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Unknown and Unknowable

Russell Madsen and James Agalloco

Quality cannot be verified through testing, especially at the limit of detection, and no test method can confirm the absence of a microbe or particle.

When determining what to measure and how, it is wise to remember what Albert Einstein once wrote on a blackboard in his office at Princeton University's Institute for Advanced Studies: "Not everything that counts can be counted, and not everything that can be counted counts"(1). Any measurement comes with questions, not only of accuracy and precision, but of relevance. Often, the numbers most critical for managing a given situation or an organization are "unknown and unknowable," a phrase that quality advocate W. Edwards Deming often repeated (1). Too often, one may try to force fit measurable limits (e.g., zero microbes or particles) on situations even though those limits are impossible to achieve.

Regulators emphasize the importance of measurement and validation. For instance, FDA's current good manufacturing practices (cGMPs) regulations stipulate that an organization's quality control operations should be responsible for "approving or rejecting all procedures or specifications [that have an impact] on the identity, strength, quality, and purity of the drug product"(1). This requirement embraces design and operational controls in several areas including utility systems, operating environments, packaging components, raw materials, and intermediate and finished goods release, and considers not only physical, but chemical and microbial attributes. Implicit in these determinations is the idea that the methods of analysis that are used must be valid. As written in the regulations, "The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented"(2).

Russell Madsen is principal of The Williamsburg Group (madsen@thewilliamsburg-group.com), and **James Agalloco** is principal of Agalloco & Associates (jagalloco@aol.com).

All test methods, however, are limited when they are required to confirm the absence of something. An instrument may record zero, but that only means that whatever is being measured is "not detected," which is different from saying that it is "not present." All tests have a limit of detection below which they cannot be used. When combined with the vagaries of sampling, the act of reporting "zero," "none," or "absent" as a test result is irresponsible. Thus, "absence of evidence is not evidence for absence"(3).

Any measurement comes with questions, not only of accuracy and precision, but of relevance.

Detection limits

These issues are confronted directly in the following situations, when:

- One attempts to measure things when the limit of detection is below the sensitivity of the measurement method.
- The sample is not representative of the material from which it is taken.
- The measurement method is not suitable for the attribute to be measured.
- Sampling influences the final measurement.

Examples include sterility testing of aseptically-manufactured sterile products; microbial environmental monitoring; container-closure integrity; visual inspection of parenteral products; trace impurity levels in APIs and excipients; blend uniformity of wet and dry granulations; and content uniformity of dosage forms, especially those with low levels of active ingredients.

When it is impossible to determine a quality attribute by testing, the correct approach is to rely on a system of measurements that yields accurate, reproducible, and definitive results for the parameters being evaluated. These results can then be used to estimate the levels of an attribute that can't be directly measured. This approach is used, for example, in the parametric release of terminally sterilized parenteral products. It demonstrates a state of control, in which every action produces the intended result every time.

The importance of validation

To produce drug products that routinely and consistently have the identity, strength, quality, and purity they are said to have, the measurement system for production and quality control must be in a state of control. Quality cannot be verified through testing, especially at the limit of detection. This is where validation comes in.

In the mid 1970s, validation requirements for sterilized products were set after some patients died after being treated with terminally sterilized parenteral drugs made in the United States and the United Kingdom (4,5). These drugs had all been tested and had passed the sterility testing requirements of the time. To prevent any future problems, processes now had to be validated, and manufacturers had to provide regulators with "documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes"(6).

Validation is based on independent verification that the operational controls (e.g., equipment, procedures, and materials) collectively provide confirmation that the system or process performs

as required. Parametric release, the most evolved state of validation, can assure what testing cannot: that the product meets its required quality attributes without analysis. Validation may not be able to provide absolute proof of the absence of a substance, but it comes closest to confirming absence and is substantially better than results derived from sampling and testing.

An instrument may record zero, but that only means that whatever is being measured is 'not detected,' which is different from saying that it is 'not present.' All tests have a limit of detection below which they cannot be used.

Patient safety concerns

A primary concern is patient safety when administering injectable products. The sterility test (7) was introduced in the 1930s, when injectable product manufacturing used primitive process equipment in minimally controlled environments and personnel often interacted directly with sterilized materials. While the test's statistical limitations have long been understood, it remains a regulatory requirement despite the many improvements that have been made to manufacturing processes since the 1930s (8). In commercial-scale operations, passing the sterility test is minimally useful and can reliably detect microbial contamination resulting from failure of the sterilizing cycle or aseptic processing system, typically in the range of 15–20% of the units processed.

There are also technical constraints to the sterility test: the test media supports a limited range of detectable microorganisms; the limit of detection is non-zero, unknown; etc. (9). Recent efforts to develop rapid sterility tests have been similarly flawed (10). Rapid sterility tests suffer many of the same limitations as the conventional test, including sampling, detectability, and sensitivity, albeit providing results more quickly.

The presence of particles in parenterals has been associated with pain and other adverse effects and patient risks (11–12), the extent and importance of which are being debated. The complete absence of particles is, like the complete absence of microbes, or sterility, a laudable but unreachable goal that cannot be demonstrated by testing. Knapp established a level of "uncertainty of outcomes" from any inspection method (13) and the US Pharmacopeial Convention (USP) acknowledged this reality in the phrase "essentially free of particles"(14). This phrase implies the goal of no particles, but acknowledges that there will be some. Unfortunately, FDA's expectations do not align with the technical realities that Knapp elucidated so clearly, and numerous recalls of entire product lots have occurred after one single particle was detected in a single vial of product (15).

Environmental monitoring

Another technical issue concerns environmental monitoring, a practice that FDA has been supporting since the agency issued its first guidance on aseptic processing in 1986 (16). Expectations went off the scale when the 2004 version of the FDA guidance was released, which included the statement, "Samples from Class 100 (ISO 5) environments should normally yield no microbiologi-

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cal contaminants"(17). This requirement creates a regulatory environment in which the only acceptable outcome, at least from a compliance perspective, is absence. This ignores scientific realities, and limitations in sampling, microbial recovery, as well as the potential for both false negatives and false positives. It also ignores the fact that microbiology is a logarithmic science, and reliable quantification below 1 log is simply not possible (11).

The globally harmonized pharmacopeial desire for absence of microbes is based upon a false premise. Simple testing cannot confirm the absence of anything.

Non-sterile products

Absence of specified organisms. Some microorganisms induce adverse reactions in patients, and their presence in non-sterile drug products is considered unacceptable. Zero-microbial limits may be well intended, but the reality is simple. Products manufactured from non-sterile materials under non-aseptic conditions without a terminal sterilization process can never be completely free of microbial content (18). Thus, the globally harmonized pharmacopeial desire for absence of microbes is based upon a false premise. Simple testing cannot confirm the absence of anything.

Blend and content uniformity. Similarly, one cannot prove that each and every unit of a solid dosage-form batch has the strength and potency that it is purported to possess. This is especially true where the percentage of active ingredient(s) in the formulation is low. Blend uniformity and content uniformity testing, combined with dissolution testing, can provide some assurance in this regard; however, the level of confidence is predicated on the robustness of the manufacturing process and conditions along the supply chain.

Sampling, including sample size and location, also affects the validity of the evaluation. To be meaningful, such testing must be based on the presumption of adequate process control. Studies have shown that, in addition to sampling location, sample size is critical in establishing the validity of the analytical result (19).

Two extreme examples serve to illustrate the point. Assuming the correct amounts of material have been added to a blender, if the sample consists of the entire blender load, the content of the active ingredient(s) will be 100% of the theoretical formulation amount. At the other extreme, if the sample from the blender consists of a single grain, the measured concentration of the active could range from zero to far in excess of the formulation amount (20).

It is only through process control, process validation, and rigorous sampling protocols that the results of content uniformity testing will be a meaningful measure of what the patient receives in each dosage unit (21). The old advertisement, "The one you took wasn't tested," is always true.

Trace impurities. Where materials are present in trace amounts, the assay limit of detection and sensitivity are important factors. Sometimes, specifications do not correspond with the limit of detection, resulting in uncertainty regarding the concentration of the impurity, or even its presence or absence.

Also, some analytical methods are developed to detect specific impurities and may not be able to detect others, especially when they are not expected to be present. Again, this points to the importance of process control and validation to ensure analytical methods and limits of detection are suitable for their intended use.

Quality cannot be tested in, especially where the parameter being evaluated is zero, none detected, or inappropriate to the analytical method used.

Presence of mold. Yet another example is mold, which is commonly found in the environment, including pharmaceutical facilities. Production sites and operating procedures must be designed to exclude mold from the product to the extent that this is possible.

Absolute control is generally unattainable

However, as is the case with other microorganisms, absolute control is generally unattainable. The presence of mold does not mean that a catastrophic contamination event is imminent. Similarly, its absence during monitoring should not be interpreted as proof that mold is not present.

