JULY 2023 Volume 35 Number 7

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July 2023

Advancing Development & Manufacturing
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NOTE FROM THE CEO

Drug Pricing's Static Changes

Prescription drug patent exclusivity was extended during Hatch-Waxman Act's convoluted negotiations to increase generic drug access and overall drug affordability. Later, around 2009, part of the prescription price increase allowance and extension argument for biologics was based on what was termed a "looming patent cliff." Patent protection is now 20 years from date of filing in the United States, but market exclusivity appears to average a little over 13 years in practice (1). Following Hatch–Waxman, the generic products' share of total prescriptions in the US increased from 36% in 1994 to 90% in 2019 (1). Loss of income due to lower pricing of generics estimated at US$185 billion was evenly balanced by price hikes for prescription drugs of US$187 billion (2). This helped create the conditions we face today where once again there is a prescription drug price crisis because 10% of prescriptions have an average cost of US$20 a day and account for 80% of all prescription drug spending, despite the fact that (largely due to Hatch-Waxman) 90% of prescriptions are generics that cost on average, US$1 a day (2).

To revisit the cost issue, President Biden signed the Inflation Reduction Act (IRA), while pharmaceuticals reportedly face, once again, a looming patent cliff (3). With regard to IRA, biopharma executives describe the Medicare drug price negotiation process "as basically enforced price fixing on certain established medicines and that it will affect how companies allocate capital and force hard decisions on investments in the very costly process of drug testing and production" (4).

However, at the 2023 BIO conference in Boston, FDA Commissioner Robert Califf stated that drug prices are too high, and that "FDA officials are providing technical assistance to their counterparts at the federal Centers for Medicare & Medicaid Services as they prepare to negotiate drug prices with companies for the first time" (5). On limiting reimbursements for accelerated clinical trials, Califf went on to say, "'sounds like common sense to me' for government health insurers to pay less for drugs that haven't yet been fully approved. 'If I had a basketball that's probably going to stay inflated and it looks pretty good in the store but we don't really know, you wouldn't really pay the same as you would for a first-rate basketball' guaranteed to stay firm" (5).

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EDITOR'S COMMENT

New Deal on the Horizon

Since 2020 and the United Kingdom's exit from the European Union, Britain has been locked out of the Horizon research programme, despite agreements being in place for associate membership, as arguments over the Northern Ireland protocol persisted. However, in March 2023, after the implementation of the Windsor framework, talks between the UK and EU about the association with the programme resumed, culminating in reports of a draft deal being reached on 5 July (1).

This draft deal is reportedly now under consideration by the UK's Prime Minister, Rishi Sunak (1). Sunak is being urged to finalise the deal to ensure the scientific community in the UK can regain the advantages of the Horizon programme, such as funding and leading multi-country research consortia.

"Outside Horizon Europe, the UK is in real danger of ceding our hard-won position in the global R&D hierarchy and becoming less attractive as a research partner and less attractive for foreign direct investment," stressed Andy Slaughter, member of parliament for Hammersmith in a parliamentary debate on the topic of Horizon Europe (2). "As part of Horizon Europe, the UK can influence the future direction of billions of pounds worth of research investment to more closely align with UK strategic priorities."

Cost has been a factor delaying the draft deal. Although not required to pay participation fees for the two missed years, the UK government has requested further discounts due to the fact that researchers and businesses in the country have been weakened when compared with EU counterparts from missing out on collaborative opportunities. Additionally, the UK government have pushed back on the matter of how much research funding the country will receive in return for its input into the programme (3).

Officially, talks are still ongoing with no confirmed deal struck yet—at the time of writing—so, for now, a return to a closer scientific research relationship between the UK and the EU remains just out of reach on the horizon.

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Improvements to EMA's PRIME Designation Scheme

Changes to PRIME scheme are set to drive greater harmonization across major pharmaceutical markets.

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The Priority Medicines (PRIME) scheme focuses on the development of novel medicines that address an unmet medical need, such as those that offer a major therapeutic advantage over existing treatments, or which benefit patients with no current treatment options for their disease (1). Launched in 2016, the European Medicines Agency (EMA) developed PRIME in line with the European Commission's (EC) priorities and the common strategy to 2020 for the European medicines regulatory network (1).

PRIME is an entirely voluntary scheme that aims to optimize development plans and speed up evaluations through early and enhanced interaction between the regulator and developers of promising medicines with a view to achieving expedited marketing authorization approval (MAA) in the European Union (EU). The scheme gives medicine manufacturers an opportunity to open communication with EMA's Committee for Medicinal Products for Human Use (CHMP), or the Committee on Advanced Therapies (CAT) early in the development process (2). Proof of a potential drug's efficacy must be provided from preliminary clinical evidence which clearly demonstrates that the medicine has the potential to provide a clinically meaningful improvement in effectiveness or that it can improve patient mortality/morbidity rates.

From March 2016 to June 2021, a total of 18 medicines that had received PRIME support were approved in the EU. Among these, 10 received a conditional marketing authorization (CMA), facilitating earlier access to the market; seven are Advanced Therapy Medicinal Products (ATMPs), which have the potential to reshape the treatment of a wide range of conditions, and 16 are aimed at rare diseases (3). In December 2021, the first academia-led development of an ATMP, intended to treat relapsed or refractory acute lymphoblastic leukaemia in adults over 25 years old, was granted PRIME eligibility (3). EMA strongly encourages all academic developers to interact with regulatory authorities to obtain early support for the development and clinical translation of their products.

As of May 2022, the overall approval rate for PRIME sat at 25% of applications, 40% of which were granted to small and medium-sized enterprises (SMEs), 61% to others, and 4% to academia; while in terms of therapeutic area, oncology gained the highest number of approvals at 29% (4). According to the Regulatory Affairs Professionals Society, "PRIME medicines represent significant progress in their therapeutic areas as they include innovative technologies such as CAR T-cells therapies, one-time curative gene therapies, treatments for rare cancers, and a vaccine to protect against the Ebola virus" (5).

Improvements to the PRIME pathway

In 2022, EMA published a report analysing the experiences of the first five years of the scheme, along with lessons learned (6). Accordingly, the report highlighted some opportunities for further strengthening the scheme, which aims to "facilitate and accelerate the generation of robust and relevant evidence for the evaluation of a MAA, which will give patients earlier access to transformative treatments that can make a real difference" (6). The measures include:

1. Regulatory roadmap and development tracker. A roadmap for each PRIME-designated product is being established alongside a product development tracker to optimize the early scientific and regulatory support provided to sponsors with promising medicines in the scheme. Starting as a pilot from March 2023, the roadmap and tracker will replace the PRIME annual update for any products that have not yet been discussed in a kick-off meeting. Under the new guidelines, applicants are required by EMA to maintain and update the regulatory roadmap and development tracker which

includes information on planned regulatory submissions and interactions with regulators. The roadmap includes plans for scientific advice/protocol assistance requests and other regulatory interactions, with applicants urged to consider feedback received from regulators, while the development tracker aims to facilitate the efficient tracking of critical development aspects which may arise during the kick-off meeting or subsequent product development (7). The guidance states that "both tools will facilitate the continuous dialogue between regulators and developers as the progress of the development is continuously monitored and as critical aspects for further discussion can be identified throughout the development process" (8).

It is hoped that improvements to the PRIME scheme will help drive greater harmonization across major pharmaceutical markets.

2. Expedited scientific advice. Expedited scientific advice can now be provided for PRIME designated products in instances where there are issues with a specific development programme that has already received comprehensive initial advice. To qualify for expedited scientific advice, the new guidance states that all the following criteria must be met:

- The initial scientific advice procedure has already been sought on the overall development (in the PRIME indication), that is the request is for follow-up advice.
- The advice concerns issues with a specific, well-defined scope (not limited to a single quality/non-clinical/clinical discipline).
- The advice is justifiably required more urgently than the standard scientific advice timelines allow (8).

The expedited scientific advice feature is being tested in a 12-month pilot that will run until March 2024. According to EMA, the scientific advice pilot programme is "meant to help significantly expedite the ability of sponsors to get answers to key queries from the agency in a faster timeframe" (8).

3. Submission readiness meetings. EMA offers a submission readiness meeting with the developer approximately 9–12 months ahead of the applicant submitting their MAA for purposes of discussing the development status and dossier maturity, application type, requirements for post-marketing evidence generation, and potential regulatory challenges (9). Prospective applicants would also be expected to present mature plans for post-marketing evidence generation, as applicable. According to the updated guidance, "applicants are asked to contact their PRIME scientific coordinator about 15 months before their expected application submission date to set up a submission readiness meeting with the PRIME Rapporteur and the assessment team, relevant national experts, as well as the EMA product team" (8).

Anticipated outcomes

The experience gained during the COVID-19 pandemic has given EMA greater insight into the types of tools and features that would better assist the acceleration, development, and approval of life-saving medicines. As a result, the new features aimed at bolstering the PRIME scheme are designed to address the perceived shortfalls in tools and support mechanisms needed to enhance and expedite the innovation and development process.

Furthermore, the changes also bring the PRIME scheme into closer alignment with the United Kingdom's (UK) Innovation Licensing and Access Pathway (ILAP), which was initiated in 2021, and is sponsored by the Medicines and Healthcare Product's Regulatory Agency (MHRA). The UK's ILAP initiative more closely mirrors the United States Food and Drug Administration's Fast-Track process, which enables rolling reviews and allows applicants to submit completed sections for review, rather than waiting until the entire application is complete (10).

With the improvements to the PRIME scheme brought about in 2023, it is hoped that medicine developers throughout the EU can expect a more transparent and easier drug development process, thereby benefiting patients with life-threatening illnesses to have earlier access to medicines. It is also hoped that improvements to the PRIME scheme will help drive greater harmonization across major pharmaceutical markets with regard to scientific advice and regulatory support for innovative products (10).

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Gaining a Deeper Understanding of Aseptic Needs

To overcome the challenges of the widening range and scope of products that require aseptic processing and the evolving regulatory landscape in this field, companies should deepen their knowledge base on best practices.

Felicity Thomas

Parenteral drug delivery is a common and useful option for drug developers and manufacturers when dealing with substances that have poor bioavailability, low solubility, or a narrow therapeutic index. According to research, the proportion of parenterally administered drugs in the pipeline is rising, which is mostly attributed to the growth in biologics (1).

Any drug product that is to be introduced to the patient via a parenteral route must be sterile as the patient's natural defence system is bypassed. However, terminal sterilization methods involving heat are not always applicable or suitable.

"Aseptic manufacturing is needed for dosage routes that are more targeted than oral ingestion," specifies Waiken Wong, manager, Product Development Engineering, Woodstock Sterile Solutions. "Those entry points are more vulnerable to microbial intrusion, so maintaining sterility of those drug products through aseptic manufacturing is critically important for patient safety."

Assuring sterility

"Sterile products need to be manufactured with considerable robustness and assurance of sterility," continues Tim Sandle, head of GxP compliance and sterility assurance at Bio Products Laboratory (BPL) in Elstree, United Kingdom. "With the types of sterile products, aseptic processing presents the highest risk area of pharmaceutical manufacturing because the drug product in the final container cannot be subjected to any additional sterilization treatment (as any additional processing would damage the product). This designation includes many complex drug products, including ophthalmic suspensions, sterile injectables, reconstituted lyophilized powders for injection, and aqueous-based aerosols for inhalation. Therefore, considerable attention needs to be paid to the design and control of the filling and dispensing process."

There are multiple points at which contamination can infiltrate a drug product and, hence, put the drug product's integrity at risk. The importance of aseptic formulation and manufacturing begins with sterile filtration, points out Sandle, in which companies must ensure the filtration controls are in place to protect the filter integrity and control the filtration process within its validated state. Then, careful sterilization of containers and the maintenance of a filling environment that meets relevant regulatory requirements is critical, he adds.

"The filling environment is at a particular risk from microbial contamination, and the product needs to be protected by barrier technology (ideally through an isolator subjected to a decontamination cycle) and by the maintenance of unidirectional airflow," Sandle says. "Any incursion into the filling zone is a considerable risk,

along with any activity that disturbs 'first air' (such as the use of gloveports on an isolator) and, therefore, these activities need to be understood and risk assessed."

Additionally, there is a preference within industry to work with larger batch sizes, which can lead to certain sterility complications. "An important control element is time, and this can affect everything from the validation of sterile filtration to the length of the filling period, which will require qualifying through media fills. In designing media fills (or 'aseptic simulations'), it is important that all worst-case conditions have been evaluated, including the different types of interventions and the frequency at which they are conducted," Sandle states.

"Companies that have a well-developed infrastructure for formulation and manufacturing can easily scale operations to meet the needs of complex drug products and larger batch sizes," remarks Wong.

Regulatory revisions

Regulatory bodies have set out numerous guidance documents on the matter of aseptic processing, to help chaperone industry toward best practices. Recently, the European Union's good manufacturing practice (GMP) Annex 1 guidance was revised to improve clarity and extend the scope of the products included within the guidelines (2).

"When addressing any changes to regulatory guidance, the first point must be to clearly understand the intent of the changes, and more specifically what has actually been changed," emphasizes Andy Whittard, managing director, Cherwell. "This is where easy-to-use comparisons between old and new can be informative in focusing on those elements that could have the biggest impact to manufacturers' processes and facilities."

For Helen Sauter, director Quality Assurance, Vetter, to ensure compliance, pharmaceutical and biotech companies, along with contract development and manufacturing organizations (CDMOs), need to view the aseptic process as a collection of interdisciplinary tasks. "Enhanced process understanding is a key element of the revised Annex 1," she says. "Therefore, risks must be well understood, and it is important to talk to all relevant subject matter experts about the requirements, any gaps, or needs prior to a successful implementation."

Generally speaking, there are key challenges for pharma and biotech companies described in the revised Annex 1 guidance, Sauter continues. "A major requirement is the implementation of a contamination control strategy (CCS)," she states. "The Annex 1 document says to implement a CCS across the facility, which can pose a major obstacle for some companies. Although this requirement is not new, it is now more formal and detailed, leaving less room for interpretation and expecting all companies to have their CCS in place."

