mid-size pharma sectors already highly penetrated, CDMO industry growth will depend to a significant degree on the industry’s ability to gain a bigger share of global bio/pharma’s manufacturing requirements. Big Pharma doesn’t need capacity in the traditional manner in which CDMOs have supplied it, but they are open to new service models that emphasize flexibility, technology, and cost and risk sharing. A number of the innovation-driven CDMOs have crafted offerings that effectively deconstructed the traditional CDMO offering into its component parts like tech transfer know-how, shared overhead, and regulatory expertise, and are putting together customized packages of services that meet the individual company requirements. It will require these kinds of innovative arrangements to get significant penetration into global bio/pharma’s supply chains.

Finally, the impact of new therapeutic and manufacturing technologies bears close attention. New targeted therapies mean that the average volume per product is declining; even when more sophisticated processing commands a higher unit price, overall revenue per product is falling. Some technologies such as autologous cell therapy don’t really fit into the traditional CDMO business model. Developments in manufacturing technologies such as vastly improved yields for biologics, single-use systems, and continuous processing simultaneously require CDMOs to invest in new technologies while making investment in captive capacity more attainable for many companies.

The CDMO industry is robust today and will remain a vital part of the bio/pharmaceutical industry. But significant challenges loom and individual companies will need strong leadership, vision, and operational discipline to succeed.
Predicting Multiparticulate Dissolution in Real Time for Modified- and Extended-Release Formulations

Process analytical technology, based on monitoring particle size distribution and tracking coating thickness measurements in real time, can be used to predict the dissolution of polymer-coated multiparticulates.

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*To whom all correspondence should be addressed.

Process analytical technology (PAT) describes the use of analytical instruments to measure specific product attributes during manufacturing, substantially minimizing the need to sample product for off-line analysis. This approach offers several key advantages including the ability to take process measurements in situ, with instant access to data, facilitating rapid decision making during product development and manufacturing.

Although the time between product sampling and obtaining off-line results may range from minutes to days, depending on the test being performed and the analytical structures in place, many PAT systems can measure results in real time. This capability enables process control decisions to be made, not just based on a recipe, but on the critical quality attributes (CQAs) of the material at that point in time. Access to data in real time can compensate for variabilities in raw material or mechanical wear in processing equipment components, and supports compliance with newer quality assurance (QA) initiatives such as continuous verification.

Many PAT instruments support the measurement of several physical and chemical quality attributes. One CQA that cannot be directly measured inline, however, is dissolution, due to the length of time required for testing. This is particularly true for modified- or extended-release formulations, for which dissolution testing can take several days or even weeks. If a method were available to generate dissolution data in real time by accurately predicting the dissolution test results of a modified-release product, development and production cycle times could be reduced significantly.

This article discusses tests that were conducted to show the feasibility of predicting dissolution drug release profiles on multiparticulates in a Wurster coating process. This approach required measuring coating thickness inline, based on growth in the material’s particle size distribution.

The goal of this work was not only to predict dissolution, but to explore the use of PAT for particle size distribution to measure coating thicknesses across a wide range of formulations (as shown in Table 1).

Process settings were chosen based on the functional coating material. In each case, coating was added to achieve a predicted 20% weight gain. Samples were extracted from the process at time points corresponding to a predicted weight gain of 2.5%, 5%, 7.5%, 10%, 12.5%, 15%, 17.5%, and 20%, based on the quantity of coating solution sprayed.

Additionally, for the aqueous-based functional coat (Surelease, Colorcon), samples were taken at 30 minutes and 1 hour of curing, and analyzed to determine dissolution. Separately, particle size distribution was measured.

Materials and equipment
Chlorpheniramine maleate (CPM) and propranolol hydrochloride (PRP) were layered onto sugar spheres (Suglets, Colorcon) with mesh sizes of 18/20 (850–1000 µm) and 20/25 (710–850 µm), respectively. CPM and PRP layered pellets (1.5–2 kg) were coated with aqueous ethylcellulose dispersion (Surelease, Colorcon) as a barrier membrane coating and Opadry hypromellose-based coating system (YS-1-19025-A, Colorcon) as a pore former, at 80:20 ratios.

The coating dispersion was prepared by dissolving Opadry in deionized water and then added to coating to obtain total solid content of 15% w/w. A ethylcellulose (EC) organic coating system (Opadry EC, Colorcon) was used as an alternative fully formulated barrier membrane organic coating to evaluate the performance on CPM- and PRP-loaded pellets.

The coating solution was prepared in a 90:10 ratio of ethanol to water. The targeted coating weight gain was 18–20%, and samples were taken at every 2.5% of weight gain.

Coating system. A lab-scale fluid-bed dryer (GPCG-2, Glatt Air Technologies) with a six-inch Wurster product container was used for experiments. Critical process parameters are spray
rate, atomizing air pressure, air volume, product temperature, orifice plate configuration, and partition height. Understanding and control of these parameters are crucial for a robust and reproducible process.

The product container used for these tests featured multiple suitably specified viewing windows to allow for installation of non-product-contact PAT, to avoid having the analytical equipment come into direct contact with product. The particle size analyzer (Eyecon2, Innopharma Technology) was installed on the lowest positioned window, as shown in Figure 1, for optimal measurement of pellets, in real time, during Wurster processing.

In general, the use of particle size, as well as moisture and API content measuring devices, can be utilized to gain full process understanding at an economic scale. Process understanding gained from designs of experiments (DOEs) at this scale can be translated into a robust commercial process with integrated real-time in-process product measurement and process control.

Analytical instrument. An non-product-contact direct-imaging particle analyzer (Eyecon, Innopharma Technology) was used to measure particle size change in real time, in-line, during processing, providing D Value and shape data as well as images of the particles.

A typical lab type instrument using the principle of dynamic image analysis (Camsizer, Retsch Technology GmbH) was used to measure particle size distribution off-line, to assess the correlation of in-line and off-line measurements. Drug release was measured using a UV spectrometer from 1 gram of CPM and PRP barrier membrane-coated pellets in a dissolution bath using US Pharmacopeial Convention (USP) apparatus I (baskets) at 100 rpm. USP purified water was used as a dissolution media (1000 ml) at 37.0 ± 0.5 °C.

Results and discussion

Figures 2 and 3 demonstrate the data from the in-line particle size analyzer, tracking two of the coating processes. While data are captured on a continuous basis, only data points corresponding to every 2.5% weight gain are shown here for clearer presentation and later comparison to off-line samples taken.

Dv50 is the volumetric median particle diameter, while Dv10 and

<table>
<thead>
<tr>
<th>Experiment substrate</th>
<th>Functional Coating</th>
<th>Batch Size</th>
<th>Inlet air temp</th>
<th>Product temp</th>
<th>Spray rate</th>
<th>% Solids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPM-SR-1</td>
<td>CPM-coated 18/20 mesh sugar spheres Surelease / Opadry 80:20</td>
<td>2 kg</td>
<td>70°–75°C</td>
<td>44°–46°C</td>
<td>15–20 g/m</td>
<td>15</td>
</tr>
<tr>
<td>CPM-SR-2</td>
<td>CPM-coated 18/20 mesh sugar spheres Surelease / Opadry 80:20</td>
<td>2 kg</td>
<td>70°–75°C</td>
<td>44°–46°C</td>
<td>15–20 g/m</td>
<td>15</td>
</tr>
<tr>
<td>CPM-EC</td>
<td>CPM-coated 18/20 mesh sugar spheres Opadry EC</td>
<td>1.75 kg</td>
<td>40°–45°C</td>
<td>30°–32°C</td>
<td>20–25 g/m</td>
<td>8</td>
</tr>
<tr>
<td>PRP-EC</td>
<td>PRP-coated 20/25 mesh sugar spheres Opadry EC</td>
<td>1.75 kg</td>
<td>40°–45°C</td>
<td>30°–32°C</td>
<td>20–25 g/m</td>
<td>8</td>
</tr>
<tr>
<td>PRP-SR</td>
<td>PRP-coated 20/25 mesh sugar spheres Surelease</td>
<td>1.75 kg</td>
<td>70°–75°C</td>
<td>44°–46°C</td>
<td>15–20 g/m</td>
<td>15</td>
</tr>
</tbody>
</table>

One critical quality attribute that cannot be directly measured inline is dissolution due to the length of time required for testing.

Figure 1: Particle size analyzer in place on the product container.
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Dv90 define the 10th and 90th percentiles. Together these three values provide a simple description of the particle size distribution. A clear growth can be seen in each graph, though the overall size of the materials differs by approximately 100μm. This corresponds with the differing mesh sizes of the CPM and PRP pellets used. It is also evident that the final two data points in Figure 2 show negligible growth. These correspond to the curing process applied to the aqueous-based coating, during which no further material is sprayed, thus causing no weight gain at this point. Because the size does not appear to change either, it can be concluded that minimal density, abrasion, or film shrinkage effects are at play during the curing step.

To allow for dissolution model building and establishment of the repeatability of the overall process and measurement techniques, two CPM experiments were run with identical process parameters. Figure 4 shows the Dv50s of each of these experimental runs. Minimal variance between the two processes can be seen. Because the offset between the two is relatively consistent across the duration of coating, the cause of the variance can most likely be attributed to minor variability in the starting material.

Next, the data measured with the in-line particle analyzer were compared to measurements using the off-line image analyzer. Because some variation is always present between different particle size measurement techniques (e.g., sieve, laser diffraction, back-light imaging), the primary goal was to establish a strong correlation between these two methods rather than to seek direct agreement. Figure 5 shows measurements from the in-line particle size analyzer graphed against those from the off-line instrument. While a clear offset is present between the methods, a similar trend can be seen. Figure 6 plots the in-line and off-line results against each other for D10, D50, and D90 from the CPM-SR-1 experiment. It is evident from the fit lines that a high quality of correlation was present for all three values, with R2 for the Dv10 and Dv50 greater than 0.98. To ensure that this correlation holds across other experiments.
and material sizes. Figure 7 graphs the Dv 50s derived from inline measurements against those from off-line measurements for all sample points during the DoE. The two populations visible are due to the distinct size ranges of pellets used in the CPM and PRP experiments. A strong correlation is still present with an R2 for all points of almost 0.99. The D10 and D90 results correlate similarly.

If a method were available to generate dissolution data in real time by accurately predicting the dissolution test results of a modified-release product, development and production cycle times could be reduced significantly.

Calculating film thickness from measured particle size distribution
Although particle size and distribution can be measured using many off-line methods, dissolution performance is related more to the thickness of the functional coating, or the film thickness applied, than the overall size of the pellets. As such, the film thickness must be determined from measured size data. While the principle involved is simple (diameter increase during coating/2), there are different ways to define diameter increase. Figure 8 explores three methods: difference in the Dv50s, difference in the average of the Dv10, Dv50, and Dv90, and difference in the average of all the volumetric percentiles made from in-line measurements. In practical terms, the results of all three of these methods match closely, so Dv50 was chosen as the value used for further analyses. Figure 9 shows the calculated film thickness for the CPM coating experiment. Although a similar trend is evident, the total film thickness is considerably lower due to differing densities of the functional coating.

Predicting dissolution using in-line measurement
Because a number of factors affect dissolution beyond functional coating thickness, it was necessary to build a formulation-specific
model for prediction based on the in-line-measured particle size. In the CPM-SR experimental runs, this was accomplished using data from CPM-SR-1 to build a correlated model against film thickness growth, which was then used to predict the dissolution results for the samples taken from CPM-SR-2. Although more data would result in a more robust prediction mechanism, this approach was considered sufficient to demonstrate a proof of concept.

These studies showed that a strong correlation exists between functional coating thickness and dissolution profile.

To build a prediction model from CPM-SR-1, the film thickness at each sampling point was first calculated as in Figure 9. Results were then graphed against the dissolution result, divided into data sets for each dissolution sampling time-point (as shown in Figure 10). Figure 10 shows the result of this process, applying best-fit polynomials to each of the data sets. The equations of the best-fit polynomials shown in Figure 11 effectively form the basis of predicting dissolution performance based on a measured film thickness. For a given thickness, an equation exists to describe the expected dissolution percentage for each time point measured in CPM-SR-1. To apply this to CPM-SR-2, the measured film thicknesses for each sample point were substituted into the polynomial equations from Figure 10, producing the data shown in Table II. Data from any point in the coating process could be used for this step, enabling dissolution to be predicted for any moment, but only sample points could be compared to off-line results, to validate the method.

These data, when graphed, predict the dissolution curves. Figure 12 overlays the analytical measured dissolution data, denoted (A), over the predicted (P) dissolution performance.
Generally, the predicted dissolution curves overlap well with the measured results, showing the viability of the prediction method. Based on the limited size of the data set, better prediction could almost certainly be achieved by expanding the model data set from repetition of the experiment. For future experiments, the results of CPM-SR-2 can also be integrated into the predictive model to improve the accuracy and robustness of the prediction algorithms.