Only robust process control and validation; facility and equipment design and qualification; meaningful quality systems; and high levels of personnel qualification and training can reliably and consistently produce drug products exhibiting the levels of quality, purity, and potency they are intended to possess. Quality cannot be tested in, especially where the parameter being evaluated is zero, none detected, or inappropriate to the analytical method used. Unfortunately, product release reflects an overemphasis on measured results. In parametric release, the quality attributes must be firmly established by the process controls and quality systems when the parameters being measured are essentially unknown and unknowable.

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Distinguishing Between Cleanroom Classification and Monitoring

James Agalloco, Russell Madsen, and James Akers

A one-size-fits-all approach to monitoring practices and results is never appropriate, given the diversity of practice within the pharmaceutical industry.

Although classified environments are used even more extensively in microelectronics, defense, and other high technology enterprises, they are crucial to the manufacture of drugs, biologics, and medical devices. International standards governing cleanroom design and certification are not industry specific because their implementation cuts across a broad swath of modern industries.

The first cleanrooms were built more than 70 years ago, and, for many years, US Federal Standards 209 (FS2009), first published in 1963 (1), was used to confirm their suitability. The methods and practices that evolved from this initial effort are still widely used today.

Since that time, however, the principles of cleanroom design, construction, commissioning, and operation have matured. In 1999, a new global standard, International Organization for Standardization (ISO) 14644 – Cleanrooms and associated controlled environments, replaced FS 209E while retaining its original scope (2).

Two different activities, classification and monitoring, are crucial to understanding cleanroom standards and their utilization. These two activities are broadly defined as follows:

- Classification—"[a] method of assessing the level of cleanliness against a specification for a cleanroom or clean zone ... Levels should be expressed in terms of an ISO Class, which represents maximum allowable concentrations of particles in a unit volume of air"(2).
- Monitoring—"Defined, documented program which describes the routine particulate and microbiological monitoring of processing and manufacturing areas"(3).

Classification relates to particles, while monitoring may include both viable and non-viable considerations. It intentionally avoids any consideration of internally generated contamination, because that is outside the control of the designer, builder, and classification contractor. The numbers of sample locations, their selection, sampling equipment, and other specifications are

James Agalloco is principal of Agalloco & Associates (jagalloco@aol.com); **Russell Madsen** is principal of The Williamsburg Group (madsen@thewilliamsburggroup.com); and **James Akers** is president of Akers, Kennedy & Associates (akanckc@aol.com).

defined in the ISO 14644 series. Classification does not consider viable contamination, which is supposed to be controlled by the facility owner during building use. Much of this control occurs at the process level. Related aspects of cleanroom operations are outside the control of cleanroom engineers, ventilation engineers, facility designers, construction firms, and certifying firms.

Monitoring

Monitoring provides information about contamination generated by processes and operators and other workers within the facility. The means for assessment are adapted to the specifics of the cleanroom's use.

An aseptic environment is expected to meet more stringent controls than an environment where materials are yet to be sterilized.

The presence of contamination is influenced by many factors: activity levels; cleaning and decontamination practices; gowning materials; numbers of personnel; and material entry procedures. As a consequence, microbial populations and process-generated non-viable particulate do not correlate directly to ISO class.

Monitoring should include areas of limited activity (i.e., those that pose minimal risk to product) such as corridors and storage areas to ensure that these are maintained in the desired state. While these areas may appear in 'as-built' condition, they are subject to the same operating influences as the rest of the facility. ISO 14644 indicates that classification can be performed in the operational state; however, this is restricted to non-viables. The healthcare sector routinely considers the levels of particles present during use, thus the ISO classes can be to used to designate the expected level of performance while equipment operates and personnel are present. This must be recognized as monitoring, however, because the operational controls will dictate the conditions observed.

Classification or monitoring?

Perhaps the most important reason for standards of any type is to facilitate communication between and across organizations regarding the system upon which the standard is focused. Classified environments, due to their complexity and rigorous but varied performance expectations, are no exception. The following summarizes the typical activities of classification and monitoring employed for a new cleanroom (4).

Owner. The firm using the cleanroom will identify the environmental performance required by the facility to minimize contamination potential during 'operational' use. This will consider the regulatory expectations for the intended use.

Designer. The operational expectations will be translated into a suitable design considering the budget, performance expectations, and internal activities that might contribute to contamination. Routinely, the intended design will result in a system that substantially exceeds the owner's operational expectations when tested in the 'as-built' state.

There are multiple reasons for this:

- The uncertainty of measurement
- The need to provide a margin of confidence in meeting the 'operational 'performance target
- The need to accommodate internal particle generation expected when the facility is in operation. Although this practice is not defined in ISO 14644 (2015), it represents good engineering practice across the cleanroom community (2).

Builder. The builder will execute the design to fulfill the owner's needs and designer's vision, then handle cleaning in preparation for certification.

Classification contractor. Using defined methods from the ISO 14644 series confirms that the completed facility meets the standard in the 'as-built' state. This is a formal process with documented reports certifying the

performance. At this point, the facility is turned over to the owner. The certification considers only non-viable particles and it comprises the 'classification' of the facility. The certifying classification is repeated on a periodic basis, as well as after any repairs or modifications to the facility.

Owner. The owner performs initial decontamination(s) to reduce microorganisms to the desired levels and commences operations within the facility. The initial activities are commonly training, engineering, and process simulations. Owners use this period to identify 'worst-case' locations for monitoring (viable and non-viable) in the 'operational' state. Once in regular use, the firm maintains the facility with cleaning and periodic decontamination and monitors it periodically.

Regulator. The regulator reviews the performance of the facility against regulatory standards, with the focus on monitoring conditions during operation, when contamination of materials would occur.

ISO 14644-1 explicitly excludes viable particles from its expectations, but embraces a number of other constraints (e.g., temperature, humidity, and noise levels). The ISO 14644 series of standards provide comprehensive treatment on cleanrooms and associated controlled environments classification and drives expectations for their design and operation. Because these standards are non-industry specific, additional expectations have been established to address particular needs. FDA's guidances on aseptic processing; European Medicines Agency's *Annex 1 on Sterile Medicinal Products,* and other specific guidances have added requirements beyond those in ISO 14644 to define conditions for cleanroom operations (5,6).

These should be understood as monitoring environments during their use. Although the term 'classifcation' is used in these documents, extending ISO 14644 criteria to viable expectations, the expected values in these documents are completely arbitrary (see **Table I**). ISO 5 environments used in the pharmaceutical industry include:

- Closed isolators without personnel access
- Open isolators
- Restricted access barrier systems (RABS) for high speed filling
- Nominally enclosed unidirectional airflow hoods in manned filling rooms
- Localized undirectional air hoods in preparations areas (e.g., located above washing, drying, and wrapping activities prior to sterilization).

The effectiveness of the microbial controls employed in these different configurations varies widely and precludes singular expectations for the microbial population present.

Microbial classification

Ongoing efforts aim to impose a facility classification scheme under ISO 14698 (7) that would require specific microbial levels. There are difficulties associated with this effort, including absence of calibration standards; absence of calibratable equipment; absence of validated sampling methods; and diversity of application. In addition, other constraints suggest that the entire effort is misguided:

- Environmental monitoring samples only a tiny portion of any environment's air or surface.
- Operators and other staffers are the primary source of microbial contamination and their participation in monitoring perturbs results.
- Media-based sampling has a limit of detection that is substantially higher than 1 colony forming unit, severely restricting its utility as a way to provide evidence of microorganisms.
- Media-based sampling recovers roughly 1% of the microorganisms present.
- Rapid methods can detect viable, but non-culturable microorganisms, but, with no commensurate

Table I: Comparison of classification and monitoring. HEPA is high efficiency particulate, and RODAC is replicate organism detection and counting.

	Classification		Monitoring	
Why	Confirmation of facility design expectations		Confirmation of operating practices: (i.e., cleaning, decontamination, gowning, human activity)	
	Non-viable	Viable	Non-viable	Viable
When	Static, prior to use	Execution prior to introduction of operational controls precludes useful values.	Dynamic, during activity	
Where	Random locations		Locations of greatest risk	
What	Air		Air	Air, surface personnel
Who	Certification firm		Facility owner	
Calibrated device	Particle counter		Particle Counter	Active and passive air samplers, settle plates RODACs, Swabs
Calibrated device	Yes		Yes	No
Recovery	Counts all		Counts all	Misses most
Influenced by	Design, air changes, HEPA coverage, return locations		Design, air changes, HEPA coverage, air return locations, cleaning, gowning decontamination practices, personnel practice, equipment, components, procedures	

means of controlling them, add cost and confusion without adding value.

At this point, it is not clear what value this classification would provide. Monitoring is already a common practice that addresses conditions during use. Is there any identified benefit to the adoption of this standard? For these reasons, classifying cleanrooms based upon microbial population is an unnecessary objective. In short, there is a clear distinction between classification and monitoring. Classification using particle counts focuses on the design performance of the cleanroom in the absence of the complicating activities associated with microbial control. Monitoring confirms the effectiveness of all the functional controls on the environment. It incorporates microbial assessments because that is a universal concern in cleanrooms in the healthcare industry.

Confusing these very different activities can create a host of problems for the practitioner. For one thing, imposing arbitrary microbial expectations adds no value to an activity where microbial control has yet to be established. In addition, variations in facility design, cleaning, and decontamination regimes and the major variations in usage and operating practices makes the imposition of a 'microbial' çlassification wholly inappropriate.