The greater focus on a broader level of risk assessment and strategy is considered critical to the Annex 1 revisions by Whittard. "The establishment of a CCS that takes a holistic approach will be the foundation from which all decisions will be driven," he specifies.

"Overall, it is beneficial to call for multiple viewpoints, such as insights from external conferences and authorities to navigate and best interpret the regulations," confirms Sauter. "A variety of perspectives gives a more comprehensive evaluation of what the revised Annex 1 guidance requires."

Sandle points out that the changes to Annex 1 were extensive. "One important aspect is with harnessing the best available technologies to exclude personnel from any direct interaction with the product," he says. "Other important sections relate to sterilization methods, cleanroom classification and control, and cleaning and disinfection."

As a result of the revised Annex 1 guidance, CDMOs are under greater pressure to increase their inspection compliance, notes Brian Korson, director of Finishing, Grand River Aseptic Manufacturing. "New inspection equipment and technology increases inspection capabilities and quality results, while decreasing time out of refrigeration, which is a big win for pharma manufacturing," he adds. "It is imperative that CDMOs take the steps to have the right processes and equipment in place to supply patients with safe and effective products."

The right equipment

"There are several technologies available for use in development and aseptic production," explains Stefan Kuehnhold, director Pharmaceutical Production, Langenargen Site, Vetter. "These options include the classic isolator technology, which is a closed system, as well as the restricted access barrier system (RABS). Every system has its advantages, and it is up to each company to choose the right technology for its specific purpose."

Deciding between RABS and isolators is the first choice, according to Sandle. "Here, RABS is the minimum standard; although, within the RABS paradigm, there are 'closed' and 'open' variants (with the 'closed' versions being superior as the risk of surrounding room air ingress is lowered)," he says.

"Isolators are superior because they provide a complete barrier, and they can be subject to biodecontamination through an automated disinfection process," Sandle continues. "A complexity remains in that product contact parts need to be subjected to a separate sterilization process (including filling needles and stopper bowls)."

However, both RABS and isolators have a weakness with potential air leakage—a risk that is particularly high with the gloveport gauntlets, Sandle explains. "Systems that can be fully automated and do away with gauntlets entirely (that is robotic systems) are optimal," he affirms.

Focusing on inspection technologies, Korson reveals that there are a variety of options available that can help to support increased compliance in aseptic manufacturing. "Fully automated inspection solutions use innovative

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Frontrunner in Therapies for Complement-Mediated Diseases

A novel complement therapeutic CTx001 offers a novel approach to treating geographic atrophy.

Bianca Piachaud-Moustakis is a lead writer at PharmaVision.

Complement Therapeutics (CTx) is a Germany-based preclinical stage biotechnology company focusing on the R&D of novel therapeutic approaches to address unmet needs in disorders that affect the body's immune system, known as the complement cascade. The complement cascade is a part of the immune system that enhances (or complements) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane (1). When activated by one of several triggers, the complement system works in conjunction with other components of the immune system to clear invading pathogens (1).

Based on the research of the company's founders, Simon Clark, Paul Bishop, and Richard Unwin from the University of Manchester, CTx aims to develop innovative and effective therapeutics to address unmet needs in complement-mediated diseases, particularly in the fields of age-related macular degeneration (AMD), kidney disease, and various haematological conditions. Through an extensive programme of translational research, the scientists have gained powerful new insights into the ways the complement cascade works and how it is dysregulated in AMD.

Founded in 2020, CTx has subsidiaries in the United Kingdom (UK), operating as Complement Therapeutics Ltd, and in the United States (US), trading as Complement Therapeutics Inc., as well as research laboratories in Stevenage, UK.

Research conducted by Tracxn Technologies indicates that CTx ranks fourth among 94 active competitors (2). CTx's key competitors include: CureVac, a Germany-based biopharmaceutical company that develops messenger RNA (mRNA)-based therapeutics focused on prophylactic vaccines, cancer immunotherapies, and molecular therapies. CureVac was the world's first company to successfully use mRNA for medical purposes (3); Rezolute Inc. (formerly Antriabio), a US-based biopharmaceutical company specialized in the development of drugs for metabolic and orphan diseases. A leading candidate under development is a plasma kallikrein inhibitor (PKI) designed to treat diabetic macular oedema (DME). This oral therapy, formulated to be administered once a day, is designed to reduce inflammation and vascular leakage caused by DME through targeting the kallikrein-kinin system (4); and Visus Therapeutics Inc., a US-based clinical-stage pharmaceutical company that specializes in developing therapeutic solutions for vision care. One of the company's flagship products includes VT-1051, a novel, injectable, sustained-release delivery system that delivers a Ciliary neurotrophic factor (CNTF) analogue and a FAS/TNF-α inhibitor which has the potential to preserve photoreceptors, prevent programmed cell death, and improve vision in patients suffering from geographic atrophy (GA) (5).

Investor funding

CTx was spun out of the University of Manchester and has raised a total of €77 million over three rounds of financing according to data derived from Crunchbase (6). In 2021, CTx secured initial seed funding from BioGeneration Ventures (BGV), subsequently receiving a further €5 million in Round 2 seed funding from BGV and Forbion in February 2022. With this funding, CTx advanced its lead investigational product, CTx001 through pre-clinical proof-of-concept, and secured an Innovation Passport from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (7). CTx001 is a highly innovative adeno-associated virus (AAV) gene therapy designed for the treatment of GA secondary to dry AMD, which is a leading cause of blindness, and for which no licensed treatment currently exists.

Through the financing received from BGV and Forbion, CTx also initiated a one-year, natural history non-interventional i-GAIN (investigating Geographic Atrophy Insights) study in patients who have a confirmed diagnosis of GA in one or both eyes in the UK (8). The study is designed to evaluate the relationship between genetics, blood biomarkers, and phenotypic changes in the eye of people with GA. Data derived from the

i-GAIN study is designed to support the clinical development planning for CTx001, particularly in enabling the identification and stratification of patients with complement-driven AMD for future interventional studies (8).

More recently in April 2023, CTx announced that it had successfully secured an additional €72 million in Series A financing. The third round of financing was led by Gimv, a Belgian-based private equity and venture capital fund, co-led by Forbion (as an existing investor), and further joined by BGV, Panakès Partners, Cambridge Innovation Capital (CIC), Hadean Ventures and Seroba Life Sciences (9). With this latest round of financing, CTx will continue the development, as well as complete a Phase Ib clinical proof of concept of its lead product CTx001. The novel therapy is expected to have the potential to offer superior efficacy compared to competitive drugs, as well as reduce the burden of treatment among patients through a "one and done" approach (10).

CTx will also use the funds to expand its laboratory-based activities at its site in Stevenage, UK, as well as evaluate its pipeline assets for non-ocular indications. According to Rafiq Hasan, CEO and managing director at Complement Therapeutics GmbH, "the support of this broad syndicate enables us to generate additional data demonstrating CTx001's unique and differentiated mechanism of action, with the potential to transform the treatment landscape in [GA]" (9).

The financing will also be used to further develop the company's novel Complement Precision Medicine (CPM) platform, which enables the quantification of over 30 complement cascade proteins from a single systemically drawn blood sample (11). The CPM platform will also facilitate the stratification of patients with AMD and other conditions for enrolment into future clinical trials, and support the subsequent commercialisation of CTx's assets. According to Cipriani *et al.* (2021), the CPM platform has been validated in normal human samples and two distinct disease cohorts (12).

Alongside the financing, Michaël Vlemmix (Gimv), Rob Woodman (Panakès), Anne Horgan (CIC), and Roger Franklin (Hadean Ventures) will join the CTx board as new members.

AMD and the complement

AMD is a chronic and progressive degenerative disease of the macula, the central part of the retina (or the light-sensitive tissue at the back of the eye) that controls sharp, straight-ahead vision (13). AMD is a common condition that blurs a patient's central vision and is a leading cause of blindness for older adults. Research conducted by Guymer *et al.* (2023) estimates that AMD is present in 8.69% of the global population, affecting 196 million people in 2020; and its prevalence is expected to increase to 288 million by 2040 (14).

According to the US National Eye Institute (NEI), dry AMD has three stages: early, intermediate, and late, with the disease usually progressing slowly over several years. Also termed GA, there is currently no treatment for late dry AMD, which is driven by a combination of factors including genetic predisposition, natural ageing changes, and lifestyle factors, such as smoking and nutritional intake. Genetic and molecular studies have identified the complement system as a key driver of AMD onset and progression, and there is increasing evidence that complement inhibition can slow the progression of GA (15).

Future developments

Over the past few years, R&D efforts in the field of complement-mediated diseases have received the support of the US National Institutes of Health (NIH), which has awarded grants worth US$837 million for research in this domain (16). With enhanced funding and growing recognition of the complement system as a multidimensional innate immune surveillance mechanism, it can be expected that more novel therapeutic targets will be discovered in the future. CTx is therefore well placed to take advantage of potential future opportunities by addressing unmet needs in complement-mediated diseases, particularly AMD, to which it can strive to achieve market dominance and leadership position. With the active involvement of big pharma players as well as new entrants, the drug development landscape of complement therapeutics is likely to expand further with the market poised to witness steady growth over the coming years.

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Overcoming Analytical Challenges in High Potency Formulation

Sample dilution, sensitivity, excipient interference, and containment are key issues that must be addressed.

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Highly potent drugs exhibit a combination of high toxicity and therapeutic efficacy at low doses. They also often suffer from poor aqueous bioavailability, have specific release requirements to minimize potential toxicological effects, and bitter taste. As such, they present formulation challenges, including selection of necessary and appropriate excipients such as solubility and permeation enhancers to improve bioavailability, polymeric excipients to modify release profiles and flavour compounds to mask taste, according to Marcus Jenkins, Technical Consultant with SGS.

Analysis of high-potency formulations can also be difficult. The main analytical *in-vitro* release tests required for pharmaceutical drug products are confirmation of identity and quantification of the drug substance and impurities, as well as performance tests, such as determination of dissolution behaviour for solid-dose products. In addition to the use of numerous and varying excipients, dose-form design and solubility pose specific challenges for analytical method development and implementation for highly potent drug formulations.

Numerous issues must be resolved

There are a few main analytical challenges that developers of highly potent drug formulations face. First, the high potency and low concentration of the drug substances in these formulations make it necessary to limit sample dilution in order to achieve suitable nominal concentrations for testing. "While the limitations will depend on the physicochemical properties of each drug substance, low sample dilution typically results in high excipient contributions to samples when they are tested," Jenkins comments.

Low sample dilution may also enable greater external interference of samples via contamination from glassware, processes, or equipment. Such an issue is generally not observed for higher-dose products because the low levels of contaminants present are often diluted out of testing concentration ranges, according to Jenkins.

A second issue is the level of sensitivity needed for effective impurity analysis. "Due to the low doses for highly potent drugs, analytical testing concentrations will often be low and thus provide a challenge to the sensitivity of any method or equipment used," Jenkins states. The use of higher sample loading to improve the response and sensitivity for low-dose products creates the third challenge, which is that larger injection volumes increase the quantities of injected excipients.

This approach can not only result in reduced equipment lifetimes, but also require the addition of extra cleaning steps, contributing to increased equipment downtime and reduced throughput and capacity in testing laboratories, Jenkins adds. Furthermore, to minimize or eliminate excipient interference requires additional preparation steps, which lengthen the process and increase complexity, potentially leading to greater variability.

To ensure the safety of operators and the environment, handing of highly potent drug samples must be pursued with the proper controls in place, which can include containment such as hoods or isolators. Jenkins notes that this additional complexity can also introduce variability to testing processes.

Uniformity determination

For highly potent, low-dose drugs, ensuring the uniform distribution of the drug substance throughout the matrix is essential and often challenging. "Accurate and reliable analytical data [are] needed to enable effective and efficient product-development decisions. Should there be any doubt about the the accuracy of the analytical data regarding drug substance uniformity, development time, effort, and associated cost may be wasted trying to resolve potential formulation issues that are not real," Jenkins observes.

The biggest issue often relates to detection difficulties due to the presence of excipients that absorb

in UV wavelength regions similar to those for drug substances. One way to avoid this issue is to consider the analytical impacts of excipients during early screening and selection efforts before too much time and effort have been invested in prototype generation, according to Jenkins. Another approach is to choose alternative detection wavelengths that minimize excipient contribution, but the ability to do so depends on the absorption properties of the drug substance.

Polymeric excipients used to modify the *in-vivo* release of drugs can impact accurate extraction during sample preparation. "For some high-potency drug formulations it may be necessary to complete additional preparation steps to ensure full recovery of the drug substance as required to meet industry in-process checks or finished-product specifications," Jenkins says.

Polymeric excipients may also present challenges to lab equipment such as chromatographic columns, as they can be difficult to remove and may create the need for additional cleaning/regeneration steps to return columns to optimal performance or irreversibly reduce column lifetimes, according to Jenkins. "Column deterioration during analysis can, in fact, increase the risk of an analysis failing to meet typical system suitability criteria, leading to the need to repeat analyses, thus reducing testing efficiency and cost-effectiveness," he states.

Solvent selection essential

To achieve effective analysis, all ingredients of interest in a drug formulation must be soluble in a solvent suitable for the intended method of analysis. That can be an issue for highly potent drug substances with poor water solubility, as organic solvents are typically required. "For a particular formulation, the solvent should effectively dissolve the drug substance or other ingredient of interest (e.g., preservative or anti-oxidant) but not the other formulation excipients in order to minimize excipient contributions; however, drug substances and excipients often exhibit similar properties and tend to be soluble in the same solvents," Jenkins explains.

Careful column stationary- and mobile-phase selection can be used to separate unwanted excipient interference from peaks of interest ensuring acceptable specificity. These choices can be guided somewhat by consideration of the chemical structures of the compounds involved, according to Jenkins. "Polar functionalities in the drug substance will interact with imbedded polar groups on columns, while delocalized electron systems will interact with similar systems in certain stationary phases such as pentafluorophenyl, and alkyl chains will interact with C8 or C18 stationary phases, etc. Modern analytical columns now have combinations of these groups to allow for a wider range of stationary phases for evaluation during analytical development," he observes.