Predicting the dissolution of a coating process in real time using particle size data and a formulation-based model is a viable control method. In short, these studies showed that a strong correlation exists between functional coating thickness and dissolution profile. In addition, research proved predicting the dissolution of a coating process in real time using particle size data and a formulation-based model is a viable control method. The work also illustrated the benefits of PAT in achieving greater process understanding and faster, more efficient process profiling. This approach could be used during process development, optimization, scale up and transfer, and showed the potential for using PAT particle size distribution trending as a process control or troubleshooting tool.

Table II. Predicted dissolution results using in-line particle size measurements

<table>
<thead>
<tr>
<th>Sample Point</th>
<th>Predicted dissolution @ (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Film Thickness</td>
</tr>
<tr>
<td>0% WG</td>
<td>0.00</td>
</tr>
<tr>
<td>5% WG</td>
<td>6.36</td>
</tr>
<tr>
<td>10% WG</td>
<td>16.34</td>
</tr>
<tr>
<td>15% WG</td>
<td>26.19</td>
</tr>
<tr>
<td>20% WG</td>
<td>36.50</td>
</tr>
<tr>
<td>30 min cured</td>
<td>38.81</td>
</tr>
<tr>
<td>60 min cured</td>
<td>38.08</td>
</tr>
</tbody>
</table>

In Figure 11: Film thickness vs. dissolution.

In Figure 12: Predicted dissolution, with analytical results overlaid.

CPM-SR-2 is chloropheniramine maleate-coated 18/20 mesh sugar spheres.
The history of poly(lactide-glycolide) (PLG) for drug-delivery applications can be told through the number of products that has steadily emerged on the market since the first product was launched in 1986. More than 35 commercial drug products have relied on the beneficial physical and chemical properties of PLG, its long safety record, and the reliable commercial supply of this polymer.

The first PLG drug delivery patent
US Patent 3,773,919 (1) was the first issued drug-delivery patent describing PLG/drug compositions. This patent, assigned to E.I. du Pont de Nemours and Company, was issued on 20 Nov. 1973. George Boswell and Richard Scribner were the groundbreaking inventors. They were experimenting with PLG-based drug delivery in the late 1960s, as indicated by the 1969 filing date. The patent describes the use of polylactide in drug formulations as a means of providing slow and sustained release of the drug over a controlled period. Pharmaceutical depot compositions described in the patent include injectable particles with sizes ranging from 0.1 to 1000 micron. The patent specification defines polylactides as polyesters generally derived from α-hydroxycarboxylic acids and specifically derived from lactic acid (α-hydroxypropionic acid). Polylactide, polyglycolide, and poly(lactide-co-glycolide) copolymers, therefore, are described. The patent specification lists many classes of drugs, including small molecules and peptides, but not proteins. The inventors interestingly foresaw the potential of this drug-delivery technology for antipsychotic agents, natural and synthetic hormones, narcotic antagonists, vitamin B12, and peptides such as bacitracin, polymyxin B sulfate, and sodium colistimethate. Emphasis was placed on the delivery of endocrine agents such as natural steroids and non-steroidal agents for fertility control, progestogens, oestrogens, androgens, antiandrogens, corticoids, anabolic agents, and anti-inflammatory actives. Today, there are a number of PLG-based pharmaceutical products on the market that deliver many of the drug substances listed in the patent.

Long-acting contraceptives
In the 1970s, there was a lot of interest in controlled-release research for pharmaceutical applications. Much of this activity focused on the development of long-acting contraceptives. The goal was to develop formulations that released contraceptive steroids at a programmed rate for one month or longer following a single parenteral administration. Initially, researchers in the contraception field used non-biodegradable silicone materials as controlled-release excipients (2). PLG polymers were later found to have good biocompatibility and desirable bioabsorption properties; as a result, many investigators began to formulate contraceptive steroids with PLG as functional polymers. Various dosage forms, including injectable microparticles, implants, and fibres, were investigated for both systemic and local delivery (3).

With a global mission, the Programme for Applied Research for Fertility Regulation (PARFR) funded several contraceptive programmes. One of these programmes involved injectable PLG microparticles for the release of norethisterone for one month and three months. The Southern Research Institute and the University of Alabama at Birmingham performed this programme. Successful preclinical work led to the preparation of norethisterone microparticles for clinical trials, which represented the first use of PLG microparticles in human clinical trials in 1981 (4).

Animal contraception work funded by Syntex in 1979 led to significant discoveries. This work involved the peptide drug nafarelin, an analog of luteinizing hormone-releasing hormone (LHRH). Naferelin was difficult to microencapsulate because of its good water solubility. Also at the time, little was known about the release profile of large, water-soluble molecules such as peptides from PLG polymers. A milestone occurred when a Southern Research Institute/Syntex team developed a phase-separation microencapsulation process for LHRH peptides that was much different from emulsion-based, solvent evaporation processes used to encapsulate steroids. This achievement opened the door to...
producing one-month formulations that showed sustained release of LHRH in animals (5, 6).

Debiopharm, a Swiss-based biopharmaceutical company, recognized that controlled-release LHRH for the suppression of testosterone had greater potential for the treatment of prostate cancer than contraception. Having licensed triptorelin, another LHRH analog, Debiopharm contracted Southern Research Institute in 1981 to develop triptorelin microparticles with PLG. This effort led to the market launch of Decapeptyl SR (sustained-release triptorelin) in Europe in 1986, which was the first PLG injectable microparticle product on the market as well as the first injectable peptide-releasing product to be commercialized (7). It is still on the market today distributed by Ferring and Ipsen-Beaufour.

TAP, a joint venture of Takeda and Abbott, also used PLG microparticle technology for the one-month delivery of another LHRH analog, leuprolide. Again, the indication was prostate cancer. The product was launched as Lupron Depot (leuprolide acetate depot suspension) in 1989 (8), and it became a blockbuster drug with sales exceeding that of a liquid leuprolide product, which demonstrated the value of complex, extended-release parenteral products based on PLG excipients. Furthermore, because of the ability to tune the resorption rate of PLG polymers, TAP was able to extend the lifecycle of Lupron Depot with the launch of three-, four-, and six-month leuprolide microparticle products. Other LHRH/PLG microparticles emerged on the market as well, including Sanofi’s Sprecur MP for 2 diabetes).

Bydureon (GLP1 peptide to treat type 2 diabetes), Vivitrol (naltrexone for alcohol addiction), and Risperdal Consta (risperidone for antipsychotic indications), Vivitrol (naltrexone for alcohol addiction), and Risperdal Consta (risperidone for antipsychotic indications) were developed by OraPharm successfully brought the concept of local delivery to the market to treat bacterial infections using PLG excipient. Its Arestin (minocycline) PLG microparticles treat periodontal diseases. The dry microparticle powder is administered to the periodontal pocket using a cartridge system that is provided in the product's kit. Once administered, the microparticles stay in the pocket and release minocycline for two weeks. In addition to drug release, the PLG excipient plays a role in keeping the microparticles in the pocket.

Other extended-release microparticles
In the 1970s, the Sandoz drug-delivery group in Basel was actively developing extended-release, drug-delivery formulations with PLG polymers. First, Sandoz developed and launched Parlodel LAR (long-acting repeatable bromocriptine). Parlodel LAR microparticles delivered bromocriptine for one month (9). With the goal to provide a more continuous drug-delivery pattern for their next extended release products, Sandoz developed a branched PLG polymer made with glucose as the initiator. This branched PLG or star PLG polymer was the basis of Sandostatin LAR, a successful product that releases octreotide, a somatostatin peptide, for four weeks. The product was launched in 1997 and is indicated for the treatment of acromegaly and carcinoid cancers (10). In 2014, Novartis launched another somatostatin microparticle product with PLG—Signifor LAR, which delivers the peptide pasireotide for the same indication as Sandostatin LAR. Interestingly, these microparticles comprise a blend of PLG polymers. Ipsen-Beaufor has a somatostatin PLG microparticle product on the market as well, called Somatuline LA (lanreotide).

To date, Genentech is the only company that launched an extended-release PLG microparticle product for the delivery of a protein. This product, Nutropin Depot, releases recombinant human growth hormone for the treatment for growth hormone deficiency in pediatric patients. This product went on the market in 1999 (11).

Examples of other PLG microparticles on the market include Risperdal Consta (risperidone for antipsychotic indications), Vivitrol (naltrexone for alcohol addiction), and Bydureon (GLP1 peptide to treat type 2 diabetes).

**Extended-release implants**
In addition to PLG microparticles, PLG implants also played a role in controlled-release drug delivery of pharmaceutical products. A melt extrusion process, similar to fibre-spinning, is commonly used to make PLG implants. PLG drug-delivery implants are typically cylindrical rods about 1 cm long and 2 mm in diameter, with the drug dispersed within the PLG matrix core. Once an implant is injected, it can release the drug for weeks and months. After the drug is spent, the implant bioabsorbs.

While naferelin microparticles were being developed, ICI Pharma was working on a PLG implant for the one-month extended release of goserelcin, another LHRH analog. This work led to the launch of Zoladex (goserelin) in 1990 by ICI Pharma. Sanofi’s Profact Depot for the two- to three-month delivery of buserelin is another PLG/LHRH implant on the market.

Ozurdex (dexamethasone intravitreal implant) is the first PLG extended-release implant administered to the eye using a specifically designed applicator. The PLG implant releases 700 μg of dexamethasone for one month to treat macular oedema and uveitis.

The most recent PLG implant introduced on the market is Sceness developed by Evonik for the Australian company Clinuvel Pharmaceuticals. It releases the peptide afamelanotide, a photoprotective drug that protects against sunlight damage by increasing melanin in the skin. Sceness is indicated for the treatment of erythropoietic protoporphyria, a severe skin disorder caused by the body’s inability to protect itself from sunlight.

**Local drug delivery**
In the early 1980s, localized drug delivery was another novel concept pursued with PLG polymers. One programme, funded by the U.S. Army Institute of Dental Research, focused on the local delivery of antibiotics to treat battle wounds (12). The concept was for a soldier to apply a powder of controlled-release PLG/antibiotic microparticles directly into a wound. The microparticles would then slowly release the antibiotic and maintain a high level of drug at the wound site for 14 or 21 days to achieve efficacy without requiring daily, oral dosing.

OraPharm successfully brought the concept of local delivery to the market to treat bacterial infections using PLG excipient. Its Arestin (minocycline) PLG microparticles treat periodontal diseases. The dry microparticle powder is administered to the periodontal pocket using a cartridge system that is provided in the product’s kit. Once administered, the microparticles stay in the pocket and release minocycline for two weeks. In addition to drug release, the PLG excipient plays a role in keeping the microparticles in the pocket.
**In-situ forming drug delivery**

In-situ forming PLG drug delivery was an approach invented by Southern Research Institute scientists. The concept involves administering a PLG polymer solution containing the drug substance such as the antibiotic doxycycline. The resulting liquid formulation is placed into a diseased periodontal pocket. Once in the pocket, the formulation solidifies due to solvent extraction, taking on the shape of the pocket and releasing antibiotic into the pocket for seven days (13). The key with this approach is that the formulation stays in the pocket during antibiotic treatment, especially as the pocket heals and decreases in size. The technology was licensed to Vipont Research Laboratories, which later became Atrix Laboratories. In 1999, Atrix successfully launched a periodontitis product branded as Atridox. Atrix also applied this in-situ forming technology to systemic delivery, for example in its Eligard product (leuprolide acetate injectable suspension) for the extended release of LHRH to treat prostate cancer (14).

**Nanoparticles**

PLG-based drug-delivery technology can be formed into nanoparticles (i.e., particles less than 1 μm in diameter). These nanoparticles can contain encapsulated drug, typically hydrophobic ones. Proteins, such as antibodies, and other moieties can be conjugated on the surface of the nanoparticles as a way of targeting them to specific cells.

Polymeric micelles represent a specific class of PLG-based drug-delivery nanoparticles, whereby a diblock of polylactide and polyethylene glycol (PEG) with hydrophobic and hydrophilic regions respectively allows for self-assembly of the polymer chains into 50-nm nanoparticles. The resulting core-shell constructs have PEG oriented on the surface. Moieties conjugated to the surface are used to target the nanoparticles to biological sites and to minimize toxicity. Genexol (paclitaxel) by Samyang is an example of a PLG polymeric micelle product on the market. Paclitaxel is encapsulated within the hydrophobic core of the polymeric micelle, and the product is indicated for the treatment of breast, lung, and ovarian cancers. The PLG polymeric micelle technology enhances the solubility of paclitaxel and allows significantly higher dosing of paclitaxel to patients without additional toxicity (15).