A one-size-fits-all approach to monitoring practices and results is never appropriate, given the diversity of practice. And finally, the use of classification type values as monitoring performance targets does not turn monitoring into classification. It merely establishes a process goal. Ideally, these two activities should be maintained as independent activities, loosely connected by the non-viable monitoring values used to record the results.

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Test Methods and Quality Control for Prefilled Syringes

Cynthia A. Challener

Empty and filled syringes must pass a range of quality control tests.

Prefilled syringes offer advantages to the manufacturer, caregiver, and patient. With fewer handling steps and ease of use compared with empty syringes, prefilled devices can help reduce medication errors. They do, however, pose challenges in manufacturing and require extensive testing.

Testing of empty syringes must be performed at the site where filling will be completed as part of incoming quality control efforts. And, filled syringes (combination of the syringe and drug product) must also be subjected to release testing.

Knowledge and understanding of the various tests involved is essential for ensuring patient safety. "The development of robust drug products based on prefilled syringes as primary containers requires an integrated holistic approach," asserts Thomas Schoenknecht, head of R&D within the drug product services unit at Lonza Pharma & Biotech. "Aspects including formulation, process, packaging, device integration, analytics/quality control, and intimate knowledge of the user needs all must be taken into account," he explains.

Complex testing requirements

Similar to other sterile products, prefilled syringes must be sterile and free from pyrogens. In addition, according to Gregory Sacha, senior research scientist at Baxter BioPharma Solutions, they must be chemically, physically, and biologically stable with no change in performance over the intended storage and use time. In general, the regulatory requirements for testing prefilled syringes need to comply with the US and European pharmacopeias, notes Nicolas Eon, global product manager for syriQ prefillable syringes at Schott Pharmaceutical Systems.

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

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Testing must be compliant with existing test and release methods for empty containers and for containers filled with the drug product solution. As such, both drug and device regulations apply to prefilled syringes. The regulatory landscape for combination products is complex and product/country specific, according to Schoenknecht. In the United States, for example, several parts of 21 *Code of Federal Regulations* (1) (211 cGMP for finished pharmaceuticals, 314 drugs, 600 biologics, and 800 devices) are applicable. There are separate requirements outlined in the European Union (EU) Medical Directives (2) and proposed revisions to EU GMP guidelines Annex 1 (3).

While International Organization for Standardization (ISO) standards are important instruments for harmonization, health authorities do not necessarily support or enforce them, but use them as a guidance for internal regulation development, according to Schoenknecht. "As an example, FDA guidance on GMP requirements for combination products (4) cites several ISO standards, such as ISO 11040," he says.

In general, test methods are defined in ISO 11040-4, Part 4 (Glass barrels for injectables), Part 5 (Plunger stoppers for injectables), Part 6 (Plastic barrels for injectables), and Part 8 (Requirements and test methods for finished prefilled syringes). Other tests are outlined in ISO 80369 for small bore connectors for liquids and gases in healthcare applications: Part 1 (Small bore connectors) and Part 7 (Connectors for intravascular or hypodermic applications, which have replaced ISO 594-1 and -2), according to Eon.

For glass prefilled syringes for biologics, the requirements are based on technical report number 73 from the Parenteral Drug Association (5), Eon adds. With respect to inspection of prefilled syringes, ISO 2859 (Sampling procedures for inspection by attributes package) and ISO 3951 (Sampling procedures for inspection by variables) are applicable. "The PDA technical report comes from industry, with key users of prefilled syringes in the pharmaceutical community teaming up with the vendors of those containers to create a document that serves the industry as a white paper. It describes in broad detail what needs to be considered for the successful combination of a prefilled syringe with biologics and what enables combination with a drug-delivery device," says Schoenknecht, who is one of the co-authors of the report.

Numerous opportunities for QC failure

Given that so many different tests must be conducted on empty syringes and syringes filled with product, it isn't surprising that there are many opportunities for these complex systems to fail to meet quality requirements.

Cosmetic defects such as scratches are common. These units are rejected because it can be difficult to determine if a scratch is only at the surface of the material or if it is a crack. Insufficient container siliconization can result in failure during break-loose and extrusion-force measurements and actual product use. For needle syringes, insufficient needle pull-out forces can occur due to weak needle assembly and imperfect adhesive polymerization control.

For filled syringes, failures depend on the drug product design (e.g., the formulation), the syringe process design, and the careful assessment of interplays, according to Schoenknecht. "One point of concern being controversially discussed as a

major risk for product development is subvisible particles. However, failing subvisible particles requirements on stability is a negligible risk for most protein formulations containing polysorbate and given adequate particle characterization," he observes. The presence of leachables and API impurities can be further challenges.

Other failures concern patient-related issues. "Patients can have difficulty using the combination product (user handling), and these issues should be considered as testing failures," Schoenknecht says. High injection forces, long injection times, and general issues with gripping the syringe are examples.

Testing of empty sterile sub assemblies

Testing empty syringes prior to filling presents a few challenges that largely relate to the fact that only one part of the combination product (sterile barrel) is being tested, according to Eon. "The impact of the drug product on the functionality of the syringe cannot be evaluated prior to filling, but testing is still needed to confirm the intended purpose for the combination drug product," he explains.

Specific tests that should be performed on empty syringes include:

- Glide force testing to evaluate syringe lubrication (ISO 11040-4)
- Pull-off force testing of the tip cap or the needle shield (ISO 11040-4)
- Flange break resistance testing (ISO 11040-4)
- Luer cone breakage resistance testing (ISO 11040-4)
- Needle penetration testing (ISO 11040-4, ISO 7864, ISO 9626, and DIN 13097-4);
- Needle pull-out force testing (ISO 11040-4)
- Luer lock adapter collar pull-off force testing (ISO 11040-4)
- Luer lock adaptor collar torque resistance testing (ISO 11040-4)
- Luer lock rigid tip cap unscrewing torque testing (ISO 11040-4).

Retention volume and deliverable volume are also tested for prefilled syringes. The retained volume is important because it will affect the fill volume and filling tolerances during manufacturing, according to Sacha. This method can be challenging to implement, however, because variances in the values obtained during testing occur between analysts and are affected by how the tip cap is treated during the test.

"All of these tests give only information about the quality and performance of the container itself, though," agrees Schoenknecht. "Final proof of a specific container closure system for a given drug product, consisting of the container with closures and liquid fill (drug formulation), suited to fulfill the requirements can be made using tests performed on the final combination product," he asserts.

Schoenknecht also stresses that device development should be driven by human factor studies (user requirement studies) that lead to design input requirements. "Performance tests such as breakout- and extrusion-force measurements should be executed against the user requirements, which should take into account the capabilities of the intended patient population/group," he explains.

Functionality testing

Functionality testing (e.g., gliding force, mechanical resistance, opening force, etc.) involves exami-

nation of the force required to initiate movement of the plunger and the pressure required to maintain the movement; the test is usually destructive. As a result, it is only performed with a reduced inspection plan (S-4) and limited sample population, which leads to a higher beta risk for the customer, according to Eon.

Carrying out these tests requires a clear understanding of the testing requirements listed in the cited ISO standard and the capability to implement and qualify the test methods in accordance to GMP standards, according to Schoenknecht. "Injection-force, break-loose force, and glide-force measurements can be particularly challenging because they depend closely on the inner diameter of needle, which can vary within tolerances," he says.

A key source of failure in functional tests is insufficient application of silicone oil in the barrel of the syringe, according to Sacha. "Insufficient application of the oil can make it difficult to start movement of the plunger and can cause the plunger to halt during movement through barrel, which is known as chattering," he explains.

Container closure integrity testing

"Sterility is the most important critical quality attribute of a parenteral/sterile drug product. Container closure integrity (CCI) testing (ISO 11040-4) is one of key tests to be performed to ensure the combination product is in full GMP compliance, guaranteeing sterility," asserts Schoenknecht. CCI is required to ensure microbiological quality and thus sterility until point of use.

CCI testing evaluates the adequacy of container closure systems to maintain a sterile barrier against potential contaminants. Currently, regulatory guidance around CCI testing is ambiguous and provides limited details on how to properly assess CCI, according to Eon. He does note, however, that revisions to regulations (e.g., the new EU Annex 1) are being made to ensure a common understanding of expectations in relation to CCI testing.

Schoenknecht adds that the limitations of the individual technologies need to be understood and the most suitable methods selected and qualified for a given product. "The best solution is to have a holistic sterility/CCI strategy that follows a quality-by-design approach and comprises a phase-appropriate testing strategy," he observes.

Issues with existing methods vary depending on the method. Some, such as dye-penetration testing, leak testing, and microbiological ingress testing, are destructive to the samples being tested. "These probabilistic methods also rely on a statistically representative number of samples from the batch and assume that any defect is uniformly present throughout the batch. All decisions are therefore made based on the small number of samples removed from the batch," Sacha comments.