Another approach is to use secondary or tertiary wavelength maxima to minimize interference from excipients in a highly potent drug formulation. "It is necessary, however, to consider the analysis of degradation products, as they can have different UV absorbances compared to their parent moieties," Jenkins states. He adds that while longer wavelengths will reduce excipient contribution to the analysis, they do not prevent physical interactions of excipients with the stationary phase and the need for additional cleaning steps.

Sustained-release

Highly potent drug formulations that are engineered to enable sustained release of the drug substance with targeted delivery to minimize potential toxicological effects often rely on alternative or novel excipients. These systems, according to Jenkins, reduce the initial onset and prolong the therapeutic effect window.

In-vitro release testing for such formulations requires detection of low levels of drug substances (particularly at early time points) released at slow rates. For instance, a sustained-release formulation may release 5–0% of the drug substance after 5–10 minutes, while an immediate-release formulation will typically release >45%, observes Jenkins. "Increased sensitivity achieved through use of higher-sensitivity detectors or modifications such as higher path-length flow cells or application of non-routine/non-pharmacopeial equipment, such as micro-dissolution and/or sample concentrators, is therefore often necessary. Justification of the suitability, control, and use of such equipment is, however, usually required during regulatory review," he says.

Other dissolution testing hurdles

It is not just sustained-release formulations that can cause challenges to effective dissolution analysis. For oral-dosage-form drugs formulated as capsules, during dissolution analysis certain combinations of excipients, dissolution media, and the polymers used to form the capsule shells can react to form pellicles that retard drug-substance release, according to Jenkins. "This issue is addressed either through the development of specific dissolution media to prevent crosslinking or the inclusion of the enzyme pepsin to degrade any formed pellicles," he says. He does note, however, that these approaches are not generally applied from the outset, as often this problem does not appear until several months into stability testing of a product.

Instrument innovation and analytical expertise

As more knowledge is gained about disease mechanisms and new drug targets are identified, the nature of highly potent drug substances continues to evolve. They are becoming steadily more potent while their solubility/permeability continues to decline. At the same time, demands for safer, easier-to-use drugs that are not only developed with patients in mind but also cost-effective are growing.

Formulation of highly potent drugs that meet those demands can be challenging, particularly given the

complexity of drug formulation and analysis for these products. "The largest contribution to the cost of new, novel medicines is the time taken for development (circa 8–12 years). Improving the efficiency of development should therefore result in a reduction in the cost-per-unit and earlier availability of drugs to patients. One way to reduce development times is through introduction of more advanced analytical instruments and methods with greater sensitivity that support quick resolution of analytical challenges," Jenkins contends.

Combining innovative systems with experienced analytical and formulation scientists using a collaborative approach would, Jenkins adds, further ensure sound scientific rationale resulting in effective development decisions. He points to, for example, consideration of the downstream impacts of formulation development decisions on required analytical methodologies. The overall result, Jenkins believes, would ultimately be expedited development timeframes for novel medicines that address unmet patient needs. PTE

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inspection algorithms to ensure high particle detection rates, plus voltage leak detection to detect very small cracks," he says. "This technology brings a unique opportunity for throughput of up to 400 vials per minute."

"Innovations in pharma inspection systems are helping US Food and Drug Administration (FDA)-regulated timelines while achieving high standards of quality and maintaining product stability," Korson asserts. "Companies should decide on the most appropriate technology solutions by evaluating the latest regulatory guidelines. Staying ahead of compliance will ensure your technology investments payoff for the future."

Rapid real-time methods have been gaining interest for some time within pharma environmental monitoring, adds Whittard. "These viable particle counters can deliver continuous monitoring and potentially speed up release of product," he says. Recently, Cherwell launched a rapid, viable detection system—MicronView BioAerosol Monitoring System (BAMS)—which allows for rapid, real-time, continuous monitoring of airborne microbes, supporting Annex 1 requirements, Whittard explains.

For Wong, blow-fill-seal (BFS) technology stands out as an excellent platform for aseptic products. "Containers are formed, filled, and sealed within a very compact sterile environment within the BFS machine itself. This eliminates the need to maintain entire rooms and suites under sterile conditions and reduces the container componentry to just the resin needed to make the units," he says. "BFS containers are also customizable in shape and size, and more robust when it comes to handling and use."

Broadening horizons

The difficult nature of aseptic needs within the pharmaceutical industry, and the evolving demands that are being placed upon companies and individuals working within the field mean that improvements in understanding of the process is imperative. Attending conferences and events on aseptic processes is beneficial to companies and individuals seeking to improve their understanding of aseptic needs, notes Whittard. "These [events] not only provide the opportunity to learn from talks and presentations, but to also share and discuss good practice with fellow delegates," he asserts. "Engaging with companies and suppliers who specialize in the pharma space is also key."

"When considering how companies can improve their understanding of aseptic needs, it is important to address both internal and external improvements," adds Kuehnhold. So, while externally speaking, it is beneficial to attend conferences and events, learn from representatives of industry and authorities, and exchange with suppliers or customers on specific aspects of aseptic processes, it is also important to promote cross-functional communication internally.

"Integrating a holistic understanding of GMP within the workplace culture promotes a sense of motivation to consider and adhere to aseptic requirements for the sake of the patients at the other end of the line," Kuehnhold emphasizes. "This [integration] is done through constant communication and well-established training programmes to support employees' gaining knowledge."

"One department alone cannot cover all aspects in the complex aseptic environment," confirms Sauter. "Only working within interdisciplinary teams provides processes that drive quality."

It is imperative to assure compliance across every facet of the aseptic chain, from facility design to manufacturing controls and risk management, Wong stresses. "Maintaining a strong foundation of quality-driven practices allows companies to respond quickly and nimbly to evolving guidance," he says.

"The aseptic filling process is continually being challenged, not least because the range and scope of products that need to be filled aseptically shows no sign of slowing down," asserts Sandle. "Spending time investing in a robust training package is important, from upper management to operators, so they are aware of microbial concerns and good aseptic practices. Each member of staff should have a basic understanding of microbiology, hygiene, cleanrooms, contamination control, aseptic techniques, product protection, and patient safety."

Kuehnhold emphasizes that the world of injectables is niche, meaning that not many pharma and biotech companies have the deep experience that they need to get their drug products to market successfully. "The more knowledge that can be gained on best practices, the better suited a company will be to advance," he concludes.

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In-Vitro Permeation Test Data Analysis with MS Excel as per FDA's Guidance

Lei Lei

This article describes the data processing procedures and US Food and Drug Administration statistical mathematics of an *in-vitro* permeation test (IVPT) study for evaluating a generic topical drug product against its reference product. IVPT-Stat v2.0, a tool composed of two Microsoft (MS) Excel files, is provided in the present paper to perform FDA statistic bioequivalence analysis with IVPT data (i.e., maximum flux [J_{max}] and total cumulative amount permeated [denoted as AMT]) of the test and reference topical drug products. The algorithms and use of IVPT-Stat v2.0 are also elucidated with examples. As a MS Excel-based tool, IVPT-Stat v2.0 is user friendly and can be easily run by most industry practitioners and should make IVPT data analysis easy.

CITATION: When referring to this article, please cite it as Lei, L. *In-Vitro* Permeation Test Data Analysis with MS Excel as per FDA's Guidance. *Pharm. Technol.* **2023**, *47* (7), 30–35.

Submitted: 17 Feb. 2023
Accepted: 29 March 2023

In October 2022, the US Food and Drug Administration (FDA) published the *Guidance for Industry—In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs* (abbreviated hereafter as "FDA IVPT guidance") (1). The guidance detailed the technical and statistical requirements for an *in-vitro* permeation test (IVPT) study, which compares the rate and extent of drug permeation through the skin for the test and reference drug products.

During an IVPT study, the product tested is dosed uniformly on the surface of the stratum corneum side of a skin section mounted on a diffusion cell, with the opposite skin surface contacting the isotonic receptor solution. The test (T) and reference (R) products are tested in parallel. By analyzing the drug concentrations in receptor solutions collected at different sampling time points during the IVPT study, the permeation rate profile (flux versus time) and cumulative amount profile (cumulative amount permeated versus time) can be plotted. The raw endpoint data, the maximum flux (J_{max}) and the total cumulative amount of drug permeated (AMT), can be read from the two profiles, respectively. The J_{max} at the peak of the flux profile should be compared for the test and reference products; this is analogous to the comparison of the C_{max} for test and reference products in the case of plasma pharmacokinetics. Similarly, the AMT across the entire study duration should be compared for the test and reference products; this is analogous to the area under the curve (AUC) of plasma pharmacokinetics.

The FDA IVPT guidance also introduces the statistics for IVPT data analysis (1). As some algorithms of the previously published IVPT-Stat (a MS Excel file first introduced in May 2022 [2]) were not adherent to the current statistics in FDA IVPT guidance, the present work introduces IVPT-Stat v2.0, which is upgraded from IVPT-Stat and can perform the current FDA-specified statistics. IVPT-Stat v2.0 utilizes a set of user-defined formulae and macro codes as well as some MS Excel functions to complete the statistical analysis. It

can help industry practitioners analyze bioequivalence (BE) data of a topical generic versus its reference drug or BE data of products before and after formulation/process changes.

IVPT data processing

Data collecting. The first step for data analysis is to obtain the cumulative amounts of drug permeated at all the time points during an IVPT study, Q_n (where Q_n is the cumulative amount permeated by the n^{th} sampling time point [ng/cm^2]). The amounts of drug permeated are calculated from the drug concentrations in the receptor solutions. The calculation equations for Q_n are different for different diffusion apparatus (e.g., vertical diffusion cell and flow through cell), thus it is not covered in this paper. With the Q_n and Q_{n-1} values, the drug permeation rate between T_n and T_{n-1}, $Flux_n$, can be calculated with **Equation 1**:

$$Flux_n = \frac{Q_n - Q_{n-1}}{T_n - T_{n-1}} \quad \textbf{[Eq. 1]}$$

where, $Flux_n$= the drug permeation rate during a time interval between the n^{th} and $(n-1)^{th}$ sampling time points (ng/cm^2/h), Q_n = the cumulative amount permeated by the n^{th} sampling time point (ng/cm^2), and T_n = the time of the n^{th} sampling (hour).

Data natural log transformation. All the data used for BE statistical analysis are the natural log-transformed values of the raw endpoint (J_{max} and AMT) data. The raw data refer to the experimental observations of J_{max} and AMT in units of ng/cm^2/h and ng/cm^2, respectively.

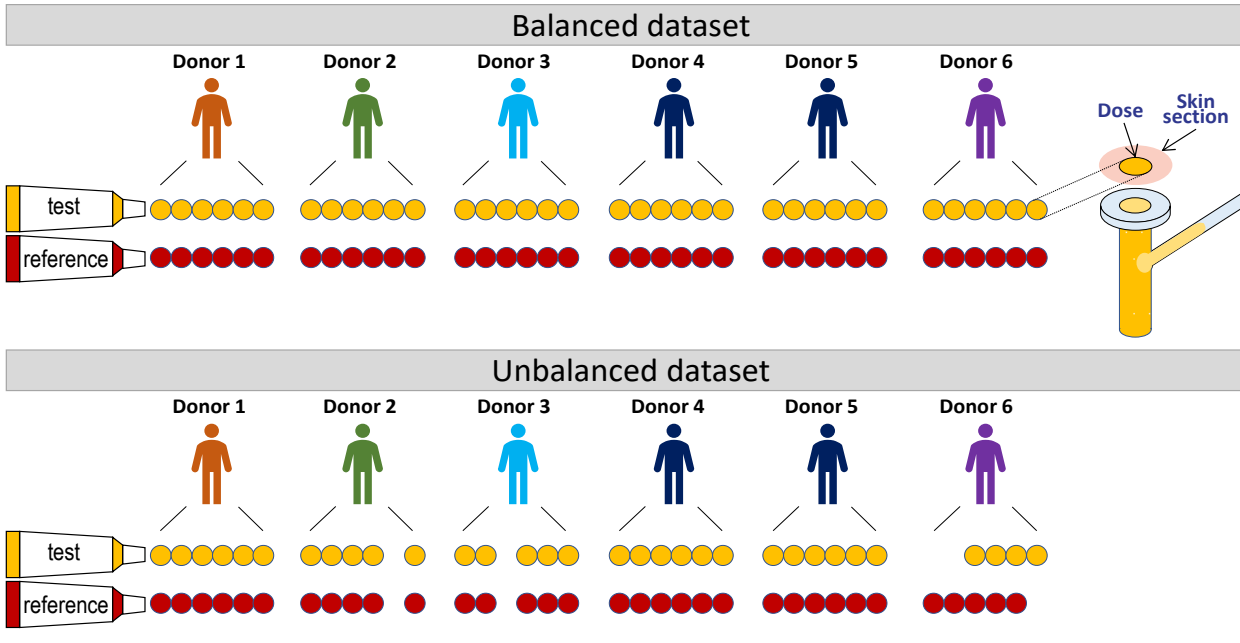
Dataset

Figure 1 illustrates the layout of a balanced and unbalanced design/dataset. It is recommended that a balanced design be utilized, in which there are the same numbers of skin section replicates per donor per treatment group (T or R), as a balanced design will give a higher statistic power. To keep the dataset balanced, if a skin section (diffusion cell) is excluded (due to a documented observation of a failure or a protocol deviation) from among the replicates in a dataset, then a replacement skin section/diffusion cell can be set up and studied (if sufficient skin remains from the same donor and no samples from that skin section have been analyzed). In certain situations, the excluded skin sections cannot be replaced (specifically, the numbers of remaining replicates are not the same per donor per treatment), which then results in an unbalanced dataset.