**Vaccines**

Researchers have investigated the use of PLG microparticles to encapsulate vaccine antigens. Microparticles of less than 10 μm in diameter are taken up by macrophages, dendritic cells, and Peyer’s patches. The engulfed microparticles then release the vaccine antigen within these cells, triggering the cells to produce immunoglobulin antibody titres, which provide mucosal and T-cell responses.

**The crucial role of commercial polymer supply**

The supply of lactide/glycolide polymers plays a crucial role in the success of PLG-based drug-delivery products. Commercially manufactured PLG has been important in supplying the quantities needed for drug-delivery products, as well as ensuring that the PLG polymers have consistent and desired properties.

During early times, laboratories had to make their own PLG polymers and monomers. These polymers, especially polymers with high glycolide content (e.g., 50:50 lactide:glycolide polymers) had solubility challenges due to their long glycolide blocks. Also, polymer solubility varied from batch to batch, making it difficult to perform robust formulation processing and achieve reproducible drug-delivery performance from microparticles and implants. Resomer polymers offer more consistent properties with better and reproducible solubility.

**The future for PLG drug delivery**

The majority of biopharmaceutical drugs being developed today will require parenteral administration, and many of these compounds will require extended-release performance. Complex, parenteral drug-delivery technologies will meet these requirements. Safe and proven excipients, such as PLG polymers with consistent properties, will play a key role in formulation development.

**References**

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Access to high-throughput synthesis and screening technologies has enabled the discovery of novel classes of small molecules that exhibit high potency. Unfortunately, many of these compounds suffer from poor solubility and bioavailability when administered in conventional solid-dosage forms, the preferred route of administration due to convenience and ease of use. Formulation as amorphous solid dispersions (ASDs)—most commonly via spray drying (SD) or hot-melt extrusion (HME) and more recently co-precipitation (CP)—is increasingly used to improve the performance of poorly soluble drugs. The choice of excipients for spray-dried formulations has a direct impact on the stability and efficacy of these ASDs.

Risking metastable forms
ASDs involve incorporation of the API in a metastable form within a polymer matrix. Spray-dried ASDs are prepared by dissolving the API with the polymer and other excipients in a solvent (or solvent mixture) and then removing the solvent through a rapid flash-drying process. “Metastable, amorphous forms have greater solubility and bioavailability, but because they are in a higher energy state, they desire, as do all things in nature, to move to a lower energy state, in this case via crystallization,” notes Márcio Temtem, associate director for particle design and formulation development at Hovione.

The challenge is to avoid or at least delay for a sufficient length of time (the shelf life of the product) this change in the metastable state. The key excipient in ASDs—the polymer—forms a matrix that provides this needed stabilization. The matrix disperses the API molecules, preventing any interactions between them that could lead to crystallization. API molecules trapped within such a matrix also have reduced molecular mobilities, which further reduces their potential for crystallization.

Formulation considerations
Several key factors must be considered when formulating spray-dried ASDs, such as the selection of the best ingredients to increase the “supersaturation effect” and the API/polymer ratio and the impact it may have on the stability and performance of the selected system.

According to Temtem, “the API and polymer must form a true solid solution in which the polymer and API cannot be distinguished from one another and are mixed in such a way and in the right proportion that the mixture is thermodynamically and/or kinetically stable and the two compounds prefer to be together rather than apart.” Finding this “sweet spot” is achieved using various computational, high-throughput screening, and other experimental tools combined with knowledge and experience.

Processing conditions
Spray drying is just one method for preparing ASDs and may not be ideal for certain APIs or target formulations. Each method—spray drying, hot-melt extrusion, and co-precipitation—produces dispersions with different morphologies, surface areas, particles sizes, and other attributes that impact product release profiles. The manner in which the API is entrapped in the matrix is very different and thus also results in different levels of “disorder,” or in other words energy levels, according to Temtem.

Process conditions during spray drying may also impact the chemical purity of some APIs. “Although the drying technique is gentle and takes place rapidly with the API droplets protected by evaporation of the solvent, it is necessary to assess an API for degradation during drying,” Temtem observes. He adds the use of solvents can also result in the plasticization of the amorphous solid dispersion, increasing the molecular mobility and thus the potential to crystallize.

Challenges of excipient selection
The first challenges to maintaining stability in ASDs, according to Meredith Perry, associate director of pharmaceutics with Pharmatek SD, Catalent, is the need to use a polymer that is chemically compatible with the API while also being miscible and improving the supersaturation of the API in aqueous media. “Although most polymers are relatively inert, some are hygroscopic or acidic and therefore inappropriate for compounds prone to hydrolysis or acid degradation,” she states.
The second challenge is to select a solvent that provides sufficient solubility and chemical stability for both the active ingredient and the chosen polymer. “A wide range of organic solvents can be safely spray dried, so usually it’s possible to find a combination of solvents, such as polar protic and polar aprotic solvents, that meet these objectives,” Perry says.

The next challenge with ASDs is excipient selection in the solid state. Any instability previously noted in the crystalline form of the API will likely be more pronounced in the amorphous state, according to Perry. “Specifically,” she observes, “hygroscopicity is typically worse in an amorphous form due to the hygroscopicity of some polymers and the high surface area of the ASD particles. Reactivity with acids, bases, and oxidizing agents is also generally worse due to the high energy state of the amorphous material.”

Common excipients
The pharmaceutical industry favours the use of excipients that have been previously approved and have data supporting their use in humans. As a result, there are three main families of polymers used to form spray-dried ASDs, according to Temtem: cellulose-based polymers, polyvinylpyrrolidone-based polymers, and acrylate-based polymers.

Common cellulose-based polymers used in spray-dried dispersions (SDDs) include hypromellose acetate succinate (HPMCAS) and hydroxypropylmethyl cellulose (HPMC). Widely used pyrrolidone polymers include polyvinylpyrrolidone (PVP, also known as polyvidone or povidone) and copolymers of PVP with vinyl acetate. A polyethylene glycol, polyvinyl acetate, polyvinylcaprolactam-based graft copolymer has also been used extensively in ASDs. Copolymers of methacrylates with acrylic acid in different ratios make up the third family of polymers used to form the matrices within SDDs.

“Polymer selection is the primary tool for chemically and physically stabilizing the API in an ASD because the two compounds are mixed at a molecular level,” notes Perry. For instance, HPMC capsules are often preferred over gelatin for hard shell capsules because HPMC has a neutral pH, low moisture content, and low hygroscopicity. Mannitol as a tablet excipient also meets these requirements.

In third-generation SDDs, surfactants, typically d-α-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) or sodium lauryl sulfate (SLS), are often added to prevent precipitation of the API during dissolution. “Surfactants help to maintain supersaturation of the API by forming micelles and/or other 3-D structures during drug product dissolution. The API is kept in solution by preventing interaction of API molecules with one another,” Temtem explains.

Surfactant use is only effective at relatively low levels (< 5–10%); when used at higher levels, surfactants often undergo phase separation in the SDD. Due to their low melting points and sometimes low glass transition temperatures, when added to formulations in large quantities, they may hinder product accumulation inside the units and result in physical and chemical stability challenges.

For compounds that are pH-sensitive, excipients with pH buffering capacity, such as citric acid and sodium bicarbonate, can have a stronger stabilizing effect on ASDs than on crystalline APIs, according to Perry. In addition, solid-dosage forms can be coated for further moisture protection. Materials such as polyvinyl acetate-based (PVA-based) coatings provide a good barrier, and can be coated more thickly than film coats to provide further protection.

Excipient developments
Excipient suppliers are taking various approaches to the development of new products for use in SDDs. Most efforts are directed at developing improved versions of existing, approved excipients given that drug manufacturers are hesitant to risk attempting to get a new drug approved with a truly novel excipient; novel excipients do not have a separate approval pathway and are only approved when a drug-product formulation in which they are used receives approval.

Thus, suppliers are looking to develop new grades of existing matrix polymers or to develop modifications to existing excipients. For instance, HPMCAS until recently was largely supplied by Shin-etsu. The company’s patent protection is expiring, and other suppliers such as Ashland and Dow are working to add this polymer to their portfolios. In addition, excipient suppliers are developing polymers with different combinations of acetate and succinate substituents to provide more options for drug developers. “These new excipients open new windows for formulators, particularly from a quality-by-design standpoint. Formulators now have many more polymer with a broad range of properties, allowing for the development of more effective products,” Temtem asserts.

Another approach is the development of higher-performance versions of existing excipients that help manufacturers optimize their production processes. Temtem notes that Dow, for instance, is developing excipients for the pharmaceutical industry that have lower viscosities and thus allow for higher solids concentrations in SD formulations and/or the ability to process spray-dried systems under milder conditions.

The development of novel excipients, or new chemical entities, is not as common but is ongoing despite the challenges in obtaining their approval. BASF, for example, is developing a new excipient with a good balance between the hydrophilic and hydrophobic moieties that provides good stabilization of APIs in solid dispersions while also maintaining supersaturation for an extended period of time, according to Temtem.

Mesoporous silica is also a substance attracting significant interest from the pharmaceutical research community as a potential excipient for ASDs. Mesoporous silica has small pores and a high surface area and has been used for many years as a catalyst in chemical processing and for various applications in the food industry. “For ASDs,” observes Temtem, “the size of the pores in mesoporous silica is ideal for trapping API molecules and preventing them from interacting. The material is advantageous because silica powder has good characteristics in terms of its flowability, which leads to improved downstream processing. Silica is also an inert material, and thus, there is no potential for interactions with the API or the GI tract.” PTE
Analysis of Total and Transferrin-Bound Iron from Serum Samples

Incorporating structural constraints into pharmacokinetic studies of iron sucrose formulations

James A. Koziol and Michael A. Grossman

Results from assays conducted independently of one another can produce findings that are incompatible with underlying physiologic constraints as a result of random errors. The authors investigate one such instance here, relating to assays of total iron and transferrin-bound iron concentrations in sera. A method of adjusting the observed total and transferrin-bound iron concentrations in these settings was outlined. The key of this approach was to satisfy the intrinsic physiologic constraint that the total serum concentration of iron is at least as great as the serum concentration of transferrin-bound iron. The adjustment method proposed by the authors can be readily applied in other settings that have physiologic constraints.

The United States Food and Drug Administration has issued a draft guidance for in vitro and in vivo studies of intravenously injected iron sucrose (1). One of the recommendations is that total iron and transferrin-bound iron concentrations are to be assessed simultaneously in sera from healthy male and female volunteers, prior to further determinations of area under the curve measures.

These recommendations are eminently reasonable, but practical implementation may not necessarily be straightforward. Assays of total iron and transferrin-bound iron concentrations are typically done independently, but can result in violations of obvious physiologic constraints. Suppose, for example, total iron is assayed in assay A, and transferrin-bound iron in assay B. Total iron should incorporate both transferrin-bound and non-transferrin-bound (e.g., free) iron, hence, one might expect that assay A should lead to a quantitative estimate of total iron no smaller than the amount of transferrin-bound iron calculated from assay B. This is not necessarily the case, however, as described in a study by Goggin et al. (2). These authors developed a spectrophotometric method for measuring total iron and transferrin-bound iron in human serum, and found a strong correlation \( r=0.97 \) between the two measurements in naïve serum samples \( n=341 \). On the other hand, they found a non-negligible proportion of paired values in which assayed transferrin-bound iron concentrations exceeded the assayed total iron concentrations. The purpose of this article is to outline a method of adjusting the observed total and transferrin-bound iron concentrations in such settings, so as to satisfy the intrinsic physiologic constraint that the total concentration of iron is at least as great as the concentration of transferrin-bound iron.

Methods

Let \( T \) and \( B \) generically refer to the serum concentrations of total iron and transferrin-bound iron, respectively, commonly in units of \( \mu g/dL \). A serum sample was taken from a random individual; from this serum sample, assay
A reports \( X_T \) as the concentration of total iron, and assay B reports \( X_B \) as the concentration of transferrin-bound iron (both in units of \( \mu g/dL \)). If \( X_T \geq X_B \), it would be accepted that \( X_T \) and \( X_B \) are valid estimates of the serum concentrations of total iron and transferrin-bound iron respectively in this individual. But if \( X_T < X_B \), these observed values are at odds with the physiologic constraint that bound iron cannot exceed total iron. In this situation, the authors propose a likelihood approach for estimation of total and transferrin-bound iron concentrations. The approach is standard, but differs in the details, depending on what is known about the operating characteristics of the assays.