With others it can be difficult to demonstrate the sensitivity of the CCI test method, particular with respect to the positive control, according to Eon. Traditionally dye ingress, which is probabilistic, also has poor sensitivity, according to Schoenknecht.

Deterministic methods are non-destructive and can be used to test every unit from the batch. These methods include vacuum/pressure decay testing, high-voltage leak detection, and analysis of the head space within the syringe, according to Sacha. New technologies on the horizon for 100% CCI inspection based on x-ray imaging

analysis or online leak testing are creating some excitement, according to Eon. The implementation of such online test methods might be extremely challenging and costly, though, according to Schoenknecht.

He points to an alternative approach that involves precise process validation of the filling process using the helium leakage method to ensure selected process parameters correlated to robust process performance. After much discussion within the industry, there seems to be consensus that the helium leak test method is one of the best methods for CCI. Lonza has developed proprietary CCI technology based on helium leakage testing in which prefilled syringes can be assessed in a very sensitive way, according to Schoenknecht. Helium gas leakage from samples is detected by mass spectrometry, with the ion counts proportional to the leak rate and thus quantifiable. The test can be used for vials, syringes, and other drug product formats at a range of temperatures, including with Lonza's method down to -80 °C.

Automated inspection for prefilled syringes

Automatic inspection equipment is used to check the product for particles, for cosmetic defects, and for proper placement of the plunger, says Sacha. With automatic inspection, Eon notes, companies can enact 100% inspection instead of statistical process control, which is limited by the sample error. "Using 100% inspection ensures the lowest customer risk, enables parts per million quality level, and acts as a tool for process optimization and capability analysis," he asserts.

Schoenknecht agrees that automatic control can ensure a 100% inspection of all syringes/containers per production batch following a robust reliable and reproducible testing process. "As such, a higher quality standard than for visual-only inspected syringes can be reached by calculating performance data out of the data pool of syringes coming out of the glass converting process and following handling steps at the syringe vender, helping to understand the robustness of the production process applied at the place of syringe production. However, inline CCI testing of the filled container usually has quite low sensitivity, and thus it is arguable if product quality is improved by using current CCI technologies on-line," he observes.

It is important to note, though, that visual inspection of prefilled syringes is required under GMP. In addition, automated inspection instruments/methods need to be qualified/validated and the automated inspection system should perform as well as a human operator regarding failure detection rates, according to Schoenknecht. False-positive detection and creating too many false rejects can occur, and users of automatic inspection systems should be aware of the potential for such issues. He also notes that for smaller batches, such as for clinical studies, manual inspection is often preferred.

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A Study of Leachable Silicone Oil in Simulated Biopharmaceutical Formulations

Xiaochun Yu, Nicholas Keyes, Neal Andrist, Ashley Hellenbrand, Jeffrey Nordin, and Roxanne Aide

Leachable silicone oil may have an effect on large-molecule APIs, making it important to establish a robust analytical method to detect and quantify the substance.

Biopharmaceutical products are becoming the driving force of the pharmaceutical industry. The primary route of administration for biopharmaceutical products is by injection, and the commonly used container/closure systems use glass vials with rubber stoppers and prefilled syringes.

Silicone oil has been widely used to coat the components of container/closure systems for biopharmaceutical products, including syringe barrels and plungers for prefilled syringes and stoppers for glass vials (1). The drug product formulations typically are in direct contact with the silicone oil coating over long periods of time; there is a general concern that the silicone oil may leach into the drug product formulations, which may affect the drug product's purity and efficacy (2, 3, 4).

Unlike small-molecule pharmaceutical products, leachable silicone oil may affect the conformation of the large-molecule APIs of biopharmaceutical products, which can cause protein denaturation and, in the long term, can lead to protein aggregation (3). Protein aggregates can result in a loss of protein biological activity and may induce immunogenic effects (4) when injected into the human body. Therefore, it is important to evaluate leachable silicone oil for biopharmaceutical products.

There are different methods for analyzing silicone oil that, in general, fall into two categories: one is based on the polymeric nature of silicone oil, using a gel permeation chromatography column to separate silicone oil from the drug product ingredients. Silicone oil molecules typically do not contain a chromophore, so the commonly used ultraviolet detector is not suitable. The detectors typically used for silicone oil analysis are refractive index detector, evaporative light scattering detector, charged aerosol detector, etc. The second category of methods is based on silica-specific techniques, such as atomic absorption spectroscopy, inductively coupled plasma–atomic emission spectroscopy , also referred to as inductively coupled plasma–opti-

Xiaochun Yu, PhD, is senior principal scientist; **Nicholas Keyes** is scientist; **Neal Andrist** is scientist; **Ashley Hellenbrand** is senior scientist; **Jeffrey Nordin** is senior group leader; and **Roxanne Aide** is senior project manager; all at PPD Laboratories GMP lab, Middleton, WI.

cal emission spectrometry (ICP–OES), and inductively coupled plasma–mass spectrometry (ICP–MS). In these methods, organic solvents such as xylenes, toluene, and others are used to dissolve and separate the silicone oil from any inorganic silica.

The objectives of this study were to:

- Evaluate an ICP–OES method for the analysis of leachable silicone oil amounts in simulated biopharmaceutical formulations
- Quantify silicone oil in typical pharmaceutical formulations (5) and evaluate the impact of commonly used ingredients on the amount of leachable silicone oil.

In this study, an ICP–OES method was developed to quantify the amount of leachable silicone oil. Leachable silicone oil in aqueous biopharmaceutical formulations was extracted with an organic solvent, either with liquid-liquid extraction or solid-phase extraction, and the organic solution was analyzed directly with ICP–OES. Method performance such as method sensitivity, linearity, non-interference, relative response factors of different grades of silicone oil, and method accuracy were evaluated.

The study was followed by an evaluation of the leachable silicone oil amount in various simulated biopharmaceutical formulations stored in silicone-coated pre-fillable syringes. Formulations of simple phosphate buffers—and those containing co-solvents, bulking agents, chelating agents, and surfactants—and with different pH levels were added to the pre-fillable syringes and stored at 5 °C, 25 °C, and 40 °C for a period of time and then analyzed for leachable silicone oil amounts. The impact of pH, co-solvent, surfactant, chelating agent, and bulking agents as well as storage temperatures on the amount of leachable silicone oil were investigated. Surfactant was found to be the most important factor affecting the amount of leachable silicone oil. Co-solvent, pH, and temperature also affected leachable silicone oil amount, while bulking agents, chelating agents, and buffer did not have a significant impact on the leachable silicone oil amount. Overall leachable silicone oil represented a small portion of the coated silicone oil. Up to 2.1 µg/mL or 4.2 µg/syringe of leachable silicone oil was observed, which represented less than 2% of the total coated silicone oil.

The study design

Silicone-oil coated pre-fillable syringes (Becton Dickinson) were used for the test system for this study. The total amount of silicone oil coating the inside of the pre-fillable syringes was determined by extracting the syringes with xylenes, followed by analyzing the extraction solution by ICP–OES. Xylenes is a strong solvent for silicone oil and extracts out all coated silicone oil in the pre-fillable syringes. The amount of silicone oil in the pre-fillable syringes was determined to be 302 µg/syringe.

The standard used for quantitation was a silicone oil (Sigma Aldrich) with a viscosity of 350 cSt and 100% purity.

The simulated biopharmaceutical formulations selected for the study included simple phosphate buffers with varying concentrations of propylene glycol (co-solvent), polysorbate 80 (surfactant), ethylenediaminetetraacetic acid (EDTA) (chelating agent), various sugars (bulking agents), and sodium chloride. A total of 15 different formulations were used in this study, as summarized in **Table I**.

The solutions of simulated biopharmaceutical formulations were added to the pre-fillable syringes, 2 mL per syringe, and the syringes were then stored in chambers at 5 °C, 25 °C, and 40 °C. The syringes were pulled from the chambers after 30 days, and the contents were transferred to silicone oil-free glass contain-

Table I: Simulated biopharmaceutical formulations for leachable silicone oil study.

Formulation number	Formulation	Buffer 20 mM	Bulking agent	Stabilizer	Tonicity modifier	Chelating agent	Surfactant	Co-solvent (propylene glycol)
1	Phosphate buffer	pH 6.8 Phosphate						
2	Buffer with co-solvent	pH 6.8 Phosphate						1%
3								2%
4								5%
5								10%
6	Chelating agent	pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA		
7		pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.5 mM EDTA		
8	Surfactant	pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA	0.05% Tween 80	
9		pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA	0.1% Tween 80	
10		pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA	0.5% Tween 80	
11		pH 6.8 Phosphate	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA	1.0% Tween 80	
12	pH	pH 5.0	7% Sucrose	Sucrose	150 mM NaCl	0.1mM EDTA	1.0% Tween 80	
13		pH 8.2	7% Sucrose	Sucrose	150 mM NaCl	0.1 mM EDTA	1.0% Tween 80	
14	Bulking agent	pH 6.8 Phosphate	7% Mannitol		150 mM NaCl	0.1 mM EDTA		
15		pH 6.8 Phosphate	7% Trehalose	Trehalose	150 mM NaCl	0.1 mM EDTA		

ers, then analyzed for leachable silicone oil using the ICP–OES method described in **Table II**.