FDA requires that only donors that have at least three replicate skin sections from each (T and R) treatment groups can be included in the statistical analysis. For a balanced dataset, each of the n donors has r replicates in the test product group, and r replicates in the reference group ($r = r_1^T = r_2^T = \cdots = r_n^T = r_1^R = r_2^R = \cdots = r_n^R$); each group has $r \times n$ J_{max} (or AMT) values. For an unbalanced dataset, the test and reference product groups have $r_1^T + r_2^T + \cdots + r_n^T$ and $r_1^R + r_2^R + \cdots + r_n^R$ replicates, respectively.

When any value of J_{max} or AMT happens to be 0, it could be replaced with half the lower limit of quantification value of the analytical method for drug concentra-

Figure 1. The illustration of balanced and unbalanced *in-vitro* permeation test (IVPT) design/dataset.



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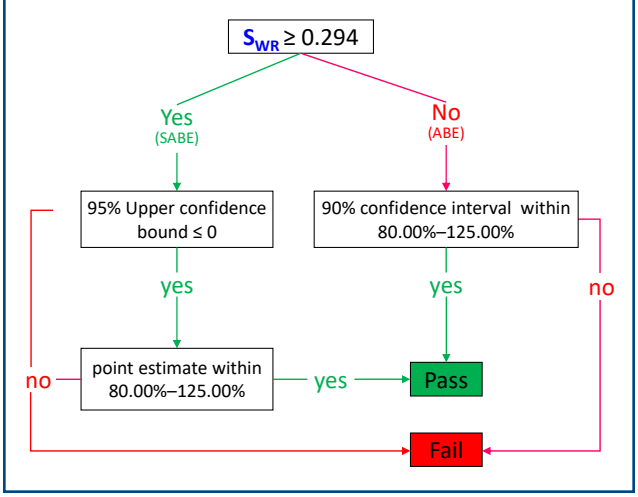
tion in receptor solution. This is to ensure the successful natural log transformation from a statistical perspective, respecting an α level.

FDA statistics

The variables used in the calculation equations are defined as follows:

- $df = n-1$
- $df_R = r^R - n$
- i = the ith one of the r replicates of the jth donor in the T or R product group
- j = the ith one of the n donors in the T or R product group
- n = the number of donors
- r = the number of replicates of the jth donor in the T or R group
- $r^R = r_1^R + r_2^R + \cdots + r_n^R$ = the total number of replicates of all the n donors in the R product group
- $r^T = r_1^T + r_2^T + \cdots + r_n^T$ = the total number of replicates of all the n donors in the T product group
- R_{ij}= the IVPT endpoint (natural log-transformed J_{max} or AMT data) of the ith one of the r_j^R replicates of the jth donor in the R product group
- $E_{\hat{I}}$=the standard error of $\hat{I}$
- $t_{1-\alpha,df} = (1-\alpha) \times 100^{th}$ percentile of the Student's t distribution with df degrees of freedom
- T_{ij}= the IVPT endpoint (natural log-transformed J_{max} or AMT data) of the ith one of the r_j^T replicates of the jth donor in the T product group
- $\mu_T - \mu_R$ = the point estimate of the T/R geometric mean ratio, with μ_T and μ_R being the population means of the natural log-transformed endpoint values of the T and R product groups, respectively
- $\chi^2_{(1-\alpha,df_R)} = (1-\alpha) \times 100^{th}$ percentile of the Chi-square distribution with df_R degrees of freedom

Figure 2. The *in-vitro* permeation test (IVPT) bioequivalence (BE) conclusion diagram with S_{WR} as a cutoff point.



- $\theta = \frac{(ln(m))^2}{(\sigma_{w_0})^2} = \frac{(ln(1.2500))^2}{(0.25)^2}$, here m is the regulatory BE limit 1.2500 while σ_{w_0} is the regulatory constant 0.25.

For a balanced dataset, $\hat{I}$, $SE_{\hat{I}}$, and df can be calculated as follows:

- $\hat{I} = \bar{I}_\cdot = \frac{1}{n}\sum_{j=1}^{n} I_j$, where $I_j = \frac{1}{r}\sum_{i=1}^{r}(T_{ij} - R_{ij})$
- $SE_{\hat{I}} = \sqrt{\frac{S_I^2}{n}}$, where $S_I^2 = \frac{1}{(n-1)}\sum_{j=1}^{n}(I_j - \bar{I}_\cdot)^2$
- $df = n - 1$

For an unbalanced dataset, $\hat{I}$, $SE_{\hat{I}}$, and df can be approximated by running a multiple linear regression with the endpoint values (natural log-transformed J_{max} or AMT data) as the dependent response and the donor code and treatment code as independent factors. This regression can easily be done by using IVPT-Stat v2.0 as demonstrated in a later section of this paper. The df value can either be read from the regression outputs or calculated by $r^T + r^R - n$. This multiple linear regression can also be performed using the PROC MIXED (or PROC GLM) program in SAS (as demonstrated in Appendix I of FDA IVPT guidance [1]), which generate the values of lower and upper bounds of 90% confidence interval (CI) of $\mu_T - \mu_R$.

Calculation of S_{WR}. The FDA statistics have a mixed criterion for BE analysis, which uses S_{WR}, the within-donor standard deviation of data of R product group, as a cutoff point. The value of S_{WR} can be calculated as per **Equation 2**. As shown in **Figure 2** and **Table I**, when S_{WR} <0.294, the regular average bioequivalence (ABE) criteria should be used; when $S_{WR} \geq 0.294$, the scaled average bioequivalence (SABE) criteria should be used. The detailed criteria for ABE and SABE are listed in **Table I**.

$$S_{WR} = \sqrt{\frac{\sum_{j=1}^{n}\sum_{i=1}^{r_j^R}(R_{ij} - \overline{R_{\cdot j}})^2}{r^R - n}} \quad \textbf{[Eq. 2]}$$

where $\overline{R_{\cdot j}} = \frac{1}{r_j^R}\sum_{i=1}^{r_j^R} R_{ij}$ = the average of all the endpoints (natural log-transformed data) for the r_j^R replicates from the j^{th} donor in the R product group.

When S_{WR} < 0.294 (ABE). When S_{WR} < 0.294, the T and R products can be declared bioequivalent if both the two natural antilogarithms of the lower and upper bounds of the two one-sided (1–2α) × 100% CI (90% CI when α = 0.05)

Table I. The bioequivalence (BE) criteria for average bioequivalence (ABE) and scaled average bioequivalence (SABE) scenarios (α = 0.05).

Scenario	BE type	BE criteria
S_{WR} < 0.294	ABE	The natural antilogarithms of the bounds of the two one-sided (1 – 2α) × 100% confidence interval for $\mu_T - \mu_R$, $\hat{I} \pm t_{1-\alpha,df} \times SE_{\hat{I}}$, should be within [0.8000, 1.2500]
$S_{WR} \geq 0.294$	SABE	• The (1 – α) × 100% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta \times \sigma_{WR}^2$ should be ≤ 0 • The natural antilogarithm of the point estimate of $\mu_T - \mu_R$ is within [0.8000, 1.2500]

Table II. The Microsoft (MS) Excel and R formulas for returning (1 – α) × 100th percentile of the Student's t and Chi-square distributions with *df* or df_R degrees of freedom.

Distribution type	Mathematic formula	MS Excel formula	R codes
Chi-squared distribution	$\chi^2_{(1-\alpha,df_R)}$	CHISQ.INV(1-0.05, df_R)	qchisq(1-0.05, df_R)
Student's t distribution	$t_{1-\alpha,df}$	T.INV(0.05, df)	qt(1-0.05, df)

for $\mu_T - \mu_R$, $\hat{I} \pm t_{1-\alpha,df} \times SE_{\hat{I}}$ (see **Equation 3**) are within [0.8000, 1.2500].

$$\hat{I} \pm t_{1-\alpha,df} \times SE_{\hat{I}} \quad \textbf{[Eq. 3]}$$

When $S_{WR} \geq 0.294$ (SABE). When $S_{WR} \geq 0.294$, the T and R products can be declared bioequivalent if the below two criteria are both met:

- the natural antilogarithms of $\mu_T - \mu_R$ is within [0.8000, 1.2500]
- the ubound, the (1 − α) × 100% (e.g., 95% when α = 0.05) upper confidence bound for $(\mu_T - \mu_R)^2 - \theta \times S^2_{WR}$, is ≤ 0 (numbers should be kept to a minimum of four significant figures for comparison). The ubound can be approximated by **Equation 4** (1):

$$\text{ubound} = X + Y + C \times \sqrt{|V|} \quad \textbf{[Eq. 4]}$$

where:

- $X = \hat{I}^2 - SE_{\hat{I}}{}^2$
- $Y = -\theta S^2_{WR}$
- $X' = (|\hat{I}| + t_{1-\alpha,df} \times SE_{\hat{I}})^2$
- $Y' = -\theta \times \frac{df_R \times S^2_{WR}}{\chi^2_{(1-\alpha,df_R)}}$
- $V = (X' - X) \times |X' - X| + (Y' - Y) \times |Y' - Y|$
- $C = 1 \text{ if } V > 0; 0 \text{ if } V = 0; -1 \text{ if } V < 0$
- S^2_{WR} = the square value of S_{WR}.

IVPT-Stat v2.0

Calculation mechanism. IVPT-Stat v2.0 has two MS Excel files for balanced (named "FDA IVPT-Stat (balanced) v2.0.xlsm") and unbalanced (named "FDA IVPT-Stat (unbalanced) v2.0.xlsm") datasets, respectively. The "FDA IVPT-Stat (balanced) v2.0.xlsm" file has only one worksheet titled Balanced Data & Analysis, while the "FDA IVPT-Stat (unbalanced) v2.0.xlsm" file contains two worksheets, Unbalanced Data & Analysis and Supporting Layout.

For the "FDA IVPT-Stat (balanced) v2.0.xlsm" file, the Balanced Data & Analysis sheet uses a set of MS Excel functions to calculate the parameters needed for BE determination. The MS Excel functions and the corresponding R functions for Chi-squared distribution and Student's t distribution are listed in **Table II**. Simply, what a user needs to do is to enter the raw endpoint data (i.e., J_{max} [ng/cm²/h] or AMT [ng/cm²] data) into the cell blocks with a yellow background color, and then all the calculations will be completed automatically and immediately. The natural log-transformed values of these raw endpoint data will be shown in the nearby columns. The C4–C26 cells perform all the calculations and output S_{WR} into cell B1. The parameters needed for ABE criteria (if $S_{WR} < 0.294$) are placed in C4 and C5, and parameters needed for SABE criteria (if $S_{WR} \geq 0.294$) are placed in C14 and C15. A conclusion of either "BE" or "Not BE" will be shown in the cell range E3–E26.

For the "FDA IVPT-Stat (unbalanced) v2.0.xlsm" file, its Unbalanced Data & Analysis sheet is the same as the Balanced Data & Analysis sheet of "FDA IVPT-Stat (balanced) v2.0.xlsm" file, except that the values for $\hat{I}$ (cell C9), $SE_{\hat{I}}$ (cell C11), *df* (cell C12) are generated from the Supporting Layout sheet by MS Excel's multiple linear regression function LINEST(). Clicking the button titled "click to run IVPT-Stat" in the Unbalanced Data & Analysis sheet will run a custom-defined program, which transforms the natural log-transformed dataset from the Unbalanced Data & Analysis sheet into a matrix of binary codes 1 and 0 in the Supporting Layout sheet that is suitable for LINEST() function.

User manual. For the balanced dataset, open the "FDA IVPT-Stat (balanced) v2.0.xlsm" file and follow the below steps:

- Enter the raw endpoint data into the yellow-background cells in *Balanced Data & Analysis sheet.*
- Read the S_{WR} value in cell B1.
- Read the lower and upper CI in cells C4 and C5 (in case $S_{WR} < 0.294$) or read the ubound and natural antilogarithm of point estimate in cells C14 and C15, respectively (in case $S_{WR} \geq 0.294$).
- Read conclusion of "BE" or "Not BE" in cell range E3–E26.

For the unbalanced dataset, open the "FDA IVPT-Stat (unbalanced) v2.0.xlsm" file and follow the below steps:

- Enter the raw endpoint data into the yellow-background cells in *Unbalanced Data & Analysis sheet.*
- Read the S_{WR} value in cell B1.
- Click the button titled "Click to run IVPT-Stat".
- Read the lower and upper CI in cells C4 and C5 (in case $S_{WR} < 0.294$), or read the ubound and natural antilogarithm of point estimate in cells C14 and C15, respectively (in case $S_{WR} \geq 0.294$).
- Read "BE/Not BE" conclusion in cell range E3–E26.

Example 1: using FDA IVPT-Stat (balanced) v2.0.xlsm

Utilization of experimental data. This example demonstrates how IVPT-Stat v2.0 performs BE analysis with the balanced IVPT dataset "Data-Balanced.csv" included in Appendix II of the FDA IVPT guidance (1). The IVPT experiment totally used 72 skin sections dermatomed from six donors (12 replicates per donor). The skin sections are uniformly assigned to the T and R product groups (six replicates per donor per product group). During the experiment duration, each skin section (diffusion cell)

generated a series of flux and Q (amount permeated) values at different time points, of which the maximum flux value is the J_{max} of this skin section while the Q value at the last time point is the AMT of this skin section (as illustrated in **Figure 3**). The dataset "Data-Balanced.csv" included in Appendix II of the FDA IVPT guidance lists all the 72 raw AMT values (36 ones for T product group and 36 ones for R product group) as well as the 72 raw J_{max} values (36 ones for T product group and 36 ones for R product group). In this paper, we only use the AMT data for demonstration, the readers can do the same using the raw J_{max} data.

After entering all 72 raw AMT data (for T and R) into the yellow cells of the Balanced Data & Analysis sheet of the "FDA IVPT-Stat (balanced) v2.0.xlsm" file, all the statistical analysis will be completed automatically and immediately. Specifically, the calculated natural antilogarithms—listed in the ln(T) and ln(R) columns of the Balanced Data & Analysis sheet—are automatically used for statistical calculation. The calculated S_{WR} is displayed in B1; BE parameters are displayed in either cells C4–C5 (for "ABE" criteria in case $S_{WR} < 0.294$) or cells C14–C15 (for "SABE" criteria in case $S_{WR} \geq 0.294$); and BE conclusion is displayed in cell range E3–E26.