**Assay variances known**

It is assumed that as random variables, \( X_T \) and \( X_B \) have normal (Gaussian) distribution with means \( \mu_T \) and \( \mu_B \) respectively, and variances \( \sigma_T^2 \) and \( \sigma_B^2 \). For now, it is assumed that \( \sigma_T^2 \) and \( \sigma_B^2 \) are known, as might be ascertained by reference to the assay manufacturers. There is the physiologic constraint that \( \mu_T \geq \mu_B \), but otherwise these underlying means are unknown. If \( X_T < X_B \) is observed, the authors propose maximizing the joint likelihood of \( (X_T, X_B) \) over \( \{\mu_T, \mu_B\} \), subject to the inequality constraint \( \mu_T \geq \mu_B \); and are used, with the values of \( \mu_T \) and \( \mu_B \), respectively, that maximize this likelihood, as the estimates of total iron and transferrin-bound iron concentrations, respectively, in this situation.

In fact, these estimates can be easily derived using the method of Lagrange multipliers. It turns out that

\[
\hat{\mu}_T = \hat{\mu}_B = \frac{X_T \cdot \sigma_B^2 + X_B \cdot \sigma_T^2}{\sigma_T^2 + \sigma_B^2}
\]

[Eq. 1]

**Assay coefficients of variation known**

Operating characteristics of assays are not necessarily reported in terms of variances or standard deviations (SDs); a common alternative is to report coefficients of variation (CVs) rather than SDs, especially if assay variability tends to increase linearly with mean levels. The authors outline how CVs can be incorporated into the likelihood formulation.

As before, it is assumed that as random variables, \( X_T \) and \( X_B \) have normal (Gaussian) distribution with means \( \mu_T \) and \( \mu_B \) respectively, and variances \( \sigma_T^2 \) and \( \sigma_B^2 \). However, now \( \sigma_T^2 \) and \( \sigma_B^2 \) are unknown, and instead two different parameters are given, which characterize variability in the underlying assays, namely, CV \( \hat{\gamma}_T \) and CV \( \hat{\gamma}_B \), the coefficients of variation of the assays for total iron and transferrin-bound iron, respectively.

Again as before, if \( X_T < X_B \) is observed, the authors propose maximizing the joint likelihood of \( (X_T, X_B) \) over \( \{\mu_T, \mu_B\} \), subject to the inequality constraint \( \mu_T \geq \mu_B \); in writing this likelihood, \( \sigma_T \) is replaced by \( CV_T \cdot X_T \), and \( \sigma_B \) by \( CV_B \cdot X_B \). With these substitutions in Equation 1, one can arrive at \( \hat{\mu}_T \) and \( \hat{\mu}_B \) as the respective estimates of total iron and transferrin-bound iron concentrations.

For those with a more numerical bent, Matlab code for this maximization procedure is given in the Appendix, which also includes further technical details.

**Example**

Figure 1 shows a plot of total iron concentrations and transferrin-bound iron concentrations from 180 individuals. The assays from which these concentrations were derived are not equally reliable; reported coefficients of variation are 8% for total iron and 5% for transferrin-bound iron. It is clear from Figure 1 that for a non-negligible proportion of the 180 subjects, the observed transferrin-bound iron concentrations exceed the observed total iron concentrations. After applying the approach described by the authors, the “corrected” concentrations are shown in Figure 2—which is now tied data [total iron concentration = transferrin-bound iron concentration], but with no violations of the intrinsic ordering of total iron and transferrin-bound iron.

**Discussion**

On an individual level, tests and assays can yield inconsistent results, as with independent assays for serum concentrations of total iron and transferrin-bound iron.
Summary statistics can obscure these inconsistencies, for example, by simple averaging of results over large cohorts of individuals. Nevertheless, the individual consistencies remain, and the suggestion in this article is to address these inconsistencies in a logically coherent manner prior to data summarization. The authors illustrate an approach in the context of independent assays for serum concentrations of total iron and transferrin-bound iron, but the approach remains valid in analogous settings with intrinsic structural (physiologic) constraints. For example, ligand binding assays are commonly used to assess concentrations of monoclonal antibody drugs in plasma or serum samples (3). These assays are designed to measure the total or free forms of monoclonal antibody and the target ligand. Total monoclonal antibody is the sum of bound and unbound forms of the monoclonal antibody drug, hence, the value must exceed that of the free form. This constitutes a physiologic constraint on the assay determinations, completely analogous to the scenario outlined in this note.

It is implicitly assumed that the tests or assays are accurate, that is, there is no systematic bias impinging on the test or assay outcomes. In the setting described by the authors, the assays for serum concentrations of total iron and transferrin-bound iron have been appropriately vetted for accuracy, and the inconsistent findings can be attributed to random error. Nevertheless, in other settings, it may be worthwhile to rule out the possibility of systematic bias.

In practice, summary statistics may give no inkling of individually inconsistent results, and corrections to individual data may be inconsequential. Nevertheless, it can be argued that data analyses and submissions ought to be based on rigorously validated data, and the proposal described in this article is made in this spirit.

Appendix

The following outlines the Matlab code for estimation of the concentrations of total and transferrin-bound iron, in the scenarios described earlier. The authors’ methodology invokes the Matlab command fmincon, which minimizes a multivariate function (the objective function) subject to inequality constraints. In the following examples, the objective functions are saved as Matlab M files in the working directory.

Global variables are used to pass parameter values to the objective functions. The global variables are denoted:

- `tval` observed value of total iron concentration
- `bval` observed value of transferrin-bound iron concentration
- `sig2t` variance of total iron assay (if known)
- `sig2b` variance of transferrin-bound iron assay (if known)
- `cvt` coefficient of variation of total iron assay (if known)
- `cvb` coefficient of variation of transferrin-bound assay (if known)

It is assumed that assay reproducibility is expressed either in terms of variances (or standard deviations) of replicate measurements, or with coefficients of variation. The likelihood approach outlined previously is predicated on the assumption of normality for replicate assay results. Let

\[ f(z; \mu, \sigma^2) = \frac{1}{\sqrt{2\pi}\sigma} \exp \left( -\frac{1}{2} \left( \frac{z - \mu}{\sigma} \right)^2 \right) \]

represent the probability density function of a normally distributed random variable with mean $\mu$ and variance $\sigma^2$. Then, the joint likelihood $L$ of (tval, bval) is the product of the two underlying normal densities

\[ L = f(tval; \mu_t, \sigma_t^2) \times f(bval; \mu_b, \sigma_b^2) \]
and the goal is to maximize this joint likelihood over \( \{\mu_T, \mu_B\} \), subject to the simple linear constraint \( \mu_T \geq \mu_B \). This maximization is equivalent to the minimization of the negative log likelihood \(-\log L\), for which fmincon is invoked.

The objective functions specified in the Matlab M files below are proportional to the negative log likelihoods (but with extraneous constants omitted), and maximization of the likelihoods is equivalent to minimization of the objective functions.

```matlab
objfunc1.m
function z = objfun1(x)
% Objective function to be minimized if sig2t and sig2b are known
% global tval bval sig2t sig2b
z = (x(1) - tval)^2/sig2t + (x(2) - bval)^2/sig2b;
return
end

objfunc2.m
function z = objfunc2(x)
% Objective function to be minimized if cvt and cvb are known
% global tval bval cvt cvb
z = (x(1) - tval)^2/(cvt*tval)^2 + (x(2) - bval)^2/(cvb*bval)^2;
return
end
```

For completeness, the objective functions are provided if sig2t and cvb, or cvt and sig2b are given.
```
objfunc3.m
function z = objfunc3(x)
% Objective function to be minimized if sig2t and cvb are known
% global tval bval sig2t cvb
z = (x(1) - tval)^2/sig2t + (x(2) - bval)^2/(cvb*bval)^2;
return
end

objfunc4.m
function z = objfunc4(x)
% Objective function to be minimized if cvt and sig2b are known
% global tval bval cvt sig2b
z = (x(1) - tval)^2/(cvt*tval)^2 + (x(2) - bval)^2/sig2b;
return
end
```

Here is a prototypical Matlab program for the maximization procedure:
```
main.m
% Specify the observed tval and bval values, and the measures of variability % of the two assays, here
% The linear constraint \( \mu_T \geq \mu_B \) is rendered in Matlab as \( A^T x \leq b \), where \( x \) denotes the vector \( (\mu_T; \mu_B) \)
A = [-1 1]; b = [0];
% The vector x0 contains starting values for the minimization procedure
% through fmincon. We have found the following starting values to work
% well.
x0 = .5*(tval+bval)*[1; 1];
% Here is a simple call;
% in practice, the appropriate objective function should be called.
[x] = fmincon(@objfunc1, x0, A, b)
% Matlab will return the vector x here. x(1) is \( \hat{\mu}_T \), and
% x(2) is \( \hat{\mu}_B \).
end
```

Notes:
1. One can invoke fmincon regardless of the ordering of tval and bval. If in fact tval \( \geq \) bval, the linear constraint is not active, and fmincon will return \( x = (tval; bval) \).
2. If bval \( \geq \) tval, the linear constraint is active, and fmincon will return the value specified in text equation (1) for \( x(1) \) and \( x(2) \).
3. If minimization is a one-off operation, then anonymous functions might be an appropriate approach for the minimization problem in Matlab. Separate function files are used, with parameters passed into the functions via global variables, for clarity.

References

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Biopharmaceutical manufacturing has changed dramatically since 1977, when it was in its infancy. The ball really began rolling 20 years ago and has picked up speed in the past five years. Without question, single-use (i.e., disposable) technology has been one of the most significant changes. Advantages of single-use technology include greater flexibility, reduced resources for cleaning and cleaning validation, and faster turnaround between products and batches, resulting in reduced capital costs and increased speed to market. Single-use technology has also precipitated changes in upstream and downstream processing.

Pharmaceutical Technology Europe spoke with Eric Langer, managing partner at BioPlan Associates; John Boehm, chairman of the Bio-Process Systems Alliance (BPSA) and Colder Products Company Bioprocessing Business Unit manager; Eric Isberg, chief technology officer, Upstream, GE Healthcare Life Sciences; Parrish M. Galliher, chief technology officer, Upstream, GE Healthcare Life Sciences; Sabrina Restrepo, associate director in the Sterile & Validation Center of Excellence, Global Technical Operations at Merck; Helene Pora, PhD, vice-president, Single-Use Technologies, Pall Life Sciences; Peter Levison, senior marketing director, Downstream Processing, Pall Life Sciences; Fritjof Linz, vice-president, Purification Technologies, Sartorius Stedim Biotech; and Eva Heintz, global market manager, Healthcare, at Solvay Specialty Polymers about advances the industry has made and the challenges that remain.

**Advances in single-use technologies**

**PTE:** What have been the most significant advances in single-use systems for biopharmaceutical manufacturing in the past 40 years?

**Langer (BioPlan Associates):** Over the past 40 years, single-use systems have moved from simple blood and intravenous bags to simple media and serum containers, and to highly engineered, complex devices that are now mainstream technologies in bioproduction. Over the past five years, these devices have steadily made progress in bioprocess operations as their scalability has increased.

**Galliher (GE):** In the past five years, new advances include an increase in closed systems and in larger-scale, higher-throughput, high-duty applications, such as microbial fermentation and centrifugation. Single-use sensors have been developed for a variety of process parameters for downstream steps such as chromatography, tangential flow filtration, direct filtration, and fill/finish, as well as for smart mixers for measuring parameters such as temperature, pH, and conductivity.

**Linz (Sartorius):** In the past couple of years, we have seen just about every bioprocessing technology become available in a fully single-use format. Companies are implementing end-to-end single-use platforms for monoclonal antibody, antibody drug conjugate, and vaccine production. Flexible facilities are likely to become an important part of large biopharma’s production network and allow much needed agility in operations.

**Isberg (Entegris):** I think the biggest advance in single-use technology in the past 20 years was the development of three-dimensional bags, which opened the door for large-scale mixing and cell-culture manufacturing. The industry was able to scale up volume while also creating systems equivalent in shape and volume to stainless-steel vessels. Equivalency is important because much of the engineering in areas like mass transfer was performed in stainless steel.

**Pora (Pall):** In the past 20 years, the sentiment has gone from, ‘why use/trust these systems’ to ‘how do we best optimize/leverage these systems.’ Overall, the ability of single-use technologies to offer sterile connections and operate a closed system, while still maintaining flexibility, has been a game-changer. In the past five years, we have seen the technology go past acceptance to start maturing, with a range of market options and sizes to accommodate various needs.

**Boehm (BPSA):** First used for media and buffer prep, single-use manufacturing now applies from inoculum to final formulation and filling. An initial focus on small-batch clinical trials has expanded to full-scale cGMP commercial production.
More recently, drug manufacturers are using fully closed systems to make multiple drugs in large ballroom suites. **Heintz (Solvay):** The evolution of single-use containers from several decades ago to today’s gamma irradiation-stable bioreactors has been one of the most significant transformations; it was the impetus to move all other components to single use to close the loop. In the past five years, we have seen many advancements in sterile connectors and sensors that are gamma irradiation-stable and non-ion migrating.