Prior to ICP–OES analysis, the leachable silicone oil in the aqueous formulation solutions was extracted with an organic solvent, xylene, to avoid interference from inorganic silica. Inorganic silica was likely to be present in the aqueous formulations after the formulations were stored in the glass syringes for a month. Liquid-liquid extraction and solid-phase extraction were used to extract the leachable silicone oil from the aqueous formulation solutions.

The liquid-liquid extraction procedures were used for all formulations with no surfactant. Equal volumes of formulation solution and xylene were used for the liquid/liquid extraction. The xylene solution was then used for ICP–OES analysis.

For formulations with surfactant, liquid-liquid extraction with xylene caused excessive emulsion and made it difficult to separate the organic layer from the aqueous layer. Therefore, a solid-phase extraction method was used. A Bond Elut Plexa (Agilent, Part #12259506), with a styrene-divinyl benzene copolymer, was used for extraction. One milliliter of formulation solution was eluted through each column under ambient conditions and dried for one hour under a vacuum of 15–20 mmHg. The columns were eluted with three separate 5-mL aliquots of dichloromethane (DCM) under ambient conditions, which were concentrated to near dryness under nitrogen flow. One milliliter of xylene was added into the residue and used for ICP–OES analysis.

Evaluation of the ICP–OES method

To evaluate the ICP–OES method as a means to analyze leachable silicone oil in simulated biopharmaceutical formulations, this study looked at the following factors: the relative response factor of silicone oils with different molecular weights, method sensitivity, method non-interference, and linearity.

Relative response factor. Usually, leachable silicone oil quantitation will need to use a silicone oil standard of different molecular weight and molecular-weight

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Table II. Inductively coupled plasma/optical emission spectrometry (ICP-OES) method conditions.

Instrument	Thermo iCAP 6500 Duo		
Plasma view	Axial		
Analyst	Si (251.611 nm)		
Plasma	Radio frequency power	1200 W	
	Gas flow	Auxiliary (Ar)	1.0 L/min
		Nebulizer (Ar)	0.90 L/min
		Additional gas (20% 02, 80% Ar)	0.125 L/min
		Purge	Normal
Nebulizer	PFA–ST microflow, 20 µL/min		
Injector	2.0 mm inner diameter		
Spray chamber	Quartz		
Peristaltic pump	Flush rate		10 rpm
	Sample flush time		120 seconds
	Pump stabilization time		15 seconds
	Analysis pump rate		10 rpm
	Diluent rinse		15 seconds
Sample options	Analysis mode		Precision
	Repeats		3

distribution than leachable silicone oil. For accurate quantitation of leachable silicone oil, the silicone oil standard and the leachable silicone oil must have the same response factor.

There are several reasons why the molecular weight and molecular weight distribution of the leachable silicone oil and silicone oil standards need to be different:

- There are different grades (e.g., silicone oil of different average molecular weight) of silicone oil used for the coating of container/closure components. The end-user of the prefilled syringes may not necessarily know the exact grade of silicone oil used for their products.
- The molecular weight and molecular-weight distribution of the leachable portion of silicone oil may not be the same as those coated on the container/closure components. For example, the high-molecular-weight portion silicone oil may not leach out the same way as the low-molecular-weight portion silicone oil.
- The components of the container/closure systems may be coated with different grades of silicone oil. For example, the syringe barrel and plunger of a prefilled syringe may be coated with two different grades of silicone oil. Therefore, the leachable silicone oil may be a mixture of the two grades of silicone oil.

To use one silicone oil standard to quantitate leachable silicone oil of different average molecular weight and molecular-weight distribution, the response factor of the silicone oil of different average molecular weight and molecular-weight distribution must be the same or the relative response factor must be known. To evaluate the relative response factor of different silicone oils, five silicone oil standards with viscosity ranging from 50 cSt to 1000 cSt prepared at 10 ppm in xylene solution were analyzed for determining the relative response factors against the standard silicone oil of cSt 350.

In addition, volatile cyclic oligomers of silicone oil—hexamethylcyclo-trisiloxane (D3), octamethyl-cyclotetrasiloxane (D4), and decamethyl-cyclopentasiloxane (D5)—also were evaluated for their relative response factors against the silicone oil standard. The results are summarized in **Table III**.

The data indicate that the ICP–OES response factor of the silicone oil of different molecular weights were

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Table III. Relative response factors of silicone oil of different molecular weight.

Silicone oil viscosity(cSt)	Average molecular weight*	Relative response factor
Plasma view	3800	0.99
Analyst	5970	0.97
350 cSt	13,700	0.99
500 cSt	17,300	0.99
1000 cSt	28,000	0.99
D3 (hexamethylcyclotrisiloxane)	222	0.72
D4 (octamethylcyclotetrasiloxane)	296	0.42
D5 (demethylcyclopentasiloxane)	370	0.36

*The average molecular weight data are from *Viscosity Correlation to Molecular Weight for Clearco PSF Fluids* (6). The exact molecular weights of the silicone oil used in this study may be slightly different; the molecular weights are included for information purposes.

Table IV. Non-interference results.

Formulations	5 °C	25 °C	40 °C
1	0.035	0.031	0.026
2	0.022	0.009	0.007
3	0.009	-0.004	-0.003
4	0.028	0.024	0.018
5	0.011	0.016	0.012
6	0.004	-0.012	-0.006
7	-0.006	-0.005	-0.008
8	0.015	0.022	0.017
9	-0.025	-0.062	-0.089
14	-0.007	-0.004	-0.004
15	0.015	0.026	0.025

virtually the same and were independent of the viscosity (e.g., the average molecular weight and molecular-weight distribution). Therefore, a silicone oil standard of one molecular weight and molecular weight distribution can be used for the quantitation of leachable silicone oil of different average molecular weight and molecular weight distribution.

The data also show that response factors for the volatile silicone oil oligomers were lower than the silicone oil standard. This indicates that a portion of the volatile cyclic siloxanes escaped prior to atomization because of their volatility and were not detected. Therefore, volatile cyclic siloxanes will not be accurately quantitated by ICP–OES (e.g., their amounts will be under-estimated).

Method sensitivity. The ICP–OES method did not have a response distinguishable from the background noise when silicone oil concentration was below 0.1 ppm. When increasing the silicone oil concentration above 0.1 ppm, the response gradually became more distinguishable from the noise. The noise level varied significantly after adequate buildup of carbon within the instrument detector during analysis, affecting instrument sensitivity and precision. For the purposes of this study, any response with a reading below 0.1 ppm was considered noise.

Silicone oil at a concentration of 0.5 ppm can be measured with good precision. Six measurements of 0.5 ppm silicone oil solution in xylene yielded responses as follows: 0.5205, 0.5176, 0.5283, 0.5293, 0.5240, and 0.5289. The percent relative standard deviation of the six measurements was 1.0%.

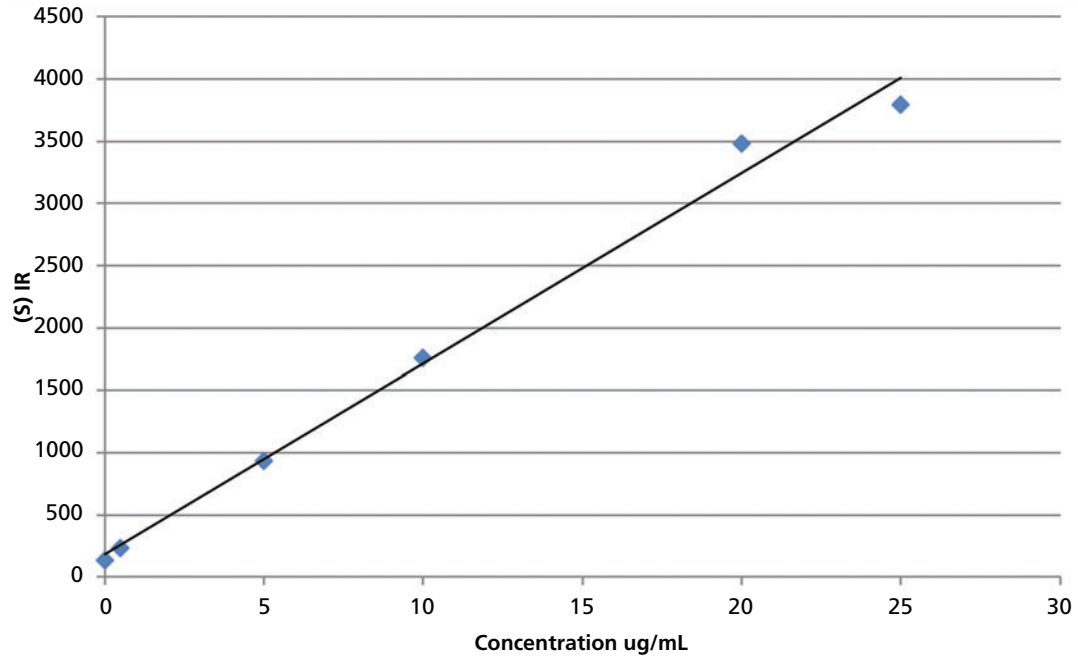
Method non-interference. Eleven of the 15 formulations were stored in silicone oil-free glass containers at 5 °C, 25 °C, and 40 °C for 30 days and were then analyzed by ICP–OES, with the data summarized in **Table IV**.