Calculation of S_{WR}. S_{WR} is calculated according to **Equation 2**, using the ln(R) data (for R product group) in the Balanced Data & Analysis sheet. The calculated S_{WR}, as shown in cell B1, is rounded to 0.502.

BE conclusion. Because S_{WR} is 0.502, which is ≥ 0.294, then, consequently, SABE criteria should be used. The 95% upper confidence bound is −0.022242279 (kept to a minimum of four significant figures), which is < 0, and the natural antilogarithm of point estimate 1.1012 is within [0.8000, 1.2500]. Therefore, BE for AMT can be concluded.

Figure 3. The maximum flux (J_{max}) and total cumulative amount at the last time point (AMT) of a skin section (diffusion cell) identified from the flux and cumulative amount profiles (simulated from the data set "Data-Balanced.csv" included in the Appendix II of the FDA IVPT guidance), respectively.

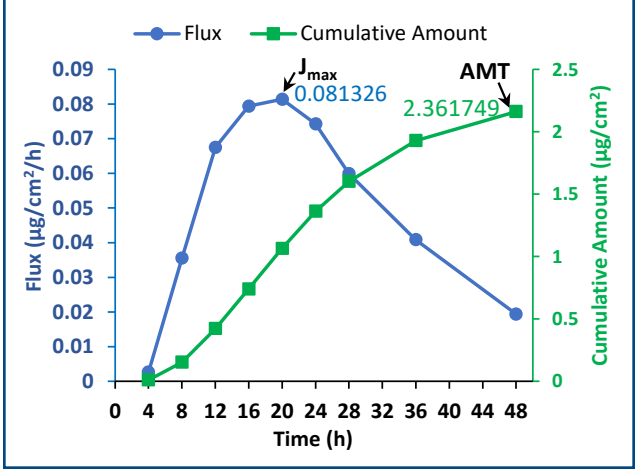


Figure 4. The matrix of total cumulative amount (AMT) data with "Donor" code and "T/R" code.

	C	D	E	F	G	H	I	J	K
1	Donor	T or R	ln(AMT or Jmax)	Donor1	Donor2	Donor3	Donor4	Donor5	T
2	1	T	0.859402446	1	0	0	0	0	1
3	1	T	-0.087115746	1	0	0	0	0	1
4	1	T	0.220133425	1	0	0	0	0	1
5	1	T	-0.116513592	1	0	0	0	0	1
6	1	T	-0.410149563	1	0	0	0	0	1
7	1	T	-0.735756188	1	0	0	0	0	1
8	1	R	0.469150766	1	0	0	0	0	0
9	1	R	0.808598611	1	0	0	0	0	0
10	1	R	0.475687446	1	0	0	0	0	0
11	1	R	0.633078654	1	0	0	0	0	0
12	1	R	0.097079523	1	0	0	0	0	0
13	1	R	0.153014606	1	0	0	0	0	0
14	2	T	-0.001155668	0	1	0	0	0	1
15	2	T	-0.205233645	0	1	0	0	0	1
16	2	T	-0.432721717	0	1	0	0	0	1
17	2	T	-0.264889149	0	1	0	0	0	1
18	2	T	0.331033186	0	1	0	0	0	1
19	2	R	-0.474222115	0	1	0	0	0	0
20	2	R	-0.182317157	0	1	0	0	0	0
21	2	R	-0.949943177	0	1	0	0	0	0
22	2	R	-0.160451656	0	1	0	0	0	0
23	2	R	-0.389028433	0	1	0	0	0	0
24	3	T	-0.781825401	0	0	1	0	0	1
25	3	T	0.320225252	0	0	1	0	0	1
26	3	T	0.775182363	0	0	1	0	0	1
27	3	T	0.561626907	0	0	1	0	0	1
28	3	T	-0.004	0	0	1	0	0	1
29	3	R	-0.176	0	0	1	0	0	0
30	3	R		0	0	1	0	0	0
31	3	R		0	0	1	0	0	0
32	3	R		0	0	1	0	0	0
33	3	R		0	0	1	0	0	0
34	4	T		0	0	0	1	0	1
35	4	T		0	0	0	1	0	1
36	4	T		0	0	0	1	0	1
37	4	T	0.151	0	0	0	1	0	1
38	4	T	0.027	0	0	0	1	0	1
39	4	T	0.07880009	0	0	0	1	0	1
40	4	R	0.52756415	0	0	0	1	0	0
41	4	R	-0.022592295	0	0	0	1	0	0
42	4	R	1.142721674	0	0	0	1	0	0
43	4	R	-0.080337334	0	0	0	1	0	0
44	4	R	0.408682593	0	0	0	1	0	0
45	4	R	0.285304498	0	0	0	1	0	0
46	5	T	0.243351587	0	0	0	0	1	1
47	5	T	0.208353922	0	0	0	0	1	1
48	5	T	0.897851367	0	0	0	0	1	1
49	5	T	0.178973458	0	0	0	0	1	1
50	5	T	0.730818617	0	0	0	0	1	1
51	5	T	0.638373627	0	0	0	0	1	1
52	5	R	0.743857405	0	0	0	0	1	0
53	5	R	-0.171700956	0	0	0	0	1	0
54	5	R	-0.01444787	0	0	0	0	1	0
55	5	R	-0.071000958	0	0	0	0	1	0
56	5	R	0.457790603	0	0	0	0	1	0
57	5	R	0.189842371	0	0	0	0	1	0
58	6	T	0.447351496	0	0	0	0	0	1
59	6	T	0.048527272	0	0	0	0	0	1
60	6	T	0.046533334	0	0	0	0	0	1
61	6	T	0.148104438	0	0	0	0	0	1
62	6	R	0.037864987	0	0	0	0	0	0
63	6	R	-0.228989355	0	0	0	0	0	0
64	6	R	-0.080595277	0	0	0	0	0	0
65	6	R	-0.248401105	0	0	0	0	0	0
66	6	R	0.347286409	0	0	0	0	0	0

In the same way, the J_{max} data can be analyzed. Only when both BE for J_{max} and BE for AMT are concluded can the T and R products be declared bioequivalent.

Example 2: using FDA IVPT-Stat (unbalanced) v2.0.xlsm

Utilization of experimental data. This example demonstrates how IVPT-Stat v2.0 performs BE analysis with the unbalanced IVPT dataset, "Data-Unbalanced.csv," included in Appendix II of the FDA IVPT guidance. The IVPT experiment generated 65

Table III. Comparison of outputs from IVPT-Stat v2.0 and SAS programs.

Statistical parameters	Example 1 (balanced) ln(AMT) Test-Ref		Example 2 (unbalanced) ln(AMT) Test-Ref	
	IVPT-Stat v2.0	SAS®	IVPT-Stat v2.0	SAS®
SWR	0.502421948	0.50242	0.506507914	0.50651
Ī. [LPOINTEST]	0.09644494	0.096445	0.067494365	0.067494
EXP(Ī.) [POINTEST]	1.101248944	1.10125	1.069824231	1.06982
UB	-0.022242279	–0.022242	-0.10907004	–0.10907
L [EXP(CI lower)]	0.804701056	0.80470	0.876274175	0.87627
U [EXP(CI upper)]	1.50708046	1.50708	1.306125318	1.30613

raw AMT values (32 ones for T product group and 33 ones for R product group) and 65 raw J_{max} values (32 ones for T product group and 33 ones for R product group). In this paper, only the AMT data are used for demonstration; readers can do the same using the raw J_{max} data.

After entering all the 65 raw AMT data (for T and R) into the yellow cells of the Unbalanced Data & Analysis sheet of the "FDA IVPT-Stat (unbalanced) v2.0.xlsm" file, the button titled "Click to run IVPT-Stat" in the Unbalanced Data & Analysis sheet should be clicked. After clicking, a message box "IVPT-Stat run successfully" will prompt out; click the "OK" button to close the message box. At this point, the whole statistical analysis is completed. The calculated S_{WR} is displayed in B1; BE parameters are displayed in either cells C4–C5 (for "ABE" criteria in case $S_{WR} < 0.294$) or cells C14–C15 (for "SABE" criteria in case $S_{WR} \geq 0.294$); and BE conclusion is displayed in cell range E3–E26.

During the above calculation, the Supporting Layout sheet calculated $\hat{I}$, $SE_{\hat{I}}$, and df by the formulae in its cells B1–B3 using the data in columns E and F–K. Column E lists all the natural log-transformed endpoint data as sorted by "donor" code (in column C) and "T or R" code (in column D) as shown in **Figure 4**, while the other six columns F ~ K display the matrix of the donor and treatment codes (1 or 0).

Calculation of S_{WR}. S_{WR} is calculated according to **Equation 2**, using the ln(R) data (for R product group) in the Unbalanced Data & Analysis sheet. The calculated S_{WR}, as shown in cell B1, is rounded to 0.5065.

BE summary. Because S_{WR} is 0.5065, which is ≥ 0.294, then, consequently, SABE criteria should be used. The 95% upper confidence bound is –0.10907004 (kept to a minimum of four significant figures), which is < 0, and the natural antilogarithm of point estimate 1.0698 is within [0.8000, 1.2500]. Therefore, BE for AMT can be concluded.

In the same way, the J_{max} data can be analyzed. Only when both BE for J_{max} and BE for AMT are concluded, can the T and R products be declared bioequivalent.

Validation of IVPT-Stat v2.0

The IVPT-Stat v2.0 was validated by comparing the outputs generated by IVPT-Stat v2.0 with the SAS outputs provided in Appendix II of the FDA IVPT guidance. The comparison, as listed in **Table III**, shows that the two programs generated the same values of statistical parameters. The minor difference in numbers is because the natural log-transformed AMT data (in the column titled "LAMT") provided in the FDA IVPT guidance had been rounded (digital precision reduced). Therefore, it is demonstrated that the two programs are equivalent, and IVPT-Stat v2.0 can be used for BE analysis of IVPT data.

For R code users, FDA IVPT guidance Appendix III provides an example of R code that performs the same calculation as the SAS code provided in Appendix I. However, a line of code is missing after the last line on page 40 of the published FDA IVPT guidance file; thus, industry practitioners may experience failure in running the R codes. To compensate for this missing line of code, the author added the missing line and two extra lines of codes to display the outputs, as shown in lines 123, 132, and 136 (highlighted in pink) of **Table IV** (editor's note: Table IV is published online at *www.PharmTech.com/view/in-vitro-permeation-test-data-analysis-with-ms-excel-as-per-fda-s-guidance*). Depending on which .csv file ("Data-Unbalanced.csv" or "Data-Balanced.csv") is used, either lines 130–132 or lines 134–136 can be deleted. Once running the R codes in **Table IV**, the output values will be displayed in the R Console window.

Conclusion

The FDA IVPT data processing procedures and BE statistics are introduced in this paper. The developed IVPT-Stat v2.0 can be used by industry practitioners to perform BE analysis of IVPT data as per FDA's statistics described in the recent FDA IVPT guidance (1). IVPT-Stat v2.0 has been validated as a tool to implement the IVPT BE analysis. With this tool, users can obtain the BE parameters and "BE"/"Not BE" conclusion by simply entering the raw data of J_{max} or AMT. IVPT-Stat v2.0 could be a helpful tool for topical drug product developers.

Access to tool. The open-source IVPT-Stat v2.0 files can be freely downloaded from IVPT_Stat@163.com.

References

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Navigating the Formality Spectrum in ICH Q9(R1)

The degree of formality in a risk management process should be customized to the organization's particular needs and the risks involved.

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Editor's Note: This article was peer reviewed by a member of *Pharmaceutical Technology*®'s Editorial Advisory Board.

Submitted: 20 April 2023.
Accepted: 11 May 2023.

The International Council for Harmonisation's (ICH) Q9 *Quality Risk Management* (QRM) guideline was published in 2005. The guideline went through a major revision in 2023, with the European Medicine Agency (EMA) publishing its endorsement of ICH Q9(R1), to become effective on 26 July 2023. The update was prompted by changes in the pharmaceutical industry and regulatory landscape, as well as advances in science and technology and stakeholder feedback. ICH Q9's revision provides guidance on QRM for the pharmaceutical industry and regulatory environment. Its purpose is to improve decision-making by offering a systematic approach that complements existing quality practices and guidelines. The revision focuses on the principles and tools of QRM, aiming to enable consistent and effective risk-based decisions for drug substances and products throughout their lifecycle. It does not create new expectations beyond current regulatory requirements. The document emphasizes that understanding formality in quality risk management can optimize resource usage and support risk-based decision-making by reflecting the level of importance, uncertainty, and complexity of the decision (1).

Furthermore, the revised ICH Q9 maintains alignment with other ICH guidelines, such as ICH Q8 (2), Q10 (3), and Q11 (4), which cover pharmaceutical development, quality systems, and drug substance development and manufacture, respectively.

Background

ICH Q9(R1) was revised to address formality among other topics and offer guidance on the appropriate level of formality to be used in a QRM process. The previous version of the guideline did not provide clear direction on the level of formality necessary for risk management processes, resulting in inconsistencies in how risk management was executed by different organizations.

The updated ICH Q9(R1) emphasizes the importance of balancing formality with practicality in risk management. It recommends that the degree of formality used in a risk management process should be commensurate with the potential risks involved, the complexity of the process, and the unique needs of the organization. The guideline presents examples of both formal and informal risk management processes and stresses that the level of formality used should be tailored to the specific situation (1).

Furthermore, a survey was conducted during a Pharmaceutical Inspection and Cooperation Scheme (PIC/S) QRM meeting in Taiwan in September 2018 to explore good manufacturing practice (GMP) inspectors' understanding and views on formality in QRM. The survey involved 27 inspectors from 14 countries, and the results showed that there was a need for clarity and guidance on formal QRM and less formal QRM applications. Most of the respondents (85%) suggested that the revision of ICH Q9 should clarify formal and informal QRM, while only 22% understood the concepts well. However, 81% of the respondents supported the use of informal risk management processes. Additionally, 76% of the inspectors felt that additional guidance was needed on what constitutes formal and informal QRM (5).