**Challenges with single-use systems**

**PTE,** What are the most significant challenges that remain for fully optimizing single-use systems?

**Heintz (Solvay):** There are still challenges to single use in the final fill/finish and storage. From upstream to downstream, single-use components are gaining traction in development and use. Fill and finish technology still has room to grow, including the delivery systems of biopharmaceuticals.

**Isberg (Entegris):** I continue to hear that one of the biggest challenges is consistency and optimization of the materials used to manufacture single-use systems. Materials of construction have changed little in the past 20 years, with polyethylene and silicone dominating. I see the industry moving towards advanced materials like fluoropolymers, which solve most if not all of the challenges posed by other materials.

**Galliher (GE):** High-pressure resistant, high-temperature resistant, solvent resistant, better, and more extensive sensors and smart films are needed, along with systems that enable high-G centrifugation, elimination of seams for bags, and larger connectors for higher flow rates.

**Restrepo (Merck):** Single-use systems need to prove themselves to be a well-understood and robust technology. That might imply driving toward standardization from different perspectives: designs, interconnectivity, technical qualification packages, certificates, manufacturing practices, and product lifecycle management aspects (from user requirement specifications to management of supplier change notifications post-implementation). The establishment of industry standards such as ASTM E3051-16 or the ongoing joint efforts between the BioPhorum Operations Group (BPOG) and BPSA definitely contributes to move toward standardization. Being able to provide consistent information from drug manufacturers to health authorities around the globe will ultimately favour the prompt launch of more medicines to meet the needs of many patients.

Two other aspects to be considered are a broader spectra of integrated process analytical technology tools that can interface with many of the control systems available in the market and ergonomic designs or solutions for safe use by operators.

Organizations are setting more aggressive environmental goals, which will drive initiatives to show that single-use systems are environmental-friendly. Since the implementation of single-use systems involves a partnership with suppliers, robust and transparent supply chains to the customers are critical.

**Linz (Sartorius):** The industry still has more work to do to ensure all technologies are fully compatible with biological systems. Single-use systems must be tested extensively to ensure that their materials of construction do not inhibit cell growth or release chemicals into the product stream during bioprocessing. Biomanufacturers repeatedly cite the robustness of single-use technologies as being a concern, and suppliers need to support their clients by helping improve process integrity. Most significantly, biopharmaceutical companies need vendors to commit to providing a high level of assurance of consistent supply with robust supply chains and highly characterized processes and raw materials.

**Boehm (BPSA):** The industry’s greatest challenges are driving down drug costs to improve global accessibility and more quickly developing new therapies. Single-use technology plays a vital role in addressing these high-level opportunities. We must drive continuous improvement in education, standardization, and technology. Industry stakeholders (e.g., suppliers, users, regulators) must continue to exchange expertise and knowledge. Collaboration between stakeholders will also be critical to navigating the potentially conflicting goals of advancing standardization and technology innovation.

**Langer (BioPlan Associates):** Although single-use systems have made great inroads at clinical scale, the advances at larger scale have been slower. Over the past eight years, the reasons biomanufacturers give for not

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expanding their use of disposables have been relatively consistent. Top concerns are the potential for breakage of bags/loss of production materials and leachables and extractables (L&E) issues. Part of this persistent concern for L&E issues is the increased use of disposables, which, in turn, has increased awareness of the uncertainties regarding related regulatory issues.

**Pora (Pall):** While single-use systems are starting to mature, automation and process monitoring (sensors) remain pain points. We have yet to see how we can fully take advantage of single-use technologies with automation—even though we now have bioreactors at every size.

**Bio reactors technology**

**PTE:** What have been the most significant changes in bioreactor technology over the past 40 years?

**Pora (Pall):** We have come a long way from the first stirred tank bioreactor—even the way single-use bioreactors look has changed—with a broad range of solutions from small to large scale. As single-use systems continue to mature, we are seeing more specialized applications and new innovations. Pall Life Sciences’ square stirred tank bioreactor design has shown clear advantages over traditional round design. And Pall’s iCELLis bioreactor system is an automated fixed-bed bioreactor, designed to simplify adherent cell-culture processes using single-use technology.

**Galliher (GE):** In the past 40 years, biomanufacturing facilities were primarily built using stainless-steel technology. That technology has grown in sophistication and scale required to produce large scale quantities of biotherapeutics (up to tons/year) and vaccines (hundreds of millions of doses/year). Steam-in-place (SIP) and clean-in-place (CIP) systems, with sophisticated automation, were technological advances in stainless-steel systems to ensure aseptic operation (where needed) and minimization of soil carryover from batch to batch or product to product.

**Advantages of single-use technology include greater flexibility, reduced resources for cleaning and cleaning validation, and faster turnaround between products and batches, resulting in reduced capital costs and increased speed to market.**

**Pora (Pall):** Single-use bioreactors present a real solution for today’s drug manufacturer, and there is no doubt that the industry now accepts and understands this fact. Over the past few decades, we have been able to clearly establish the boundaries—for instance, we know that 2000 L is the maximum level that you can leverage the advantages of single-use. Still, users are always looking for innovative ways to optimize the flexibility of single-use technologies, and we see this resonating in approaches like parallel processing, as well as the market drive towards bringing continuous processes to the upstream.

**Bottlenecks**

**PTE:** What challenges remain for optimizing/debottlenecking downstream separations?

**Levison (Pall):** The real bottleneck is in the upstream (cell culture), which is why there is so much interest in perfusion technologies for continuous cell culture. Bioprocesses cannot be fully continuous without further advances in upstream processing. Another bottleneck can often come from the cost of goods in implementing newer downstream processing technologies; this bottleneck will likely abate over time as these technologies become fully implemented.

**Linz (Sartorius):** Integrating downstream processes with continuous upstream steps such as perfusion remains a challenge. There are some options available, but they are at an early stage of development. Although downstream process intensification is possible, we are still quite a long way from having the continuous flow of product through a purification train and into the vial. That is one of the challenge for downstream processing engineers over the next decade. **PTE**
Although the pharmaceutical industry is criticized for its slowness to accept change, it has made manufacturing improvements in the past decades in response to changes in drug delivery (e.g., multi-layer tablets and prefilled syringes); market demands for cost-efficiency and the flexibility to make smaller batches; and regulatory demands for higher product quality, process robustness, and worker safety. Advances in automation, process control, and connected systems have been adopted. Continuous manufacturing has not replaced traditional batch manufacturing, but its concepts are better understood and accepted, and the first commercial, continuous solid-dosage processes are up and running.

Parenteral manufacturing and fill/finish

The pharmaceutical industry’s aging manufacturing facilities, particularly for parenteral drugs, have been pointed to as a cause of drug shortages, and organizations such as the Parenteral Drug Association have taskforces dedicated to overcoming the challenges to modernization, including post-approval changes (1). In many facilities, however, modern technologies have been implemented and shown to improve efficiency, quality, and flexibility.

One of the keys has been removing human intervention with automation and cleanroom systems, such as restricted access barrier systems (RABS) and isolators. “RABS achieves the sterility assurance level required by regulatory authorities and allows for rapid product changeover along with high safety,” explains Bernd Stauss, senior vice-president of Pharmaceutical Production/Engineering at Vetter Pharma-Fertigung. An improved RABS concept called Vetter CleanRoom Technology (V-CRT) combines the advantages of both isolator and RABS technology with fully-automated decontamination of the cleanroom using hydrogen peroxide, says Stauss.

Blow-fill-seal (BFS) technology is another aseptic technology that reduces human intervention. In the automated process, containers are formed, filled, and sealed continuously; BFS is particularly useful for single-dose containers and terminally sterilized drug products (2).

Other new drug-delivery systems, such as prefilled syringes and autoinjectors, and the development of ready-to-fill syringes, vials, and cartridges resulted in more flexible machine platforms for filling different formats. Automated inspection improves quality. In addition, 100% in-process checkweighing prevents product loss, adds Christian Treitel, director, Business Development Pharma, Bosch Packaging Technology.

The use of robots, particularly in fill/finish, continues to expand (3). Robotics were being used at Vetter by the 1990s, notes Stauss. Fully automated lines with robotics are the way of the future, says Treitel, who adds, “Connected industry solutions will bring more intelligence into production. These technologies will help achieve higher productivity, safety, and efficiency.”

Containment for highly potent drug manufacturing

Improvements in containment for working with highly potent drug substances have been driven by the growing use of highly potent APIs in solid-dosage drugs and antibody drug conjugates, as well as a push for better protection of workers and prevention of cross-contamination. Concepts such as occupational exposure bands (OEBs) and occupational exposure limits (OELs) allowed better definition of drug hazards and the containment strategies needed to handle them safely. “OEBs/OELs were used in the United States first, and Europe started to use them around 15 years ago, followed more recently by Asia,” notes Richard Denk, head of the Containment Group at SKAN. European guidelines (4) published in 2014 that require setting permitted daily exposures (PDEs) for each product have led to better data availability as well as an increasing need for containment equipment.

Equipment innovations, such as new technologies for isolators and product transfer systems, have made it easier for manufacturers to operate under low OEL conditions, but there is still room for improvement. Robotics, for one, are poised for implementation in this area and would remove human intervention. In the future, equipment such as fluid-bed dryer or a high-shear mixer
would benefit from being designed for integrated containment rather than being adapted for containment after the fact, suggests Denk.

**Capsule filling**

Capsule filling equipment has progressively obtained increased speeds, higher efficiency, and greater flexibility, along with quality measures such as automated weight control and inspection. "Dosing accuracy has become an essential feature of capsule filling machines," says Treitel.

A significant change in capsule filling has been the type of products filled. "Over the past 10 years, the production of capsules containing multiple products has increased," says Stan Matthews, sales manager of the Processing division at MG America, the US subsidiary of MG2 of Italy, which celebrated its 30th anniversary in its New Jersey headquarters in 2017. "Combinations could include, for example, two different types of pellets, tablet and pellet, or powder and pellet. Machines that are capable of filling powder, pellets, tablets, micro-tablets, and other forms on one capsule filler give manufacturers flexibility. On-board weight-control systems are capable of measuring and controlling the net fill weight of multiple components in each capsule. These changes are driven by continued changes in market demands from consumers and new advances in pharmaceutical development. A new trend in capsule filling technology is the continued push toward continuous manufacturing."

In addition to these new dosage forms, Treitel points to increased yield, using the tamping pin principle as another significant introduction. "Today, powders are dosed on high-performance tamping pin stations with minimal product loss," says Treitel. "Further requirements for capsule filling machines are combination filling, inline weighing systems that offer secure and documented processes, and containment applications in several versions for highly potent active substances. In the past 5–10 years, the focus has been more on small batches and flexible machines, as well as process analytical technology. The pharmaceutical industry is also requesting quicker product change over and shorter cleaning cycles."

**Tableting**

Tablets were a widely used dosage form 40 years ago and still are today, but the equipment used to make them has been transformed in efficiency, quality, and even safety of operation. Increasing automation and connected, "smart" machines are leading the way into the future, which is likely to see greater integration of tableting into continuous solid-dosage processes. *Pharmaceutical Technology Europe* spoke with Matt Bundenthal, direct sales and communications manager at Fette; Alex Bunting, marketing manager at I Holland; Fred Murray, president of KORSCH; Michael Fazio, sales manager, Batch & Continuous Processing Systems at L.B. Bohle; and Dale Natoli, owner and president at Natoli, about how tableting has changed and what they expect for the future.

**PTE:** What have been the most significant changes in tableting in the past 40 years and in the past five or 10 years? What have been the drivers for these changes?

**Murray (KORSCH):** The most significant changes in the world of pharmaceutical tableting is related to advancement in drug-delivery methodologies. The focus on simple, single-layer, immediate release therapies has been replaced by a wide range of innovative delivery platforms including bi-layer, tri-layer, and tablet-in-tablet technologies. Most recently, microchip in tablet technology has been developed to improve compliance with critical therapies. Extended-release products, combination products, and the ability to deliver drug substances exactly where and when they are needed have driven these changes. The equipment manufacturers have responded with specialty machines that facilitate these new tablet formats, both for product development and on a commercial scale.

A second significant change is related to the clear focus on operational efficiencies and flexible equipment. Many years ago, it was not unusual to tour a manufacturing facility and see only a small percentage of the equipment in operation. Today, under significant pricing and competitive pressures, there is a major emphasis on overall operating efficiency, uptime, and product yields. The development of new and innovative drug delivery platforms requires flexible equipment that can produce a wide range of product formats, with fast changeover, for maximum utility. Today, a single tablet compression machine can produce single-layer, bi-layer, tri-layer, and tablet-in-tablet products, in combination with an exchangeable turret capability, to facilitate the production of literally any tablet size and format, with high efficiency.