The data indicate that all the formulations stored in silicone oil-free glass containers after 30 days had ICP–OES responses below 0.1 ppm, the noise level of the ICP–OES method. This indicated there was no interference for the detection and quantitation of leachable silicone oil from the formulations.

Linearity. Silicone oil solutions prepared in xylene solution at different concentrations (0.5 ppm to 25 ppm) were analyzed by ICP–OES, and the responses were plotted against the concentrations seen in **Figure 1**. The data showed a linear correlation of the ICP–OES responses with the silicone oil concentration. The correlation coefficient was 0.995.

Method recovery. The silicone oil was extracted into the organic solvent xylene prior to ICP–OES analysis to avoid possible interference from inorganic silica. A liquid-liquid extraction was used for all formulations with no surfactant to transfer the leachable silicone

Figure 1. Correlation of inductively coupled plasma/optical emission spectrometry (ICP-OES) responses vs. silicone oil concentration. (S) IR is standardized intensity ratio.



oil from the aqueous formulations into xylene. Equal volumes of the aqueous formulation and xylene were mixed, and the xylene layer was analyzed directly. Silicone oil recovery from the formulation was evaluated using Formulation 6 (20mM phosphate, pH 6.8, 7% sucrose, 150mM sodium chloride [NaCl], 0.1mM EDTA). The recovery data are shown in **Table V**. The data indicated that with liquid-liquid extraction procedures, leachable silicone oil can be recovered from the formulation matrixes and quantified.

For formulations with surfactant polysorbate 80, the liquid-liquid back extraction generated severe emulsions, which yielded low recovery of silicone oil. A different technique, solid-phase extraction, was used to transfer the leachable silicone oil for formulations with surfactant. Silicone oil recovery from the formulation was evaluated by using Formulation 11 (20mM phosphate, pH 6.8, 7% sucrose, 150mM NaCl, 0.5mM EDTA, 1% polysorbate 80), and the recovery data are shown in **Table VI**. The data indicated that with solid-phase extraction procedures, leachable silicone oil can be recovered from the formulation matrixes and quantified.

Determining leachable silicone amounts

Leachable silicone oil for formulations with no surfactant or co-solvent. The leachable silicone oil results for five formulations with no co-solvent or surfactants are summarized in **Table VII**.

The five formulations included simple phosphate buffer and formulations containing chelating agent (EDTA), tonicity modifier (NaCl), and different bulking agents (sucrose, mannitol, or trehalose). The amount of leachable silicone oil for all five formulations stored at the three different temperatures (5 °C, 25 °C, and 40 °C) was below the detection limit of 0.1 µg/mL; no leachable silicone oil was detected after 30 days. The primary reason for this was the low solubility of silicone oil in water. The addition of the chelating agent EDTA, tonicity modifier NaCl, or bulking agents (sucrose, mannitol, and trehalose) did not significantly

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Table V. Recovery of spiked silicone oil in formulation with no polysorbate 80. Method performance evaluation-recovery test with formulation: 20mM phosphate, pH 6.8, 7% sucrose, 150mM NaCl, 0.1mM EDTA.

Replicates	Recovery %
1	92%
2	93%
3	93%

Table VI. Recovery of spiked silicone oil in formulation with polysorbate 80. Recovery test with formulation: 20mM phosphate, pH 6.8, 7% sucrose, 150mM NaCl, 0.5mM EDTA, 1% polysorbate 80.

Preparation Replicates	Recovery with Liquid/ Liquid Extraction Procedures	Recovery with Solid Phase Extraction Procedures
1	49	94
2	43	117
3	49	118

Table VII. Leachable silicone oil in formulations without co-solvent or surfactants.

Formulations	5 °C	25 °C	40 °C
1 (phosphate buffer)	0	0	0
6	0	0	0
7	0	0	0
14	0	0	0
15	0	0	0

enhance the low aqueous solubility of silicone oil for these formulations.

Leachable silicone oil for formulations with co-solvent. The leachable silicone oil analysis results for the formulations with propylene glycol as a co-solvent are summarized in **Table VIII**.

The data indicated there was detectable leachable silicone oil in all the formulations with propylene glycol as a co-solvent, but the overall leachable silicone oil amounts were low, even with 10% propylene glycol in the formulation. The amount of leachable silicone oil in the formulations after 30 days stored in the syringes at 5 °C, 25 °C, and 40 °C was still below 1 µg/mL, or below 2 µg/syringe. Considering there is more than 300 µg silicone oil coated on each syringe, only a very small portion of the coated silicone oil (less than 1%) leached into the formulations. The primary reason for this is the low solubility of silicone oil in water. The addition of the co-solvent propylene glycol only slightly enhanced the solubility of silicone oil for these formulations.

Leachable silicone for formulations with surfactant. The leachable silicone oil analysis results for the formulations with polysorbate 80 as surfactant are summarized in **Table IX**.

The data indicated there was detectable leachable silicone oil in all the formulations with polysorbate 80 as a surfactant in the formulations. The amount of leachable silicone oil ranged from 0.2 µg/mL to approximately 2.0 µg/mL. The amounts of leachable silicone oil were more than those observed for all other formulations, including formulations with propylene glycol as a co-solvent, suggesting that among all the typical ingredients in the biopharmaceutical formulations, surfactant is the most significant ingredient that may enhance the silicone oil solubility in the formulation and thus cause more leaching of silicone oil.

Storage temperature affected the leachable silicone oil amounts, with the greatest leachable silicone oil amounts typically observed at 40 °C compared to 5 °C and 25 °C storage.

The greatest leachable silicone oil amount observed in formulations with polysorbate 80 as surfactant in this study was approximately 2 µg/mL, which is equivalent to 4 µg/syringe. Considering there was more than 300 µg silicone oil coated on each syringe, the leachable silicone represented less than 2% of the coated silicone oil. This means only a very small portion of the coated silicone oil leached into the formulations, even for those with surfactants.

Leachable silicone for formulations with different pH. The evaluation of pH impact on the leachable silicone oil amounts was performed with formulations with polysorbate 80 as a surfactant because the formulations

with surfactants had the highest leachable silicone oil amounts. The leachable silicone oil analysis results for the formulations with different pH are summarized in **Table X**.

The data show that the pH of the formulations had a significant impact on the amount of leachable silicone oil. The 8.2 pH formulation had significantly more leachable silicone oil than the 5.0 pH formulation. There may be several reasons for the pH impact on the leachable silicone oil amounts. First, the bonding between glass and silicone oil molecules is attributed to the cross linking of polydimethylsiloxane to silanol groups on the glass surface (7), including hydrogen bonding between glass silanol and electronegative oxygen of polydimethylsiloxane. A higher pH may weaken the hydrogen bonding and make the silicone oil more prone to leach into the formulation. Second, pH may affect the degradation of silicone oil, especially breakdown of the end group to trimethylsilanol. The exact cause of the pH effect on the amount of leachable silicone oil will require further study.

The data also indicated that storage temperature had significant impact on the amount of leachable silicone oil. For example, 40 °C storage samples typically had more leachable silicone oil compared to 5 °C and 25 °C, consistent with the results in previous sections.

Table VIII. Leachable silicone oil in formulations with co-solvent.

Formulations	Propylene glycol%	5 °C	25 °C	40 °C
1	0	0	0	0
2	1	0.3	0.4	0.5
3	2	0.4	0.2	0.1
4	5	0.6	0.2	0.9
5	10	0.3	0.7	0.8

Table IX. Leachable silicone oil in formulations with surfactant.

Formulations	Polysorbate 80%	5 °C	25 °C	40 °C
1	0	0	0	0
8	0.05	0.2	0.2	0.7
9	0.1	0.2	0.2	2.1
10	0.5	0.5	0.3	1.0
11	1.0	0.2	1.4	1.6

Table X. Leachable silicone oil in formulations of different pH.

Formulations	pH	5 °C	25 °C	40 °C
12	5.0	0	0.4	0.3
11	6.8	0.2	1.4	1.6
13	8.2	0.4	1.9	2.1

Conclusion

ICP–OES is a suitable technique for the analysis of leachable silicone oil in biopharmaceutical formulations. Leachable silicone oil in aqueous formulations requires further sample preparation to extract the leachable silicone oil from aqueous biopharmaceutical formulations into organic solvents by liquid/liquid extraction or solid-phase extraction.

There is a low risk of silicone oil leaching into a typical biopharmaceutical formulation as long as the formulation does not contain a co-solvent or surfactant. The risk increases if the formulation contains a co-solvent or surfactant. Surfactant is the most critical ingredient affecting the amount of leachable silicone oil, while formulation pH and storage temperature also have an impact. Overall, however, the amount of leachable silicone oil represents only a small portion of the total silicone oil coated on prefilled syringes.