By providing guidance on the appropriate level of formality for a risk management process, ICH Q9(R1) ensures effective and efficient risk management. It also promotes consistency and transparency in risk management practices across organizations.

Formality in QRM

Formality in QRM is not a black-and-white concept, as varying degrees of formality can be applied during QRM activities, such as when making risk-based decisions. Formality can be viewed as a continuum that ranges from low to high. When deciding how much formality to apply to a QRM activity, there are several factors to consider. These factors include uncertainty, importance, and complexity (1).

Uncertainty refers to the lack of knowledge about hazards, harms, and associated risks. The level of uncertainty associated with a particular area being assessed for risk determines the level of formality required to manage potential risks. Effective knowledge management can reduce uncertainty, allowing accumulated and new information to be used to support risk-based decisions throughout the product lifecycle.

Importance refers to the significance of the risk-based decision in relation to product quality. The higher the importance of the decision, the more formality should be applied, and the greater the need to reduce the level of uncertainty associated with it.

Complexity refers to the level of intricacy of a process or subject area involved in QRM. The higher the complexity, the more formality should be applied to ensure product quality.

Higher levels of uncertainty, importance, or complexity may require more formal QRM approaches to manage potential risks and support effective risk-based decision-making.

The level of formality used in QRM must match the potential risks being addressed, the intricacy of the process, and the specific needs of the organization. The selection of the appropriate formality level should be based on a risk-based approach and should be periodically reviewed as the process or product evolves.

In QRM, low to high formality is defined by the level of structure and documentation employed in the risk management process. A low formality QRM usually involves a less structured, informal approach relying on the experience and judgment of the team to manage potential risks. This approach may involve brainstorming sessions or discussions to identify risks and may not necessitate extensive documentation or formal risk assessment tools. Low formality QRM may be adequate for simple risks with a relatively low impact of failure.

As per ICH Q9(R1), there are degrees of formality between the lower and higher levels that can also be utilized. This allows for the concept of moderate formality QRM to be introduced.

Moderate formality QRM involves a more structured approach that uses established risk assessment tools and methods to identify and evaluate potential risks. This may entail using standardized risk assessment matrices, checklists, or other tools to assess the likelihood and severity of potential risks. Moderate formality QRM may be suitable for complex issues or processes that require a more rigorous approach.

High formality QRM involves an extremely structured approach that includes detailed documentation and formal processes for risk identification, evaluation, and control. This may entail utilizing formal risk assessment methods such as failure modes and effects analysis (FMEA) or fault tree analysis (FTA) and may necessitate extensive documentation of risk management decisions and actions taken. High formality QRM is typically used for high-risk processes or products where the impact of failure could be severe.

Understanding the degree of formality in QRM

Companies can use standard criteria to determine the level of formality required for a process according to the new ICH Q9(R1) guidance. These criteria include evaluating the level of uncertainty, importance, and complexity in a process. By establishing what constitutes low, medium, and high uncertainty and complexity, the recommended level of formality can be determined using the formula:

Uncertainty x Complexity x Importance = Degree of Formality

Establishing pre-determined standard levels of formality is essential to ensure consistency in decision-making within the quality management system (QMS).

Formality in the QMS. The level of formality in a QMS should be appropriate to the size, complexity, and risk of the organization's processes and products. The choice of formality level should be based on a risk-based approach and should be re-evaluated regularly to ensure the QMS remains effective and efficient (3).

Change control. Formality is an important aspect of change control processes, which are designed to ensure that changes to processes, products, or systems are managed in a controlled and systematic manner to minimize the potential adverse impact on quality, safety, or efficacy (6).

The level of formality in change control processes may vary depending on the nature and complexity of the change. The following are some examples of the degree of formality in change control:

- **Low formality:** Simple, well understood, low-risk changes may be managed through rationale documentation. For example, a change to a non-critical process that has a minor or no impact on the product may be approved through a rationale documented in the change and approved by applicable stakeholders.
- **Moderate formality:** Changes that are well understood that have a moderate impact on the product or process may require a more structured method to document potential risks, such as FTA, risk ranking and filtering (RRF), What If tool, etc.
- **High formality:** complex changes with minimal process knowledge that can have a significant impact on the product, process, or system may require a highly structured and use of formal tools such as process hazard analysis (PHA) or FMEA. For example, a change to a product formulation or manufacturing process that has a high impact on product quality

or safety may require a formal more rigorous documentation process that includes detailed risk assessment, validation, and verification activities.

To ensure that the level of formality is appropriate, change control processes should follow a risk-based approach and be proportionate to the level of risk associated with the change. It is essential to document and communicate the change control process clearly to all stakeholders to ensure that changes are managed consistently and effectively. Regular review and improvement of the change control process can help to ensure its effectiveness and efficiency over time.

When evaluating the impact of a change on product quality, several factors should be considered (3):

- **Potential impact on critical quality attributes (CQAs):** The change may impact CQAs of the product, which are those attributes that are essential to its safety, efficacy, or performance.
- **Potential impact on regulatory compliance:** The change may affect the product's compliance with regulatory requirements, such as those related to safety, efficacy, or quality.
- **Potential impact on patient safety:** The change may pose a risk to patient safety, such as by increasing the risk of adverse reactions or other negative outcomes.
- **Potential impact on manufacturing process:** The change may impact the manufacturing process, potentially leading to variability in product quality, reduced yields, or other negative outcomes.

If the potential risks of the change are deemed to outweigh the potential benefits, a decision may be made not to implement the change. However, if the change is deemed necessary, steps should be taken to mitigate the potential risks through appropriate risk management strategies, such as process validation, increased testing, or other design control measures. In any case, the decision to implement or not implement a change should be well-documented and based on a thorough evaluation of the potential risks and benefits.

A high level of formality is typically required to ensure a rigorous understanding of whether a change is expected to negatively impact product quality.

Deviations. When it comes to managing deviations, formality refers to the level of structure and documentation involved in the process of handling deviations from established procedures, processes, or specifications. Deviations can arise due to various reasons, such as equipment malfunction, human error, or environmental conditions, and can impact the quality, safety, or efficacy of products or processes.

The level of formality required in managing deviations may vary depending on the nature and severity of the deviation. For instance, minor deviations that do not significantly impact product quality, safety, or efficacy may be managed through simple documentation of root cause and remediations, while deviations that have a moderate or significant impact may require more structured and formal deviation management processes, including investigation, analysis, and corrective and preventive action.

The level of formality used in managing deviations should be based on a risk-based approach and proportionate to the level of risk associated with the deviation. The deviation management process should be documented and communicated clearly to all stakeholders to ensure that deviations are managed consistently and effectively. Regular review and improvement of the deviation management process can help to ensure that it remains effective and efficient over time.

The following are some examples of the degree of formality in managing deviations:

- **Low formality:** Minor deviations that do not have a significant impact on product quality, safety, or efficacy may be managed through a simple documentation of root cause of deviations and remediations. For example, a deviation that results from a missing or incorrect documentation of a non-critical parameter in a batch record review may be managed through a simple documentation of the event, cause, and remediation, such as, a missing digit in an equipment number when recording in the batch record.
- **Moderate formality:** Deviations that have a moderate impact on product quality, safety, or efficacy may require a more structured deviation management process that involves formal documentation and review. For example, a deviation that results in a change in a critical process parameter may require a formal deviation report, investigation, and approval process, such as, failure to agitate the solution for the full 30 minutes as required by the batch record.
- **High formality:** Deviations that have a significant impact on product quality, safety, or efficacy may require a highly structured and formal deviation management process. For example, a deviation that results in a failure of a critical quality attribute or parameter may require a formal investigation, root cause analysis, and corrective and preventive action (CAPA) process, such as an out of specification for an in-process test (e.g., pH, temperature).

Product complaints. When managing product complaints, formality refers to the level of structure and documentation used. Complaints can come from various

sources and provide valuable feedback on product performance and customer satisfaction. The level of formality needed may vary depending on the nature and severity of the complaint. The following are some examples of the degree of formality in product complaints:

- **Low formality:** Simple, low-risk complaints may be managed through informal processes such as verbal communication or email exchanges. For example, a customer complaint about a minor packaging defect may be addressed through a quick discussion among the team members involved, such as complaint about the number of tablets in the bottle (contained 99 vs. labelled 100).
- **Moderate formality:** Complaints that have a moderate impact on product quality, safety, or efficacy may require a more structured complaint management process that involves formal documentation and review. For example, a complaint about a potential quality issue may require a formal investigation and response process, such as complaint about colour of the tablets (white vs. pale yellow).
- **High formality**: Complaints that have a significant impact on product quality, safety, or efficacy may require a highly structured and formal complaint management process. For example, a complaint related to a serious adverse event or product recall may require a formal investigation, root cause analysis, and CAPA process, such as complaint about a patient feeling dizzy and lightheaded after taking the product. It is essential to document and communicate the complaint management process clearly to all stakeholders to ensure consistent and effective management of complaints. Regular review and improvement of the process can ensure its effectiveness and efficiency over time. The level of formality should be based on a risk-based approach and proportionate to the level of risk associated with the complaint.

Formality in decision making. Formality can be a factor in driving effective decision-making, but it is not the only factor. The level of formality required for effective decision-making can vary depending on the nature of the decision and the level of risk associated with it.

While formality can play a role in driving effective decision-making, it is not the only factor to consider. The appropriate level of formality can vary depending on the decision's nature and associated risks.

Formality can be beneficial in decision-making in several ways. For instance, it can increase clarity, consistency, transparency, and accountability in the process. Additionally, a formal decision-making process can help manage the level of risk associated with the decision. However, it is important to note that excessive formality can be counterproductive, leading to bureaucracy, slow decision-making, and discouraging innovation (7).

Therefore, decision-makers should strive to strike a balance between formality and flexibility. They should also consider the benefits and drawbacks of formality when designing decision-making processes. Ultimately, the level of formality required should be proportional to the level of risk associated with the decision, and the process should be adaptable to changing circumstances.

In summary, formality can be a helpful factor in driving effective decision-making, but it should be balanced with flexibility and a willingness to adapt to changing circumstances. The level of formality required should be proportionate to the level of risk associated with the decision, and decision-makers should consider both the benefits and the drawbacks of formality when designing decision-making processes.

Ensuring effective identification, assessment, and management of risks in QRM can be influenced by formality. Formal processes can aid in consistent decision-making and foster transparency and accountability, while also ensuring relevant information is considered. However, an appropriate balance between formality and practicality is necessary as excessive formality can cause unnecessary bureaucracy and delay decision-making, whereas insufficient formality can result in inconsistency and lack of transparency. The level of formality required should correspond to the level of risk associated with the product or process being assessed. It is crucial to establish decision-making processes that are well-documented, transparent, and based on sound scientific principles while maintaining flexibility. Regularly reviewing and improving these processes can help sustain their effectiveness and efficiency over time. In QRM, formality and subjectivity are both crucial considerations.

Formality and subjectivity

In QRM, formality pertains to the level of structure and documentation used in the decision-making process. A formal QRM process involves specific procedures, tools, and documentation to ensure consistency, transparency, and accountability. Conversely, an informal QRM process depends more on expert judgment and experience and may be less structured.

Subjectivity, on the other hand, refers to personal biases, opinions, and preferences that may affect the QRM process. It can occur due to a lack of objective data or different interpretations of available data. Although formality can reduce subjectivity, it cannot be eliminated. Expert judgment and experience are crucial for informed decision-making, and various stakeholders may have different perspectives on the risks and benefits of a particular product or process. To mitigate the impact of subjectivity, decision-making should be based

on sound scientific principles, and all relevant information should be considered. This may include using multiple sources of data, conducting independent reviews, and obtaining input from different stakeholders.

In summary, both formality and subjectivity are essential considerations in QRM, and a balance must be maintained between the two to make informed decisions based on sound scientific principles.

Factors impacting formality

Regulatory requirements may dictate a certain level of formality in QRM activities. Therefore, it is important to ensure that the level of formality applied meets regulatory expectations. For example, the United States Food and Drug Administration (FDA) does not have a specific requirement for the level of formality in risk assessments but expects companies to use a risk-based approach in quality management. This includes conducting risk assessments and using the results to make decisions about product development, manufacturing, and control.

During inspections or regulatory submissions, FDA may review a company's risk assessment and associated documentation. The level of formality in a risk assessment should be appropriate for the level of risk associated with the product or process, and the assessment should be well-documented and based on sound scientific principles. If the level of formality is not appropriate or the assessment is poorly documented or not based on sound scientific principles, FDA may require additional information or further assessment before approving the product or process. The acceptance of the risk assessment by FDA will depend on these factors, rather than the level of formality used.

The level of knowledge that is available about the product and process being assessed can also influence the level of formality required in QRM activities. The more knowledge that is available, the lower the level of uncertainty, and the lower the need for formal approaches.

At no point should the level of resources available, including time, budget, and personnel, affect the level of formality that can be applied to QRM activities.

Formality in documentation

The phrase "if it's not documented, it did not occur" is commonly used in quality management systems to highlight the significance of documentation as a means of evidence for compliance with established procedures and requirements. Documentation is a critical component of quality management, providing a record of activities, decisions, and outcomes that can be scrutinized and audited for compliance, accountability, and continuous improvement. It can take various forms, such as standard operating procedures, work instructions, records, reports, and forms. However, it is important to recognize that documentation alone cannot ensure the effectiveness of a quality management system or the quality of a product or service. Although documentation provides evidence of compliance, it does not guarantee the effectiveness of the documented procedures or the satisfaction of customer requirements. Therefore, companies should establish robust processes for documenting activities, decisions, and outcomes and regularly review and update their procedures to ensure continued effectiveness. In addition, companies should prioritize training and communication to ensure that employees comprehend the importance of documentation and its role in ensuring quality and compliance.