In the past five years, continuous manufacturing has also been established as a viable alternative to batch processing. For some products, continuous manufacturing technology offers significant advantages for new product development and scale-up, increased product quality, and reduced operator intervention.

**Natoli (Natoli):** The reintroduction of the multi-tip tool has created significant changes in tablet manufacturing. Recent developments in multi-tip tooling include assembly-type punches, which reduce costs by allowing the reuse of punch bodies and repair or replacement of individual punch tips. Vented caps allow the cleaning of punches as an assembled unit and the use of compressed air to remove residual moisture. The development of multi-tip reject verification tools provides the assurance needed by the pharmaceutical industry to validate tablet sizes and weights, making multi-tip tooling a viable option. These technological advances in multi-tip tooling, made within the past 10–15 years, have greatly increased tablet production, which reduces operational costs by saving energy, minimizing labour, and decreasing manufacturing footprints. These benefits are driven by continued pressures from both regulatory bodies and the pharmaceutical industry.

**Bunting (I Holland):** The requirement for higher productivity and efficiency, while maintaining top quality tablets, has become more prevalent during the past 40 years, and innovations have advanced to keep pace with the ever-growing demand driven by developing markets to produce tablets for the masses. Perhaps one of the major
advancements has been multi-tip tooling, which has helped to cater to this demand. Multi-tip tooling has transformed the quantity of tablets produced and it is now considered the most productive form of tablet manufacture where it can be applied. A difference in the past decade is the request for reduced lead times; multi-tip tooling has helped to keep these lead times and allow manufacturers to meet the time-to-market demand.

The influence of developing countries is also a huge driver for change. Due to increasingly strict controls and standards, these countries are aligning with good manufacturing practices (GMP) and regulatory requirements, with production volumes increasing at an astounding rate. The developing world must comply to GMP and regulatory requirements to distribute their products globally, which requires major investment in upgrading manufacturing facilities. I Holland is working in these countries to help them develop their processes and products.

**Bundenthal (Fette):** Changes in tablet press technology can be correlated with the need for a higher degree of control over finished tablet quality, at higher machine speeds; the requirement for presses that can efficaciously compress more challenging formulations; a request from end users for maximum versatility in machine design; and cost-cutting targets, relating to issues such as final yield percentages.

The introduction of pre-compression represents one of the most significant—and useful—changes. It greatly increases overall compression efficacy by helping eliminate entrapped air and reducing the incidence of phenomena such as capping and ‘picking.’ Real-time compression force monitoring and control, and the subsequent ability to automatically reject out-of-spec tablets, has led directly to increased machine speeds, better quality control, and improved yields. Computer-controlled, recipe-driven machines ultimately improved repeatability across batches, with reduced set-up time. The appearance of motorized feeders (and the elimination of ‘open’ or gravity feeders) improved die-filling characteristics. Enhancements to multi-layer functionality, especially for bi-layer tablets, include dynamic first-layer sampling, prevention of cross-contamination, and weight control for individual layers. Inventions such as removable turret assemblies have revolutionized fast changeover. The growth of potent compounds led to high-containment technologies, such as wash-in-place features, glove ports, door interlocks, and rapid transfer ports. And the need for greater operator safety led to additions such as guards and shrouds surrounding turrets, switch-controlled interlocks on access doors, protected discharge chutes, and electro-magnetic brakes.

**Fazio (L.B. Bohle):** Pharma manufacturing has come a long way in terms of mechanical engineering controls. Over the past 15–20 years, we have experienced a trend for highly contained capital equipment; more often, our clients’ formulations include a potent API. Contained oral solid-dosage equipment projects can be sophisticated and challenging because process air handling and mechanical interfaces must be more tightly managed. Contained process equipment serves as protection of both personnel and pharmaceuticals, products alike.

Automation, process control, and process analytical technology (PAT) have also changed, and it has become crucial to ensure high-quality production of pharmaceutical products.

**PTE:** What trends or new developments do you foresee for the near future?

**Bundenthal (Fette):** Tablet press manufacturers continue to design machines that offer ever-increasing versatility. Another trend is integrating tablet presses into continuous manufacturing lines, using control systems with up- and downstream control ‘handshakes.’ In addition, features allow presses to ‘talk’ to and send data to a client’s in-house network.

**Fazio (L.B. Bohle):** Continuous processing is a developing manufacturing platform for the future. We have experienced an increasing number of end-user pharmaceutical companies evaluating their drug candidates on our fully continuous manufacturing line in our Pharmaceutical Technology Center, which was built in 2014. Pharmaceutical manufacturers and the United States Food and Drug Administration sees merit in and support the evolution of pharma manufacturing from batch to continuous because of inherent features, such as smaller footprint, faster and less costly scale up, flexible batch sizes, and improved quality.

**Natoli (Natoli):** As the industry works toward continuous manufacturing, tool-to-die clearances will become even more critical in the near future. These tolerances will necessitate tooling to be engineered to meet the needs of specific powder characteristics and particle sizes. Furthermore, current estimates indicate that only 15–20% of the pharmaceutical industry use multi-tip tooling, and we predict that this usage will increase due to its advantages.

**Bunting (I Holland):** The pressure for shorter lead times and cost efficiency is leading companies to investment in new technologies and processes. On top of this, stringent quality requirements drive the need to improve production from end to end, through durable tablet tooling and the associated maintenance equipment.

The adoption of continuous manufacturing, I think, will be an important trend in the future and one which will help in reducing reaction time and time to market. The challenge, then, is for the upstream and downstream processes to keep up with each other. In the case of a quality tooling manufacturer, we continue to develop even more ways to maximize uptime by producing solutions to problems that compromise the maximum output and yield. I Holland is working toward this goal with the introduction of XDF (eXtended Dwell Flat), a novel, patented, elliptical head form that has been designed to increase dwell time on existing presses without the need for expensive modifications. As the importance of increased productivity continues to grow, XDF can give users higher press speeds for challenging products and formulations, enhancing tablet compaction and cohesion.

Contin. on page 42
A roundtable discussion moderated by Adeline Siew, PhD

Analytical testing, which deals with characterization of raw materials and finished dosage forms, plays an important role in pharmaceutical manufacturing and all phases of drug development. In this roundtable article, industry experts discuss how advances in analytical testing tools have helped address challenges in pharmaceutical analysis. Industry experts include: Guillaume Tremintin, market area manager, Biopharma, Bruker Daltonics; Lisa Newey-Keane, marketing manager, Life Science Sector, Malvern Instruments; Gurmil Gendeh, marketing manager for Pharmaceuticals at Shimadzu; Kyle D’Silva and Simon Cubbon, both Pharma and BioPharma marketing managers at Thermo Fisher Scientific; and Geoffrey Wyatt, president of Wyatt Technology Corporation.

Evolution of analytical tools

PTE: How have the tools for analytical testing of small molecules and biologics evolved over the past 10 years?

Newey-Keane (Malvern): Developments in analytical instrumentation for pharma have largely been addressing three key trends over the past decade. The first is the significant rise in small-molecule generic drug development. This development has increased the requirement for instruments that offer performance-relevant measurements and/or high informational productivity for deformulation and the demonstration of bioequivalence (BE). The second important trend is the shift towards continuous manufacture (CM). The potential ease of scale-up of continuous processes and the ability to file on the basis of full-scale experimental data makes CM particularly interesting for pharma, but its realization relies on effective monitoring and automated control. Here, the ongoing transition of core analytical techniques to fully integrated, online implementation is enabling rapid progress.

Finally, in biologics, we’ve seen growing awareness of the importance and power of orthogonality when it comes to probing the complex nature of the proteins. Identifying the optimal set of biophysical characterization techniques is crucial to comprehensively elucidate critical aspects of behavior, such as stability. Significant progress has been made in this area, and there is now growing awareness of how to complement traditional techniques with newer/less well-established ones, such as differential scanning calorimetry (DSC) and Taylor dispersion analysis (TDA), to maximize understanding and add value.

Wyatt (Wyatt): The tools have gotten more sophisticated, specific, and in some cases, more expensive too. In the never-ending quest to learn more about small molecules and biologics, the United States Food and Drug Administration has encouraged the use of orthogonal testing techniques. As a result, greater insight and understanding of these molecules has been possible.

Tremintin (Bruker): What we have seen evolve is the increased usage of high-resolution accurate-mass instruments (i.e., moving from instruments where you have a limited level of insight to higher resolutions that gives users the ability to confidently determine the identity of a target molecule). On an ultrahigh-resolution quadrupole time of flight (qTOF) mass spectrometer (MS), such as the Bruker maXis qTof, the accurate-mass and the precise relative intensities of the isotopes allows derivation of a molecular formula or a protein monoisotopic mass. On the Fourier transform ion cyclotron resonance (FT-ICR) MS side, such as solarixXR, one can even resolve the hyperfine structure of the isotopic pattern and directly read the molecular formula of the ion being measured. Building confidence and getting deeper insights through high resolution has been the biggest change.

Cubbon (Thermo Fisher Scientific): Two key areas that have contributed to accelerated evolution of biologic characterization have been the widespread adoption of high-resolution accurate mass (HRAM) spectrometry and advancement of software tools that deliver meaningful answers to non-expert users. A decade ago, characterization of biologics demanded expert mass spectrometrists to both acquire and interpret data, typically done manually over days and weeks. Instrument variability and difficulty of operation meant that a high degree of skill was required for the results to be meaningful. Today, platforms such as the Thermo
Scientific Q Exactive BioPharma with Thermo Scientific BioPharma Finder software have democratized mass spectrometry. Software tailored for drug quality attribute monitoring easily transfers this data to actionable knowledge with automated reports, reducing the demand for specialist operators. As well as being easier to use, the systems are also smaller and more affordable than a decade ago. Consequently, we see greater adoption of these technologies, not just in research laboratories, but also further down the drug pipeline in development; in chemistry, manufacturing, and control (CMC); and even in quality control (QC) environments as biologic manufacturers seek to implement multiple attribute monitoring (MAM) methods using HRAM mass spectrometry to replace a host of chromatographic testing methods performed for QC lot release.

**Gendeh (Shimadzu):** We have seen an increasing adoption of ultra-high performance liquid chromatography (UHPLC) and sub-2-micron column chemistries for both small and large molecule analysis that allows faster, better, and higher resolution chromatography. As both small molecule and large molecule become more complex, we have also seen the development and increasing adoption of higher resolution technologies, for example, two-dimensional liquid chromatography (2D-LC) and liquid chromatography combined with mass spectrometry (LC/MS/MS). High-throughput, automated, and streamlined sample preparation that is fully integrated into analytical workflows has been adopted. Moreover, data systems have been adopted that not only integrate LC and LC/MS but the complete portfolio of analytical instrumentation, including spectroscopy, with seamless data analysis and reporting that are in full compliance to existing standards.

**Recent advances**

**PTE:** What are the most significant recent advances in analytical testing tools that have helped speed up and improved the success rate of drug development?

**Tremintin (Bruker):** The most significant recent advances have been high-resolution measurements that enable users to accelerate their protein characterization tasks. Because of the simplicity of the assay, customers can perform measurements upstream in their development. They have better chance of identifying problems on a lead candidate earlier in the development, which avoids spending too much money down alleys that will lead to failure or costly remediation. Users of maXis II have been able to use this type of measurement to detect incorrect glycosylation sites very early in the development at a stage when they are still able to send the molecule back to the molecular engineering department to optimize the molecule before advancing it any further. There also is a renewed interest in MALDI ionization to perform simple characterization tasks.
such identity testing of a recombinant product without the need for a chromatography modality.

D’Silva (Thermo Fisher Scientific): When developing biologics, the biopharmaceutical industry look to achieve full structural insight into their candidate molecules, with high confidence, as fast as possible. They look to fail candidates fast. Technologies such as ion exchange chromatography using pH gradients were first proposed by Genetech in 2009 for profiling of therapeutic protein variants. Since then, unique patented products such as Thermo Scientific CX-1 pH Gradients Buffer Kits have led to a 10-fold reduction in analysis time over conventional salt gradients, dramatically accelerating drug development time.

Understanding the primary structure of a biologic candidate is a critical step performed early in the development process, but also at every stage after. This was traditionally a labour-intensive and time-consuming, 24-hour process to prepare the sample for analysis. Today, we see biopharmaceutical developers able to perform protein sample preparation in 45 minutes and achieve 100% coverage when mapping their drug candidates. The software technology for analyzing peptide digests has also increased its throughput dramatically. The time for biopharmaceutical comparative modification data interpretation can be taken down from two weeks to one day.