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The Link Between Manufacturing and Commercialization in Gene and Cell Therapy

Walter Colasante, Pascale Diesel, and Lev Gerlovin

The highly customized nature of cell and gene therapy production means that manufacturing innovations for one therapy may not be easily transferable to others.

While gene and cell therapies have been touted as the future of medicine for decades, there is evidence to indicate that they are finally poised to deliver results. Several products are already on the market, including Kymriah, Yescarta, and Luxturna, and many others are advancing to late-stage clinical development and commercialization. A number of different manufacturing platforms are being developed to manufacture both autologous and allogeneic therapies. In the United States alone, there are 34 gene therapies in pivotal trials and another 470 in earlier stages of clinical testing (1).

Although the long-term transformative promise of gene and cell therapies is becoming increasingly clear and is good news for many patients, these treatments also present unique challenges for a number of stakeholders. Factors that drug developers, regulators, investors, and others must consider include the fact that these therapies often target very small patient populations; have shorter treatment windows; offer potentially curative efficacy; have high up-front costs; lack long-term efficacy and safety data; and involve complex, expensive, and high-risk manufacturing processes.

Challenges to commercialization

Each of these factors can have a significant impact on the clinical development and regulatory review process and on the chance of successful commercialization. For teams involved in investment and planning related to technology and manufacturing, it is essential to

Walter Colasante, Pascale Diesel, and **Lev Gerlovin** are vice-presidents in Charles River Associates' Life Sciences Practice. The authors wish to acknowledge the contributions of Stephanie Donahue and Michael Krepps to this article. The views expressed herein are the authors' and not those of Charles River Associates or any of the organizations with which the authors are affiliated.

consider commercialization issues, because strategies are planned and implemented from the earliest stages of development.

Production methods for most gene and cell therapies are lengthy, complex, and difficult to expand as production needs rise.

Manufacturing and supply chain complexity

More traditional therapies, including small molecules and even monoclonal antibodies, generally involve a simpler and more straightforward production process than gene and cell therapies do. Such processes offer the potential for scalability and opportunities for cost efficiencies through economies of scale. The production methods for most gene and cell therapies, however, are lengthy, complex, and difficult to expand as production needs rise. For example, the manufacture of autologous therapies such as chimeric antigen receptor T (CAR-T) cells or stem cell therapies requires a process that must be replicated in individualized batches to meet demand at every stage.

With allogeneic therapies, the patient-specific nature of production makes it extremely challenging to scale up production. The administration of these therapies also creates challenges that can be affected by decisions in technology and engineering. For autologous treatments, a sample is taken from the patient, sent away for processing and modification (often to a single location regardless of geographic origin), and then dispatched back to a designated treatment center for re-administration to the patient. This process requires strict traceability and a robust and reliable chain of temperature control. Planning for this process can face considerable regulatory hurdles related to licensing, monitoring, and troubleshooting.

Production of gene and cell therapies can also require customized technologies and innovations in production that require the active review and contributions of regulators and experienced outside consultants to achieve target goals in compliance with both regulatory standards and costs. In early clinical stages, the feedback from regulators and others on production procedures will typically focus more on safety and issues such as viral banks, raw materials, and serums. At later stages, feedback tends to focus on the impact of manufacturing decisions on a therapy's potency, consistency, and variability.

More efficient production platforms

The rapid growth in development of gene and cell therapies in recent years means that there are now several examples of pharmaceutical companies developing much more efficient production capabilities for these drugs. For example, Novartis and Kite have created systems that can produce individualized CAR-T cell therapies in 22 and 17 days, respectively (2). ZIOPHARM Oncology is advancing a non-viral platform called the Sleeping Beauty system that rapidly produces genetically modified T cells within two days with potential for rapid scalability. The highly customized nature of production, however, can often mean that innovations in manufacturing of one therapy may not be easily transferable to others.

Considerations in production can also differ within the broad category of gene and cell therapies. For example, production of allogeneic thera-

pies, while they can present challenges related to distribution and shelf life, might be less challenging compared to CAR-T cells and other autologous therapies, given their similarity to cell-based proteins that can be produced in batches and distributed for use off the shelf. The class of drugs known as radiopharmaceuticals, which have extremely short shelf lives, have shown that this challenge can be well managed. Cellectis is exploring new production strategies for off-the-shelf allogeneic therapies. Rather than developing CAR-T cell therapies from patient samples, the company is using healthy donor T cells, which could allow for earlier supply chain preparation, better control over production volume, and, potentially, reduced costs.

Production of gene and cell therapies can ... require customized technologies and innovations in production that require the active review and contributions of regulators and ... outside consultants to achieve target goals.

Accessing new technologies and resources

As the range of new options in technology expands, companies will continually need to access new levels of skill and insight to identify and acquire the innovations necessary to support production goals at every stage through commercialization. Generally, by Phase II, manufacturers should at least be aware of the technologies they will need to achieve target goals in scalability and be prepared to make these investments at the appropriate time. By Phase III, the full range of technologies that companies will need to support commercial production should be in place. Many industry insiders expect that there will be greater demand for advanced technologies including, among others, cryopreservation tools and services, and that development of biomarkers and related diagnostics will become more common and even essential tools in the successful commercialization of gene and cell therapies (3).

To identify the optimal options in technology, many manufacturers are now considering engaging contract research organizations (CROs) that have specialized expertise in gene and cell therapies, especially for those targeting rare diseases. Some CROs are now well positioned to provide guidance related to regulatory compliance, production scale, and product portability for gene and cell therapy developers. Their teams can provide guidance on how to refine manufacturing processes while maximizing purity and safety with a focus on continuity of care. One example of this type of collaboration is seen in the alliance between the Center for Commercialization of Regenerative Medicine, GE Healthcare, and the Federal Economic Development Agency for Southern Ontario, which joined forces to form the Center for Advanced Therapeutic Cell Technologies in Toronto. The Center was established to help industry partners incorporate new technologies and provide expertise to solve manufacturing challenges, especially for emerging gene and cell therapies (4).

Maximizing commercial opportunities

When planning for manufacturing needs, drug developers should also consider using a produc-

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tion process that can be adapted for use in different therapeutic areas. While production decisions often focus on basic factors including geographic location, some gene and cell therapies present opportunities for a diversified development platform with a unifying focus.

The Human Genome Project and the International HapMap Project are examples of initiatives that aim to better understand the genetic factors that are associated with many diseases. Research can lead to the development of more gene and cell therapies with the potential to expand treatment to additional indications, potentially including disease states that affect large patient populations. It can be advantageous for manufacturers to expand their focus on production beyond efficiency and to include methods and technologies that may be adaptable and expandable in the future, for use in additional indications.

Collaboration with stakeholder groups, especially patient communities, can help make sure that manufacturing decisions are in line, [not only] with commercialization goals [but with] factors that affect patient access and management of care.

Addressing long-term safety and efficacy

Limitations on data and the potential for curative efficacy requires manufacturers to put systems into place for long-term safety and efficacy monitoring. These current limitations can have a profound impact on costs and commercial viability. When an FDA Advisory Committee unanimously recommended approval of Spark Therapeutics' Luxturna for treatment of inherited retinal disease in October 2017 (5), they cautioned that a lack of long-term follow-up data makes it unclear whether efficacy could diminish over time. They also raised questions about the potential for future adverse events that had not been demonstrated in clinical research (6).

Limitations on data can also fuel the perception that some gene and cell therapies do not provide incremental clinical value over existing therapies, making it difficult to justify their high prices. Here again, companies must plan for technologies and procedures that can meet target goals in long-term patient monitoring to avoid costs and cumbersome record keeping and other requirements that can affect commercial potential of new drugs.

Engaging with stakeholder groups

In part to support the collection of real-world data, manufacturers should also consider new levels of engagement with key stakeholders, potentially including healthcare providers (HCPs), payers, and clinicians. Alliance with a wide network of stakeholders spanning different geographies could provide valuable resources and facilitate long-term post-marketing surveillance efforts as well as support broader understanding of the benefits and risks of gene and cell therapies.

Collaboration with stakeholder groups, especially patient communities, can also help make sure that manufacturing decisions are in line with both commercialization goals and factors that can affect patient access and management of

care. GlaxoSmithKline (GSK) made the decision to offer Strimvelis, a treatment for severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), at only a single treatment center in Milan, assuming the need for a "specialized [treatment] environment."

To support commercialization goals, manufacturers might consider using predictive analytics to inform strategic decisions on [number and location of] treatment sites.

The limited options for treatment meant higher costs and challenges related to travel and cross-border European reimbursement for many patients. As a result, only four patients have been treated with Strimvelis at the site since approval in 2016. GSK has since announced its interest in divesting its rare disease division, including Strimvelis (7,8). To support commercialization goals, manufacturers might consider using predictive analytics to inform strategic decisions on the appropriate number of treatment sites, where they should be located, or whether and how they might bring gene and cell therapies directly to patients.

Conclusion

While factors including patient population, product value and efficacy benefit, and pricing play the major roles in successful commercialization of gene and cell therapies, it is essential for drug developers to recognize when and where decisions related to production can also have an impact. The application of technology is a critical consideration in planning related to production time, scalability, and product purity and safety, as well as in expansion of target indications.