When presenting to regulators, companies must demonstrate that QRM has been conducted appropriately and that the risks associated with a product or process have been adequately identified and managed, irrespective of the level of formality employed. If a low formality approach has been used, the key decisions taken during the risk management process, including the identification of potential risks, the assessment of their severity, the evaluation of available risk control options, and the implementation and monitoring of risk mitigation measures, should still be documented.

Although the level of documentation required may differ depending on the level of formality used, companies must ensure that they have adequate documentation to demonstrate that the risk management process was conducted appropriately and that the risks were efficiently managed.

When presenting to regulators, companies should furnish clear and concise documentation outlining the key decisions and the rationale behind them. This may include risk assessment reports, meeting minutes, decision logs, and other relevant documentation. To summarize, regardless of the level of formality used, documenting the key decisions made during the QRM process is essential to demonstrate that risks were effectively identified and managed by providing clear and concise documentation outlining key decisions and their rationale.

Conclusion

The revision of ICH Q9(R1) reflects the growing importance of QRM in the pharmaceutical industry and aims to support the development of safe and effective pharmaceutical products. However, implementing effective QRM can be challenging for companies due to several factors.

Firstly, a lack of understanding and commitment can lead to insufficient resources, training, and support for QRM activities. Secondly, inadequate risk assessment tools, such as templates and software, can result in inconsistent and incomplete risk assessments. Thirdly, a culture of complacency can hinder proactive identification and management of risks. Fourthly, some companies

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Automation Aids Cell and Gene Therapy Production

Manufacturers face the challenge of meeting growing demand for personalized biopharmaceuticals.

Jennifer Markarian is manufacturing reporter for *Pharmaceutical Technology Europe*®.

As more cell and gene therapies (CGT) advance through clinical trials toward potential approval and commercialization, manufacturers are looking to automated strategies and standardized systems for scaling up production efficiently. At the same time, the diversity of products—in the case of autologous cell therapy, a different product for each individual patient—means that any manufacturing set-up will need to be highly flexible.

Production challenges

Commercial production of cell therapies is currently less than 5000 doses per year, but global demand is in the millions of doses, reports Jason Arcediano, chief business officer at Multiply Labs, a robotics technology company creating systems for bio/pharmaceutical manufacturing, including an end-to-end, closed manufacturing system for CGT. Existing processes and equipment do not have the throughput needed to meet patient demand. Staffing is also a challenge. "The industry is seeing high attrition rates—over 25%—because there is a huge demand for trained teams that can run these complex processes," says Arcediano. Complex, manual handling steps limit throughput and increase opportunities for error. "The large cell therapy manufacturers are seeking to reduce failure points, and there is general agreement that automation is the solution," he adds.

Current manufacturing capacity is inadequate to meet patient demand, and as more new therapies are developed, the unmet need will only increase unless there is a manufacturing paradigm shift, adds John Tomtishen, vice-president of operations at Cellares, which is preparing to launch its proprietary, end-to-end automated system, the Cell Shuttle. "Automation can transform the manufacturing paradigm and help companies scale their therapies effectively to make them accessible to all patients in need," he says.

The manual and modular approaches used in early development tend to be carried over into commercial manufacturing, but these approaches pose challenges for scalability, adds Dan Strange, CTO, Cellular Origins, a spin-out launched in January 2023 from Cambridge, UK-based technology company, TTP, with a proprietary, automated system for scalable CGT manufacturing.

Cost and drug safety are both prominent challenges for the manufacturing process, which has traditionally been highly manual and complex. "We estimate the cell therapy manufacturing process may have upwards of 40 process steps, which is not only labour intensive but creates opportunities for errors and contamination that lead to failures," says Betty Woo, vice president of cell, gene, and advanced therapies at Thermo Fisher. "By aseptically closing and automating the manufacturing process, we're reducing the need for the highly specialized labor required to produce these therapies, thereby eliminating touchpoints, reducing expenses, and ultimately increasing the reproducibility and predictability of the process. Automating in this way will, to some extent, also help alleviate the workforce challenges we're seeing across the industry particularly in emerging geographies."

The optimal workflows for CGT are still being developed and processes are not yet standardized, leading to a need for flexible instrumentation, says Woo. "As the field progresses, we expect more standardized workflows to be established, [with] improved consistency, efficiency, speed, and throughput. These improvements will likely be catalyzed by technologies that aid in further scalability—down, up, and out; in-line sensing; and autosampling," she predicts. "Standardization reduces variability and moves us closer to a more consistent and predictable outcome, while automation provides robustness, consistency, speed, and throughput. Automation in its ideal state will drive efficiency and reduce the cost for manufacturing these life-saving therapies."

Factory in a box

With the current manual or semi-automated manufacturing systems, production space and the need for highly skilled operators are barriers to production capacity. Closed and automated systems address both of these bottlenecks.

"Current, manual systems require ISO 7 or 8 cleanrooms, but a fully closed system can be placed in a controlled not classified (CNC) space," explains Tomtishen. The Cellares Cell Shuttle platform is a "factory in a box" with all unit operations inside the closed system, which is about the size of a typical cleanroom workstation. Robotics perform material transfer from one unit operation to another. The throughput of the Cell Shuttle depends on the production process, notes Tomtishen. "With a seven-day process, you could manufacture approximately 800 batches per year per Cell Shuttle. Additional Shuttles could be added to scale-out if more capacity is needed," he explains.

All the software and hardware in the platform has been developed by Cellares over the past four years. "The software enables flexibility to develop the manufacturing workflow. The research scientist has full control over the parameters in the unit operations," says Tomtishen. He works with users to help them develop workflows and to transfer any processes already developed on other equipment to the proprietary Cell Shuttle equipment.

Partners in Cellares' Early Access Partnership Program include the Fred Hutchinson Cancer Research Center, PACT Pharma, and Poseida Therapeutics. The partners helped evaluate prototypes and assess product requirements, release criteria, and process workflows. Cellares is continuing to refine the technology and expects the Cell Shuttle to be market-ready in 2024, which will make it available for process development and clinical and commercial manufacturing. In the "single-platform" approach, development and all manufacturing stages take place in the same equipment, which accelerates time to market.

Throughput step-change

Multiply Labs has designed a fully automated system with robotic handling that offers a solution to the need for increasing throughput, reducing error, and allowing flexibility, Arcediano says. The system has been designed to be compatible with existing equipment through a consortium launched by Multiply Labs in 2021 to tackle the challenge of debottlenecking commercial manufacturing of CGT using robotic automation. Manufacturing development is overseen by the University of California, San Francisco (UCSF) under a sponsored research agreement. Other consortium members are contributing their expertise to bring robotic automation to their equipment within the Multiply Labs' Robotic Cluster, including Cytiva's bioreactors, Thermo Fisher Scientific's incubators, and Charles River Laboratories' rapid microbial detection platform and endotoxin testing system for automating quality control (1).

"We aim to integrate with all major equipment manufacturers, so that a CGT manufacturer can use the validated equipment and instruments they want in their process," states Arcediano. "We've started with the consortium members, but we are working with other vendors already." Using validated equipment, process, and software leads to a shorter path forward with regulatory agencies, Arcediano adds. All equipment will be integrated with the robotic handling and Multiply Labs' in-process control system in a standardized, "plug-and-play" method of information flow that is aligned with best practices from industry organizations, such as the Alliance for Regenerative Medicine. The equipment-agnostic system can use the best currently available instruments as well as be easily updated to use next-generation instruments, Arcediano adds.

Another feature is that all data are captured digitally. Arcediano explains that the end-to-end system could be run with only one operator; the operator loads the materials and then the robots transfer material from step to step through the aseptically controlled, fully closed system. Fluid transfer is handled with a proprietary robotic click connector system that eliminates the need for tube welding.

The automated system has a much smaller footprint than traditional manual processes. Because operators do not need access to the unit operations, the modules can be stacked two to three high and five to six deep. "A ballroom facility might have 1000 to 2000 square feet, while our system requires between 200 to 300 square feet," says Arcediano. Throughput is also higher than traditional methods. "Instead of one client [i.e., patient product] at a time, our system can prepare up to 36 products at the same time," he adds. The system can be scaled out as needed by including more modules for greater throughput. It can also be used for product development or commercial manufacturing, eliminating tech transfer.

Flexible workflows

Cellular Origins' platform is a configurable robotic automation solution that enables scalable, cost-effective, and space-efficient cell therapy manufacture that is designed for adaptability, says Strange. The platform consists of a universal transport system for automated movement of consumables, reagents, and patient materials; a tube-management system that enables automated routing; and a sterile fluid-transfer system that welds tubes, moves fluids, and provides real-time analysis and quality control, he explains. "These tasks are carried out by a combination of autonomous mobile robots with proprietary, future-proofed end-effectors and a configurable automation console that integrates existing third-party equipment. These tasks are all integrated within a data management system to ensure

full traceability of every process undertaken," Strange explains.

"Our platform enables therapy developers to use the tools and technologies from third-party vendors and combine them into a modular factory that can quickly scale to producing 10,000 therapies per year with a fraction of the labour of existing methods. Because the platform is built upon proven familiar technologies, it can potentially be used to scale those therapies currently in late-stage development."

Strange adds that the company is beginning to work with its first customers to develop system configurations and to deploy these systems at customer sites.

Patient-scale platform

Lonza's platform for autologous cell therapy manufacturing, the Cocoon, is a functionally closed, automated system that is currently being used to support clinical trials in Europe and North America, in both centralized and decentralized manufacturing models, says Tamara Laskowski, head of Clinical Development, Personalized Medicines at Lonza. "With a growing number of clinical-pipeline applications, we are optimistic about the future use of the Cocoon Platform in commercial applications as well," she adds.

Several unit operations—from starting materials through to final harvest—take place inside the functionally closed, single-use cassette, in processes which are tailored for each product. The Gen2 Cocoon, introduced in April 2022, added magnetic cell separation capabilities, allowing separation of cell types of interest, such as T cells, for processes that require this additional upstream sample preparation step, says Laskowski.

Decentralized manufacturing, which is closer to the patient at the point of care, reduces logistic challenges but can present quality concerns. Automated, closed systems, however, may resolve these concerns. "Producing cell therapies in automated, closed manufacturing systems will help to reduce reliance on manual operations and variability in process performance, improve data management, and may enable the realization of a standardized level of quality across point-of-care sites," suggests Laskowski.

Automating allogeneic CGT

Allogeneic CGTs aim to use a single source of cells to treat many patients, with manufacturing at a larger scale than autologous CGTs. Automation, however, is expected to be important for these processes as well.

"Given the large-volume productions in allogeneic processes, automated systems that support final product harvest, formulation, and fill/finish are advantageous," says Laskowski. "Such systems can reduce risks associated with manual processing and human error, ensure proper addition of cryoprotectant, and decrease time requirements to cryopreservation and storage of the product. As additional allogeneic CGT modalities emerge, we anticipate new developments in automated platforms to support culture and expansion of adherent cells and enable multi-stage manufacturing processes involving modified culture regimens and conditions for cell differentiation."

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may view regulatory requirements as a barrier to effective QRM implementation, leading to a compliance-focused approach rather than truly managing risks. Finally, limited resources can make it difficult to prioritize and allocate the necessary resources for risk management.

To overcome these challenges, companies need to prioritize risk management, invest in necessary resources, and foster a culture that values QRM. This includes committing to QRM principles and understanding its benefits, using appropriate risk assessment tools, proactively identifying and managing risks, and allocating the necessary resources for risk management. By doing so, companies can ensure the safety and quality of their products and maintain regulatory compliance.

In QRM, maintaining formality is crucial as it promotes consistency, transparency, and documentation of risk assessments and decision-making processes. Formality entails adhering to established guidelines and documentation requirements that ensure all relevant factors are considered and decisions are made objectively and consistently. It also supports accountability and traceability, which are vital in regulated industries such as pharmaceuticals, where regulatory compliance is paramount. Furthermore, a formal approach to QRM can enhance communication and collaboration among various stakeholders, such as quality control, production, and regulatory affairs. Ultimately, formality in QRM can improve the quality and safety of pharmaceutical products by ensuring that the process is conducted in a rigorous and systematic manner.

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Monitoring for Microbes

Data from environmental monitoring can assist in keeping sterile environments sterile.

Susan Haigney

Manufacture of medicines is most often required to be performed in a sterile environment to ensure the quality and safety of these products. Microorganisms lurking in the air or on surfaces may degrade APIs and impact their effectiveness, according to Anne-Grit Klees, PhD, BioMonitoring Portfolio Manager for The Life Science business of Merck KGaA, Darmstadt, Germany. "Furthermore, pathogenic and even many non-pathogenic microorganisms can cause serious and life-threatening infections in patients, especially if immunodeficient. For this reason, particularly injectable drugs must be sterile. This can be achieved by final sterilization of the drug or, if not possible, by aseptic manufacturing."

It is recommended by regulators that microbial monitoring of cleanrooms and isolators is performed by a combination of methods, says Klees. "Air monitoring is performed with a combination of volumetric microbial air samplers (active air monitoring) and settle plates (continuous passive air monitoring). Surfaces and personnel should be monitored with contact plates or swabs. Using alternative methods is also permissible if these have been validated and show comparable or superior efficacies."

Pharmaceutical Technology Europe® spoke with Anne-Grit Klees to find out some environmental monitoring (EM) best practices manufacturers can follow to ensure the safety of their products.

Best EM practices

PTE: What are the differences between environmental monitoring in aseptic versus non-aseptic manufacturing?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): The environmental monitoring methods are usually the same for both. The higher the cleanroom grade, the higher the monitoring frequency and number of sample locations. The monitoring equipment and culture media should possess features to match the cleanroom-grade requirements. For air samplers, features such as cleanability, resistance towards disinfectants, emission of particles, and disturbance of the unidirectional air flow are important to consider and should match the cleanroom concept. For culture media, there is a choice between single bagged ones for lower risk areas and irradiated, double, or triple bagged ones for the different manufacturing lines.