Gendeh (Shimadzu): Mass spectrometers have definitely seen the biggest advances in terms of speed, resolution, and sensitivity gain over the past decade. The Shimadzu triple quadrupole mass spectrometer LCMS-8060, for example, delivers high sensitivity, fast scan speed, and fast polarity switching that enable collection of high-quality data and information. Having these features allows big pharma to fail candidates early, fast, and cheaply in preclinical studies, thus accelerating the pace of drug discovery and bringing safer and more efficacious drug candidates to market faster.

Wyatt (Wyatt): The tools we know best are those that we develop. Our DynaPro Plate Reader II (DynaPro PRII) is but one example. Until it came into being, the only way to make a dynamic light scattering (DLS) measurement was to use one-at-a-time, batch measurement techniques in small cuvettes. The measurement required an operator to prepare a sample, pipette it into a cuvette, then place the cuvette in the instrument, close a lid, make a measurement, open the lid, remove the cuvette, and, as the saying goes ‘lather, rinse, and repeat.’

The DynaPro PRII has taken industry standard well plates of 96-, or 384-, or 1536-well formats and enabled them to be used as massively multiple cuvettes. An entire plate of hundreds or thousands of small molecules or other biologics can be pipetted into the wells, the well plate inserted in the instrument, and … that’s it. The technician can walk away and do other work while the instrument makes DLS measurements, ramps temperatures, etc. In fact, the DynaPro PRII enables researchers to perform tasks that were heretofore impossible. The daunting challenge of, for example, screening thousands of samples at different pH levels, or investigating promiscuous inhibitors, is no longer an impediment to making huge numbers of DLS measurements.

Newey-Keane (Malvern): Morphologically-directed Raman spectroscopy (MDRS) is a relatively new technique that combines the capabilities of automated imaging and Raman spectroscopy. It delivers particle size and shape data, along with chemical identification for individual particles in a blend, making it a powerful tool for deformation as well as many other pharmaceutical applications. MDRS data was recently used to establish in-vitro bioequivalence, in lieu of clinical trial data, in the approval of a generic nasal spray application by Apotex, highlighting its value in the time-critical world of generic drug development.

A relatively new addition to the biophysical characterization portfolio is TDA, which provides ultra-low volume, solution-based molecular size measurement. Technology that combines TDA with Poiseuille flow for relative viscosity assessment has been shown to be valuable for robustly identifying drug candidates with a poor developability profile early in the drug development pipeline, thereby saving time and money. TDA extends label-free measurements into highly complex solutions and is able, for example, to detect and size monomeric insulin, even in the presence of its hexameric form.

Finally, our latest technology launch exemplifies the trend of enhancing instrumentation to make it easier for researchers to access robust data for secure and effective decision-making. The MicroCal PEAQ-DSC is a fully-automated differential scanning microcalorimeter that extends the use of DSC—the ‘gold standard’ for protein stability assessment—throughout the development cycle. Key features include: unattended 24-hour operation; automated data analysis; built-in automated cleaning; and self-validation protocols.

Data interpretation

PTE: With so many features and functions on new analytical instruments (such as capabilities to measure various parameters using one equipment), does the industry or the people using them actually understand the concept behind these measurements, how the results are obtained, and how to interpret them correctly?

Wyatt (Wyatt): This is a frightening and very realistic possibility. Too often vendors sacrifice ease-of-use for ‘black boxes’—instruments that simply produce numbers. The researcher has little indication of whether the numbers mean something or whether they may as well be random because there is something wrong in the measurement itself or with the sample preparation. At Wyatt Technology, our customers come to Santa Barbara, CA to participate in Light Scattering University, a course that demystifies light scattering by teaching some of the theory, practice, sample preparation, and data interpretation. The result is that we create a cadre of customers who have an understanding of the powers—as well as the limitations—of the measurements that the instrument makes.

Newey-Keane (Malvern): Given productivity pressures, well-documented skill shortages, and the ever-increasing number of analytical techniques routinely deployed, it's
important to consider what level of understanding is actually optimal. For example, if you are carrying out routine QC, then a highly automated, standard operating procedure-driven, modern instrument with integrated method and data quality checking software can eliminate any need for understanding or interpretation, and will effectively remove any subjectivity in data analysis. Techniques such as laser diffraction have already matured to this point. Indeed, it could be argued that for many industrial applications, modern systems can now be more effectively differentiated on their ability to make their performance accessible than on their performance itself.

Conversely, if you are investigating a more complex concept, such as protein stability, then greater understanding is vital, and orthogonal testing is key. Here, the analytical instrumentation expert understands best the merits and limitations of the technology, but the researcher knows their sample and what information is most useful, so collaboration is vital. Interaction with applications specialists can be incredibly helpful, and the best instrumentation companies invest heavily to develop relevant in-house expertise. However, embedding expertise in instrumentation software is also an important and growing trend that has the potential to greatly enhance the support available to industrial users at the benchtop.

Tremintin (Bruker): It is the responsibility of the instrument manufacturers to deliver companion software solutions that harness the hardware capabilities and enable the users to gain the insights they need. For example, the recently released BioPharma Compass 2.0 software takes high-resolution protein measurements and translates them to actionable information such as a glycosylation profile or degradation levels. Similarly, the matrix-assisted laser desorption/ionization (MALDI) PharmaPulse solution takes 100,000s of measurements and derives possible active ingredients against a defined substrate. This substantially improves the library screening approach by providing high throughput while not requiring any labels.

Gendeh (Shimadzu): Analytical instrument companies such as Shimadzu continuously innovate not only new analytical instruments but also complete solutions that solve challenging real-world problems. Many of the early product and solution conceptualization and development are driven through partnership and collaboration with the industry. These new solutions are initially used by the industry partners or collaborators, who are often people that clearly understand the technology, the results, how to interpret the data, and more importantly, the value the data brings to their work. Over time, these new solutions are improved and packaged into ‘analyzers’ for the mainstream users. As an example, Shimadzu recently released one such ‘complete analyzer’ solution for the biopharmaceutical industry. The Shimadzu Cell Culture Profiling ‘analyzer’ combines optimized and validated UHPLC coupled with a triple quadrupole mass spectrometry method to simultaneously analyzes 95 compounds and metabolites in cell culture supernatant. The multi-parameter data from the LC/MS/MS platform is crucial in the cell culture process development and media optimization to promote cell growth; rebalancing media components and quantities by introducing new media components at variable levels to support continuous manufacturing; to monitor cell development to determine optimal harvest endpoints; or when it comes to development of cost-effective media.

D’Silva (Thermo Fisher Scientific): Traditionally, trying to understand a certain aspect of a complex biologic would require various techniques and painstaking analysis of any data—once you’d managed to acquire it, that is. Ensuring that manufacturers meet the ever increasing challenges that their customers face requires them to listen and develop instrumentation that simplifies analysis, alongside impactful software that drives scientists to their ultimate goal: results.

The Thermo Scientific Q Exactive BioPharma platform, for example, allows scientists to analyze complex biotherapeutics using a single system: from native, intact, and sub-unit mass analysis through to peptide mapping, with minimal training and maintenance. Combined with Thermo Scientific BioPharma Finder integrated software, you have a data collection and interpretation workflow that streamlines scientists’ access to their results, allowing them to make rapid, informed decisions, rather than spend time setting systems up and learning complex software platforms. So, provided scientists have the right tools (no matter how complex they may be), the industry is in good stead to be able to acquire and interpret those all-important results.
Room for improvement

PTE: What areas are still lacking that make analytical testing challenging and what developments can we expect to see in this field over the next five to 10 years?

Tremintin (Bruker): Where you see the most movement is in terms of sample preparation and data processing. The big changes will be bringing more automation to streamline the sample preparation and make it more consistent and less dependent on the skill of the operators. On the back end, it would be to have smarter software that is able to process data faster, more effectively, thus allowing companies to compare larger data sets and derive trends and have feedback on the processes based on analytical results. Additionally, chromatography remains a challenge for some compounds, and so the improvements in ion mobility will add an additional dimension of separation that can help solve problems that challenge conventional chromatography techniques. For example, the Bruker trapped ion mobility separation (TIMS) has enabled the separation of isomers that until now could not be separated.

Gendeh (Shimadzu): Biologics are large and complex molecules, and sample preparation for their characterization and bioanalysis (e.g., absorption, distribution, metabolism, and elimination [ADME]/toxicology) has always been a challenge. We can expect to see more innovation and advancement not only in the automation but also in innovative chemistries to simplify the sample preparation workflows. The Perfinity platform from Shimadzu is one such example that fully automates tryptic digestion and brings sample preparation online with LC-MS. Shimadzu also recently introduced a nano-technology based antibody bioanalysis sample preparation solution called the nSMOL Antibody Bioanalysis Kit. This kit performs selective proteolysis of the antibody Fab region and greatly simplifies and streamlines antibody bioanalysis sample preparation. We expect to see many more similar innovations in nano-technology and micro-fluidic based sample preparation for the biopharmaceutical industry in the next five to 10 years.

Newey-Keane (Malvern): For biologics, the informational need is still being refined, particularly when it comes to biosimilars and the demonstration of BE; and analytical requirements are evolving in tandem with this. Getting more information from each sample remains crucial as this enables information gathering earlier in the drug development pipeline. Robustly identifying the best candidates as early as possible clearly cuts the time and cost of biopharmaceutical development.

The application of orthogonal techniques is bringing significant challenges in terms of data handling. The quantity of data is one issue, but a more taxing one is how to handle what can appear to be divergent data sets. Software platforms that integrate and rationalize data from an optimal set of techniques will be the way forward.

In terms of online implementation, we already have techniques such as laser diffraction particle size analysis that have successfully completed this transition but, over the coming years, others will follow suit. Such instrumentation will need to deliver exemplary reliability as CM matures, but will also be judged on ease of integration as automated control becomes a more routine feature of pharmaceutical processing.

Cubbon (Thermo Fisher Scientific): The list of molecular characterization assays demanded by regulators for biologic drugs is extensive. Typically, more than 30 individual chromatographic or immunoassays are performed to test for critical quality attributes of drug candidates by biologic manufacturers, which is both labour- and time-intensive.

Over the next five years we will see technologies emerging to amalgamate multiple assays into one and simplify the process. An area where this is already being implemented in the area of multiple attribute monitoring (MAM) using HRAM—a single workflow capable of replacing multiple individual steps. Several companies already have drug candidates in late-stage development using this workflow. In 10 years, this technology will move from a laboratory process off-line, to being beside the bioreactor at/on-line to inform the manufacturer immediately of the structural properties of their candidate molecules.

Wyatt: I believe that artificial intelligence (AI) will lend its benefits to our industry in the not-too-distant future. With more data being generated, it may become harder to distill information from the data. AI holds the promise of aiding the data interpretation and becoming wiser, the more data to which it’s exposed.

Drug Product Manufacturing — cont. from page 37

Murray (KORSCH): These trends of more complex drug delivery platforms, and an increased emphasis on operating efficiencies will continue. The use of continuous process technology will also be more widely used and accepted. From an equipment perspective, tablet compression machines are going to become smarter and more connected. They will self-diagnose, include on-board help systems to guide the user through every aspect of the operation and maintenance, and be fully integrated to central SCADA [supervisory control and data acquisition] and manufacturing execution systems. They will monitor and report on operating efficiency, and leverage new technologies to permit remote support by service experts.

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Packaging Improves Medication Adherence

A staggering percentage of people do not take their medication correctly, but pharmaceutical packaging aims to improve patient compliance using new technology to address reasons for non-adherence.

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Despite decades of effort to design packaging that helps people take the right dose of the right prescription at the right time, the number of prescriptions that are not taken as directed has been stuck around 50% since at least 1993 (1, 2). Sometimes the reason for lack of compliance, or what increasingly is referred to as “adherence” is financial. The patient can’t afford the medication, so the prescription goes unfilled. But more often, lack of compliance is due to difficulty accessing and dispensing the proper dose and remembering dosing times.

“The severity of medication non-adherence has been so well documented that the healthcare industry is taking a much more serious look at how to improve patient behaviour,” reports Ward Smith, director of Marketing at Keystone Folding Box Co. “People are starting to recognize compliance is a really important factor in determining the outcome for the patient,” agrees Graham Reynolds, vice-president and general manager of Global Biologics at West. Reynolds explains, “Non-adherence has significant financial consequences. The patient ends up in the hospital or back in the hospital and puts additional strain on the healthcare system. From a pharmaceutical company perspective, non-adherence is widely recognized as a cause for a significant loss of revenue; a number recently estimated at $600 billion.”

Solid-dosage compliance packaging

To improve adherence, many compliance packaging designs have been introduced. The Pharma Compliance Pack from August Faller Group features an integrated sliding mechanism (see Figure 1). As doses are taken, perforated tabs are removed to provide access to the next dose(s) on the blister card. “The patient can directly see which tablets he/she already took,” says Tanja Feldmüller, head of Marketing and Innovation at August Faller.

Keystone’s child-resistant Key-Pak and Ecoslide-RX packaging also calendarize medication dosing. “This type of packaging has been documented to improve medication adherence,” says Smith. He notes, however, that it appears to be less effective for patients on multiple medications. “…if a patient takes more than five medications; all of the packages (blisters and bottles) can become overwhelming,” he explains.

Some patients on multiple medications resort to pill minders with compartments for each day and/or various times of day. However, this solution can be problematic. Filling errors can result in missed doses or overdoses. Sensitive medications can be exposed to detrimental environmental conditions, and product information is separated from the dose.

“No one solution seems to exist to solve non-adherence,” says Smith. As a result, there’s growing interest in more holistic approaches that integrate packaging with interactive devices, software, rewards programmes, and personalized support.

An example of a more holistic approach is a smart, wireless pill bottle from AdhereTech. Used primarily for specialty medications like cancer drugs, each bottle contains a wireless cellular chip and numerous sensors. It collects adherence data in real-time, analyzes the information, and populates a secure dashboard. If a dose is missed, the system sends an automated alert via phone call or text message to the patient, caregiver, or pharmacist. The bottle itself offers alerts via blinking lights or audible chimes.

The smart bottles are child-resistant and supplied free to patients and pharmacies through programmes sponsored by pharmaceutical companies. When the prescription is dispensed, the pharmacist inputs the necessary information into the system, and the bottle is ready for use. Sensors detect when the bottle is opened and reclosed and can monitor other attributes such as the contents of the bottle, battery level, and signal strength. “If the bottle is in an area with no cellular coverage, the bottle holds data on up to 180 doses for later transmission,” says Josh Stein, CEO and cofounder of AdhereTech. The pharmacist can access the compliance dashboard and intervene if the patient needs help. Results to date show the wireless pill bottle boosts adherence up to 20%, while persistence (the time on therapy) jumps to 30%.
With the iCap, the pharmaceutical company sees firsthand when a patient takes a medication. "That knowledge helps fix side effects and other issues and determine why a drug works for some and not others," says Larry Twersky, CEO of TimerCap. As a result, healthcare providers have a better chance of knowing how a particular drug will work for a patient.

Smart labels equipped with a near-field communication (NFC) chip and/or QR code also can support adherence (see Figure 2). "NFC has multiple advantages compared to a QR code, such as a very high security level for authentication purposes, the possibility to individually change or protect specific information or the enhanced convenience to read the tag with your Smartphone," says Gene Dul, president of Schreiner MediPharm US. “However, the advantage of including both [code and chip] is that online information is also available to those users that do not have an NFC-enabled Smartphone available.” Labels also can be equipped with other features such as anti-slip varnish, hologram for authentication, or a temperature indicator that changes colour when a certain ambient temperature is reached.

Medication management tools from Compliance Meds Technologies (CMT) can be tailored to the needs of various settings such as senior care, addiction treatment, and clinical trials. Tools include the CleverCap LITE; the CleverCap PRO; an optional mobile app called Companion App CMT; and secure, cloud-based reporting/analytics portals. The devices are distributed through the pharmacy, incorporated into existing medication vials/bottles, shipped directly to enrolled patients, or given out by a participating doctor.

Moses Zonana, founder and CEO of CMT, described how the integrated technology works. “The CleverCap PRO … detects when a pill is dispensed and can control the dose, ensuring the patient receives the right dose at the right time. The information is automatically transmitted through cellular 3G networks into the CMT Reporting, Analytics, and Engagement System. Devices can generate visual and sound alerts at predefined timeframes or operate under silent mode. The CleverCap LITE does everything the CleverCap PRO does except it doesn’t actually track at the individual pill level of granularity or control dosage. It tracks when the vial/bottle is accessed or is not properly reclosed to provide an extra layer of security.

“We have observed regimen adherence levels of 95% using CleverCap PRO and regimen adherence levels of 96% using CleverCap LITE. In the majority of our programmes, there is an intervention layer in addition to the technology layer, which allows us to obtain those types of successful results. These interventions may incorporate nurse support groups and incentives for better medication habits.”

Smart and holistic systems

Adherence-enhancing smart systems for products other than solid-dosage forms also exist. Options include Eovin’s Intuityject self-injector (3). A digital monitoring system from Kali Care integrated with dispensing technology from Aptar Pharma supports ophthalmic clinical trials (4).

A similar partnership between HealthFactors and Koronis Biomedical Technologies focuses on capturing and sharing inhaler use data in real-time to improve outcomes for people with respiratory conditions. In some cases, changing the delivery format may improve adherence, particularly for diseases such as schizophrenia where 30–40% of relapses stem from non-compliance. A matchstick-size implantable device, recently patented by Delpor, enables the sustained release of antipsychotics and other molecules and thereby lengthens the interval between doses to several months. The sustained release results in a smoother pharmacokinetic profile and enhanced safety and tolerability. Initial applications for Delpor’s Prozor technology are likely to be a six-month formulation of risperidone and a three-month formulation of olanzapine (5).

Holistic solutions often expand interaction with patients to include simulation, education, and incentives. “As treatment regimens become
complex, using engaging technology will help with patient adherence,” predicts Teek Dwivedi, CEO of Ehave, a provider of software that supports planning, treatment, and capture of patient- and clinician-reported outcomes. The patient interacts with Ehave Connect via a dashboard and a mobile app, which help track adherence, symptoms, and side effects. There’s also an incentive component. Dwivedi explains: “The incentivization comes in two forms: a daily goal to complete a task and achievement badges. Our strategy is to treat patient-reported outcomes similar to how activity trackers motivate individuals to reach their exercise goals.”

Improving outcomes via personalized coaching is the driver behind a partnership between Fit4D, a provider of diabetes patient engagement software, and Glooko, a global diabetes data management company. “Glooko’s mobile app enables people with diabetes to automatically sync their blood glucose data from over 95% of the blood glucose meters, continuous glucose monitors, and insulin pumps available on formulary and then augment that data with food, exercise, and medication data,” says David Weingard, CEO of Fit4D. “That data is then made available to Fit4D coaches through the Glooko Population Tracker.”

The impact of the combined technologies can be significant. Weingard reports, “Patients who were engaged in the Fit4D programme saw an increased incremental fill rate compared to the control group. Fit4D was able to improve adherence by 20% with non-adherent patients, resulting in better health outcomes and a 3X ROI [return on investment] for the client …. With the addition of data from the Glooko app, Fit4D certified diabetes educators will be able to improve adherence even more because they can reach out to patients proactively based on blood sugar levels to give them timely and relevant guidance.”

Something already in many homes, the Amazon Echo smart speaker, could become an adherence tool. A partnership between Orbita, a provider of voice-first software for connected home healthcare, and ERT, a developer of the EXPERT technology platform for clinical trial data collection, processing, and analysis, is improving how data are captured from participants. “We’re excited … to give patients the power of voice—an important, emerging technology—to complete surveys, verify completion of care pathway tasks, and report health concerns, all of which enables pharmaceutical researchers to move ahead in their clinical development programmes quickly and with confidence,” says Andrea Valente, executive vice-president and chief development officer at ERT. With the combined solution, study coordinators can create and manage care plans, and patients and family members can review and manage care tasks via voice as well as mobile phone or web environments (6).

A Smart Injection Pad Training System from Noble, a specialist in biopharma onboarding and device training, helps patients learn how to use self-injectors correctly. A needleless device and pressure-sensing touch pad detect errors and alert the patient. The Smart Injection Pad also helps collect patient data via onboard NFC, Bluetooth, and wi-fi connectivity that enables interface with devices such as smartphones. These data can identify patients who need extra support. “The Smart Injection Pad improves the patient onboarding experience, which is often the most critical time period for establishing adherent behaviours and patient satisfaction,” notes Joe Reynolds, research manager at Noble. The simulation overcomes anxiety associated with self-injection and reduces chances that a patient will avoid starting treatment or discontinue it.

West is collaborating with HealthPrize Technologies to integrate West’s self-injection technologies with their Software-as-a-Service medication adherence and patient engagement platform. HealthPrize rewards can be monetary, educational, or appeal to the patient’s competitive nature. Results can be dramatic. In one demonstration, rewards improved refill rates by 50%.

Although rewards can have a positive impact on adherence, Reynolds notes good scores start with an understanding of the needs and concerns of the patient. “You really have to … design the whole system from the point of view of optimizing adherence,” says Reynolds. Is the patient worried about the pain of self-injection? The complexity of the device? “The more the process can minimize stress, worry, and pain, the better the adherence is likely to be,” he says. However, he notes, even the most adherence-enhancing design needs to be accompanied by training and onboarding.

A good example of whole system design is West’s SmartDose platform. The wearable electronic injector delivers injections slowly to reduce injection-associated pain and can support lengthening the time interval between doses. A multisensory training system, being developed in collaboration with Noble, will talk patients through the process from carton opening to completion of the injection. “It’s a good example of all factors coming together to provide a drug-delivery system that meets the needs of newer drugs, addresses patient concerns, and hopefully helps improve adherence,” concludes Reynolds.

References
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The ROB 50 is a robotic system for handling of tablet containers, to close the gap between the tablet press and film coating process. As indicated initially, L.B. Bohle developed this system for the continuous production line. However, the ROB 50 can also automate the product transfers in batch environment. In this case, the ROB 50 is also available for larger container sizes.

In addition, in case of long process times for the film coating process, the ROB 50 can serve coaters positioned next to each other in an alternating manner. Customized versions with an additional degree of freedom are available, too. For higher throughput or long relaxation times, L.B. Bohle also has solutions to automate the storage rack.

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Watson-Marlow Fluid Technology Group (WMFTG) has unveiled its innovative Quantum peristaltic pump with patented ReNu SU Technology cartridge. Engineered by the world leader in peristaltic innovation, Quantum sets the new standard for high-pressure feed pumps in SU tangential flow filtration (TFF), virus filtration (VF) and high-performance liquid chromatography (HPLC). Quantum represents a step-change in pump technology for bioprocessing by enabling higher downstream process yields throughout the pressure range, delivering virtually pulse free linear flow, lowest shear, and easy validation aligned with BPOG guidelines.

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Our manufacturing facility is inspected regularly by various agencies. There are differences between these inspections, but one constant is that we always kick off with an opening presentation. Do you have any suggestions how we can make our opening presentations most effective?

This is an astute observation, and it is indeed important to give the opening presentation much thought. In fact, the opening presentation is the only time when a company is in control during an inspection and is the opportunity for the company to present the information that they consider important.

Let us consider what makes an opening presentation stand out and achieve its objectives. The main objective should be to present the company and facility being inspected in a positive light. Think of the inspectors as customers; ask yourself the following so you may provide the essential information they seek: What do they want to know? Why are they here?

The following are some practical suggestions to prepare for the presentation:

- The presentation should be complete, reviewed, and approved weeks before the inspection. Trying to improve it minutes before the inspectors arrive is never a good idea. Mostly companies use programmes such as Microsoft PowerPoint, which works well, so long as presentations do not become overwhelmed by unnecessary transitions or effects.
- The length of the presentation should not exceed 30 minutes, if possible. It is not uncommon for inspectors to cut presentations short if they think that time is being wasted. One should allocate three minutes per slide, considering time for potential questions to be addressed. While additional slides can be prepared, they should be kept as backup.
- Technology should be thoroughly checked the day before the inspection to ensure that all is in working order. A back-up copy of the presentation should be ready on a portable device, just in case.
- The presenter can be the head of quality, the site manager, or the sales manager. The exact title or role of the chosen presenter is less important than their competency and confidence when discussing the contents of the presentation. Far too often, presenters click through a slideshow without portraying passion or genuine interest.

Presenters should communicate that they are proud of their plants, quality systems, and place of work. Inspectors will pick up on a lack of enthusiasm and that often impacts inspection results.

After the inspectors have arrived, the presentation can begin. A colour copy of the slides (one slide per page) should be printed and be available for inspectors so that they can take notes and make annotations.

A presentation’s contents should include a site layout plan, one to two key organizational charts, key operations on site, and inspection history. But what about the quality system? As one inspector put it: ‘usually the level of quality is inversely proportional to the number of times quality is mentioned in the opening presentation.’

In recent years, inspectors’ time is at a premium. It is key that only essential, pertinent facts and figures are included in the slides shown, presenting a company’s commendable aspects, people, and systems. If your presentation follows these suggestions, respecting the time and needs of inspectors, you should see happy inspectors beginning their work, which will ideally lead to a positive inspection.

The opening presentation gives the company a chance to put their best foot forward, according to Siegfried Schmitt, principal at PAREXEL.
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