PTE: What are some best practices for air monitoring?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): When selecting an air sampler, important features to consider are sampling volume accuracy, a good efficiency of the method to collect small particles, and whether damage to microorganisms is avoided during the sampling process. The recovery efficiency should be validated by the supplier according to ISO [International Organization for Standardization] 14698. What also matters is ease-of-use to minimize the risk of human errors, low particle emissions to prevent contamination of the cleanroom, good cleanability, and minimal disturbances of the unidirectional air flow. If the air sampler can be integrated into external tracking software systems, all data can be handled. This helps to observe trends.

PTE: What are some best practices for surface monitoring?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): Surface monitoring is usually performed either with contact plates or swabs, depending on the accessibility of the sample location. Culture medium selection should be based on the ability over the complete shelf-life to detect a broad range of microorganisms. Furthermore, the media formulation should ensure that any potential growth-inhibiting substances such as disinfectant residues or antibiotics are inactivated. To maintain the cleanliness of the sampled surface

any culture media residues should be removed after sampling.

PTE: What are some best practices for personnel monitoring?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): Personnel monitoring is always performed on the gloves, but also on gowning. The growth promotion properties of the selected media must [often] allow in-house skin flora of the personnel to grow. It is important that contact plate samples are taken of the personnel's gowning or gloves before leaving the cleanroom. If glove tests are performed after critical interventions, the outer gloves should be replaced before continuing manual work.

PTE: What are the latest advancements in processes and workflows for environmental monitoring?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): These are stated in the current 2022 version of the EU [European Union] CGMP [current good manufacturing practice] Annex 1. While the well-established volumetric air samplers, settle plates, contact plates, and swabs are still recommended to be used frequently, a new focus is on the importance of a contamination control strategy of the pharmaceutical company. This should include a risk-based sample plan that states the frequency and sample locations for those methods. There are additions about using validated rapid or automated technologies, also for continuous volumetric air sampling. These need to be equal to or superior to the above-described methods.

Tools for performing EM

PTE: What are some of the best tools for performing environmental monitoring of cleanrooms?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): Some portable microbial air samplers (e.g., the MAS-100 NT) offer high accuracy and excellent sampling efficiency. It is small enough to sample close to critical sample locations, can take up to 30 samples in one cleanroom, is easy to disinfect and available with an exhaust filter. It minimizes disturbance of the unidirectional air flow and is compatible with several EM software systems. Triple-bagged and gamma-irradiated ICR or ICR+ culture media for grade A and B cleanrooms reduce the contamination risk because outer bags can be removed in the material lock. Plate versions with locks allow safe transportation for incubation after sampling.

PTE: What are some of the best tools for performing environmental monitoring of a restricted-access barrier system (RABS)?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): In a RABS, the same environmental monitoring tools can be used as in a cleanroom. However, if a RABS system is decontaminated with vapourized hydrogen peroxide (VHP), it must be ensured that the culture media within the RABS during decontamination are protected by VHP-impermeable bags. These can be hung up during decontamination. To prevent false negative results, all ICR settle plates, contact plates, and ICR swabs are formulated to neutralize VHP residues. The MAS-100 NT can also withstand VHP decontamination if in switched-off mode. Alternatively, MAS-100 air samplers specially designed for isolators can be used.

PTE: What are some of the best tools for performing environmental monitoring of isolators?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): In isolators, space is limited, so the control unit of the dedicated air samplers (e.g., MAS-100 Iso line) for isolators are positioned on the outside, saving space inside. The distance can be up to 10 m. A double-valve system prevents cross-contamination and the air tubing can be decontaminated with VHP (e.g., with the MAS-100 Iso MH, one control unit can handle up to four sampling locations.)

Certain packaging designs (e.g., IsoBag rapid transfer bags) save space in isolators. They readily provide ICR settle or contact plates in a DPTE [differential pressure transmitter for air] beta bag. Plates can be safely transferred via rapid transfer alpha ports whenever needed.

Analytics of EM data

PTE: How are data obtained from environmental monitoring? How are these data used in pharma manufacturing?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): The data are usually obtained as colony forming units from the culture media used in active and passive air sampling as well as surface and personnel sampling. The new EU GMP Annex 1 suggests using the data both for batch release decisions and for trending analyses. It is possible to detect adverse trends by increasing excursions from action limits or consecutive excursions from alert levels. Also, noticing changes in the microbial flora is important. This helps to maintain the level of cleanliness and address issues by corrective and preventive actions.

PTE: Are there specific analytical tools that work best for different types of environmental monitoring?

Anne-Grit Klees (The Life Science business of Merck KGaA, Darmstadt, Germany): As the amount of data generated by environmental monitoring is huge, the PDA [Parenteral Drug Association] Technical Report No. 13 outlines computer-based tracking tools as essential. Specific software systems designed for environmental monitoring help to find adverse trends, and the stored data may allow conclusions as to what the root cause is. One important feature of the sampling equipment is that it should allow data transfer into such software systems, so that all tracked data are handled in a single database. This helps to stay compliant with the standard rules for data integrity. **PTE**

Top 10 Considerations when Meeting with Regulators

Preparation is essential for regulatory meetings—it not only crystallizes what is needed from the regulators, it helps them better understand the development programme and potential challenges.

Mark Lane,
is vice president of Development Consulting and Scientific Affairs at PharmaLex.

Think of regulators as allies. They share the goal of bringing life changing medications to the patients that need them and are partners in development. Meetings with regulators should, therefore, not be seen as discussions to avoid or as hurdles to overcome but as opportunities for sharing critical information and gaining alignment.

Aside from gaining the regulatory agency's feedback on your development programme, such meetings enable drug developers to build strong relationships that facilitate moving a drug to market. Through such meetings, it is possible to gain a better understanding of what regulators need and when they need it, which increases the ability to reach an aligned position.

In this article, the top 10 considerations for meetings with regulators are detailed.

1. What are the various types of meetings that sponsors can expect to have with regulators?

The United States Food and Drug Administration (FDA) has four basic types of regulatory meetings for new chemical entities: Type A is generally when a programme is stalled; Type B is typically an end-of-phase or key milestone meeting; Type C is designed to capture everything else needed for a development not included in the other meeting types and includes meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. Type D is a newer meeting designed to address a narrow spectrum of issues in a shorter time frame. FDA expects the sponsor to present a position on their development strategy, to which FDA can provide input.

When establishing a clinical trial in a targeted country in Europe, meetings with regulators might be held at the national level, whereas scientific advice meetings would be held with the European Medicines Agency (EMA). Innovator companies seeking to navigate within EMA can take advantage of Innovation Task Force (ITF) briefing meetings.

2. What are some of the key differences between FDA meetings and those with EMA or national authorities?

In Europe, requests for meetings with EMA are submitted via a defined calendar, whereas meetings can be requested at any time with FDA. In the United States, the type of meeting a company/drug developer is interested in is pre-defined based on the meeting types described earlier and all requests for meetings, briefing documents, and other collateral are submitted based on specific schedules outlined in the FDA guidance. The meeting request and associated briefing book describe the drug under development, the status of the programme, the questions addressed to FDA and an associated company position and rationale for the position.

In contrast, the EMA scientific advice process takes the form of questions posed by the product developer, along with the way the company plans to develop the product and its potential solutions. EMA offers its recommendations on the proposals and, depending on the complexity of the questions, may request a meeting with the developer. Another difference is that there is no charge for meetings with FDA whereas in Europe, depending on the status of the developer, there may be a fee.

3. Are there timelines that regulators must meet when responding to a company request?

There is significant variation within FDA, depending on the type of meeting requested. This includes when the agency must respond to the request, when the meeting has to be scheduled, the timing of the meeting, and the delivery of the briefing package to the agency. It's not just one process.

In Europe, timings also vary according to the nature of the meeting requested and the complexity of the questions. For both agencies, relevant laws and regulations allow for flexibility around scheduling meetings, so it's important to properly position the request so that the agency understands the urgency of the matter.

4. What are common mistakes that companies might make regarding agency meetings?

Underpreparing. A strategy must be well thought out and finalized, and the briefing book must be in a mature stage before submitting a meeting request. This means having a clear understanding of the objective of the meeting requested and preparing accordingly. Invariably the content of the specific questions will change somewhat based on the details of the company position and rationale. EMA, for example, will respond to specific questions on the development plan about a specific medicine, so a target product profile is important when preparing a briefing package. It is also critical to have a fallback position that will advance the programme in the event FDA does not align with the company position. This makes proper preparation key, so rehearsals and clearly defined roles and responsibilities for each team member are recommended.

5. What are the key points to remember?

The regulatory agency should be viewed as a partner, and it is recommended for the company/drug developer to become familiar with how the agency might view the development programme before a meeting is requested. The agency is focused on safety and efficacy, so may have a different perspective to company clinicians or key opinion leaders—try to get on the same page before the meeting. Furthermore, assume that the agency has a broader view on the matter and may have information that is not openly accessible, such as other sponsors' programmes. It is essential to have the right subject matter experts in these meetings. For example, experts in preclinical models for early-stage meetings versus clinical experts at later phases of development.

It is critical that the sponsor or their service provider designate a project manager who ensures that the team adheres to timelines built in for all stages.

6. Are there tips on how to develop a plan and timeline for meeting with regulators in different regions?

FDA and EMA do have an option for obtaining joint advice. Of course, the advantage is obtaining the view of both agencies at or nearly at the same time. However, this does not afford the possibility of adapting the questions or, perhaps most importantly, the company position and rationale for meeting with additional agencies based on the feedback from the first agency. Treatment guidelines, regulatory guidance, and precedence often differ, for example, between FDA and EMA. Meeting with one first before meeting with the other likely strengthens the company position and increases the likelihood of gaining alignment.

7. Are there particular schemes or designations in the US to consider?

FDA has numerous special designation programmes that are designed to assist sponsors who are developing products that are innovative and/or hold promise in certain disease areas. These programmes vary in their requirements and benefit to the sponsor, so careful consideration of the suitability of each designation is critical.

8. Are there also particular schemes in Europe that should be considered?

In addition to the orphan drug designation, EMA's Priority Medicines scheme (PRIME) is designed to enhance the support of drugs that target an unmet need. The scheme enables companies to build a close relationship with EMA, with continuous support dialogue. However, the eligibility criteria for this scheme are strict, with only about a quarter of applicants being successful.

9. What should be done to keep to timelines set for meetings with regulators?

It is critical that the sponsor or their service provider designate a project manager (PM) who ensures that the team adheres to timelines built in for all stages. The PM also serves as point of contact for their counterpart at the agency. Have a clear understanding of questions and goals before requests for meetings with agencies are submitted. Agencies expect information to be delivered when they ask for it, so, prior to requesting a meeting, the project should be at the refining stage, not starting the package from scratch.

10. What is different about FDA's Type D meetings?

This is a new meeting type that gives companies the opportunity to address more focused issues in a shorter timeline than Types A, B, and C. For example, if there is a follow-up question from a previous meeting with the regulator, or if there is a narrow issue that requires agency input, and there are only a limited number of questions, a Type D meeting can be requested. The benefit of these meetings is the timelines generally result in answers quicker than Type B or C meetings. **PTE**

The Inspection Result: Warning Letters and Form 483s

USFDA Warning Letters and Form 483s can offer a path to better compliance, says Siegfried Schmitt, vice president, Technical, at Parexel.

Q: The United States Food and Drug Administration (FDA) publishes redacted Warning Letters and Form 483s with inspection observations on their website. What can we learn from these, and where do we need to be cautious?

A: Such information can be considered compliance intelligence (i.e., it forms part of the pool of information a company relies on to build an appropriate quality management system, design its systems and operations in such a way that they adhere to the regulations and deliver a product that meets its predetermined quality attributes, and to build and staff their organization adequately). Regulations and laws are limited in their comprehensiveness, which means that there are many possible ways for companies to achieve compliance. Sometimes, the appropriateness is challenged or found defective in inspections by regulators, and this will lead to observations on FDA's Form 483. In cases where FDA finds that the shortcomings are not addressed sufficiently and completely, the agency may issue a Warning Letter (WL). These are meant to be a last warning (1,2).

It is important to understand the context of the observation and appreciate its seriousness.

Clearly, any company can learn from mistakes made by others, helping them to prevent making the same mistakes. To understand the benefits and limitations of the learnings from WLs and form 483s, we need to look at what information they contain, or not. An observation on Form 483 may read like this: "Your media fills failed to accurately simulate commercial operations. Our inspection found the aseptic operations simulated during your media fills were not sufficiently representative of commercial aseptic manufacturing operations for (b)(4). For example, the type and frequency of manual interventions was not representative." What we can learn from this is that media fills must be as similar as possible to normal aseptic operations.

However, there are many things that we do not know, such as:

- The reason for that behaviour:
  - Did the company apply a risk-based approach that was not acceptable to the inspectors, or was it simply that the company decided to do less during the media fills?
  - Were the operators following the protocol or did they deviate?
  - Did the protocol provide sufficient clarity and detail or did the company rely on the experience of the operators?
  - Is there an appropriate quality culture in that company?
- Level of competency:
  - Were operators and managers insufficiently trained or aware of the regulations, or were they knowingly ignorant?
  - Was there adequate quality oversight or not?
  - Was this the first time, the company performed media fills?
- Complexity of the operation:
  - Does the operation require many different manual interventions or only a few?
  - Did this happen throughout the media fill or perhaps only during start-up, or perhaps only one of the shifts, or perhaps only with some of the media fills?

It is very unlikely that a reader of the FDA observation will have the answers to these questions. Yet, this is not necessary. It is important to understand the context of the observation and appreciate its seriousness. Then you need to ask the above questions about your operations, about your media fills. That is the real value that you will gain from these regulatory observations.

References

1. FDA. ORA FOIA Electronic Reading Room. *FDA.gov* (accessed 7 June 2023).
2. FDA. Warning Letters. *FDA.gov* (accessed 7 June 2023). **PTE**

Your opinion matters.

Have a common regulatory or compliance question? Send it to shaigney@mjhlifesciences.com, and it may appear in a future column.

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