Without access to skilled expertise, many drug developers risk making decisions related to production that can limit or even jeopardize commercial potential. Conversely, companies that can access the talent and insight necessary to make the right technology decisions at the right time at every stage in a development program can build a considerable competitive advantage.

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Supply Chain Challenges for Single-Use Systems

Jennifer Markarian

Suppliers address the complexity of supplying disposable components to the global biopharmaceutical manufacturing industry.

The implementation of single-use systems (SUS) for biopharmaceutical manufacturing as an alternative to or in combination with traditional stainless-steel equipment offers advantages such as reduced capital cost, faster facility construction, and more flexible and efficient manufacturing (1). In a fully disposable or hybrid facility, however, because pieces of equipment (e.g., reactors, transfer tubing, holding vessels) are now consumables, the supply to the manufacturing facility is more complex. The demand for customized systems and the overall growth of demand for SUS add to the pressure to improve supply.

Most SUS are currently made in the United States and the European Union, but suppliers are exploring manufacturing of SUS components in Asia to serve the region's growing biopharma market more efficiently. In September 2018, MilliporeSigma announced its first Mobius single-use manufacturing facility in Wuxi, China would begin production in 2019 (2), and in November 2018, GE Healthcare announced a collaboration with Chinese healthcare technology supplier Wego Pharmaceutical to produce single-use consumables in Weihai, China using GE's Fortem platform film (3). Shorter lead times are one potential benefit. Local production could also reduce the environmental impact of shipping components over long distances (4).

Pharmaceutical Technology spoke with Andrew Bulpin, head of Process Solutions at MilliporeSigma; Jeff Carter, strategic project leader at GE Healthcare Life Sciences; Eric Isberg, director of Life Sciences at Entegris; and Helene Pora, vice-president of Technical Communication and Regulatory Strategy at Pall about some of the issues facing the industry as companies look to SUS for biopharmaceutical manufacturing.

Global supply chain

PharmTech: What are some of the challenges with supplying single-use systems and components globally today?

Isberg (Entegris): One area of concern is availability of customization. Large suppliers tend to focus on systems with larger quantity production, leaving short-run, highly custom systems to small boutique suppliers. Consolidation of the single-use suppliers has exacerbated this issue.

Bulpin (MilliporeSigma): Single-use supply chains are complex and dynamic. The large number of raw materials makes forecasting demand more difficult and requires robust materials management, supplier quality management, quality control, and business continuity planning to ensure continuity of supply. Common materials (e.g., silicone) are used across many vendors, which can create single points of failure within the supply chain for both the single-use supplier, as well as the end-users of their products.

The key is to adopt a comprehensive, 'risk-smart' approach to supply continuity and control. It is important that suppliers proactively identify the potential risks and minimize the probability and impact of supply disruptions through effective demand planning/forecasting, capacity planning, business continuity planning, change control management, disaster recovery planning, supply-chain mapping, and continuous improvement. At MilliporeSigma, a cross-functional team of subject matter experts assess risks related to demand volatility/forecast accuracy, manufacturing capacity, process and equipment, sole/single-sourced raw materials, facilities (e.g., water, utilities, power, information technology/systems), and more. Risks above a certain risk priority number are mitigated and monitored. Business continuity plans are revisited on a regular basis, and risk mitigation activities are updated continually.

Pora (Pall): Sourcing and lead times have long been challenges for both suppliers and consumers, with some of the key pain points including lead times and an ever-changing and advancing industry.

One of the most critical challenges is that biopharma is a high-risk industry. Although there have been a multitude of advances in the industry, the fact remains that the end products being made with SUS consumables are being used in humans and can mean life or death for a patient or a patient population. Even at the clinical trial manufacturing phase, a full understanding of how the process will scale is needed. Particularly in cases where high customization can be called for, the supply chain becomes more complicated and impacts the lead time.

Another challenge is just-in-time (JIT) delivery and customization. Warehousing requirements for larger spaces helps to solve storage and availability issues for off-the-shelf consumables but does not address the JIT approach or customized needs many consumers require for their process consumables.

A third challenge is that as suppliers (and the industry) evolve, product ratings, design, or supply chain sources may change, and it is critical to keep users informed. Transparency is a necessity, yet changes can impact existing processes and lead times.

As an industry, and through supplier associations like BPSA [Bio-Process Systems Alliance] and BPOG [BioPhorum Operations Group], we are working to overcome these challenges. There is a greater focus than ever on creating realistic supply-chain mapping models that address the global nature of today's market. And a deeper importance is being placed on forecasting by end users so that the supplier and consumer can work together more effectively.

Carter (GE): Issues include logistics (including time to clear customs as goods move across borders, which can counter the speed element of the single-use value proposition) and managing complaints or investigations on product that is overseas. Geographical distances and language barriers can make general communication and relationship building challenging.

PharmTech: What are the challenges/potential benefits of manufacturing SUS locally in Asia?

Bulpin (MilliporeSigma): With the establishment of manufacturing capacity and capabilities in China, we can reduce our product lead times and help our customers bring new products to market faster. In addition to shorter lead times, end-users can carry less inventory and have an enhanced level of supply security, with the ability to source their assemblies from multiple manufacturing sites.

All manufacturing sites should be working under the umbrella of a single, global quality system, and customers need to qualify the new site so that they have the ability and flexibility to receive assemblies from multiple sites

Carter (GE): Proximity to a large and rapidly growing customer base does allow us to step up our service level to our Chinese customers. One practical example is the efficiency of working in native language and local time zone, particularly for configured and customized single-use systems. Developing manufacturing operations in China to complement our existing single-use manufacturing network provides an added capability in how we consider and structure contingency plans to maintain business continuity even under challenging circumstances.

GE Healthcare published a peer-reviewed single-use system lifecycle analysis (4). The results of this analysis showed that single-use consumables provide a better choice from the environmental impact perspective vs. the clean and re-use paradigm. The more variable aspects of the single-use lifecycle analysis and some of the more environmentally impactful elements of the value chain were the distribution of what are often large volume, low bulk-density products across various distances and transportation modes. Based on this study, localized manufacturing should have a reduced environmental impact affect; of course, there are, however, diminishing returns based on manufacturing facility capacity and plant efficiency.

Pora (Pall): Over the past decade, [biopharmaceutical manufacturing] has become an increasingly global industry. With SUS, the supply chain is complicated because, regardless of the location of manufacturing, the components are often coming from different areas of the globe. Although a lot of companies are considering moving production to other locations, with Asia having particular interest, questions remain. Most critically, expertise has to be there, and an often-overlooked consideration is shipping. What will the logistics look like, and how will that impact lead times? The country that any product is manufactured in will have its own resources and regulations, which will affect the ability to industrialize production. In addition to the considerations mentioned, what it really comes down to is manufacturing in locations that have the right balance between flexibility and supply.

Quality control

PharmTech: What are some of the best practices in ensuring quality control of single-use consumables throughout the supply chain (from polymers through to the finished components)?

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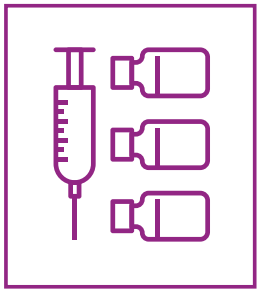

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Pora (Pall): The best way is to have quality built in from the start. There is always going to be a need to test the end product, but it is much easier if the quality of raw materials and the manufacturing environment have already been well-considered.

There is a lot to consider when looking at the raw materials, as well. How will those impact the end product? Users want components that are animal free, and there is a long list of particulates that cannot be in there (e.g., melamine and other components). The desire for BPA [bisphenol A]-free materials is also growing.

When it comes to the process, sterilizing-grade filters can be integral for protecting quality. More attention is being paid to sterility and integrity of connections and valves and minimizing the need for operator interaction, which has a proven impact on time and safety of processes.

Isberg (Entegris): I always refer people to the BPSA quality test matrices guide (5), which is an excellent resource for quality testing for single-use systems for bioprocessing applications.

Bulpin (MilliporeSigma): Resin and film suppliers are critical to the quality control of single-use consumables. These suppliers must have a good understanding of the requirements needed for the biopharmaceutical industry, a strong quality management system, and robust change control procedures. When selecting a critical raw material supplier, partnership is paramount. You need a supplier that will grow with you, evolve, and continuously improve their process to meet the changing requirements of the industry.

Single-use suppliers should continuously monitor and mitigate risks throughout their manufacturing process to ensure a repeatable and consistent level of quality. Operational excellence and lean initiatives should be used to proactively identify areas of opportunity and prevent future errors from occurring.

PharmTech: What are some of the challenges with change management?

Carter (GE): Some suppliers produce products for our industry, but their main industry is not ours. It has been observed that our industry is simultaneously a small player (in plastics) and yet among the most exacting in terms of quality requirements. Changes are common in plastics, and evaluating and qualifying these changes are resource intensive. Changes need to be managed together with our suppliers, because this can have an impact on our operations and more importantly, on those of drug manufacturers.

Pora (Pall): From an industry level there needs to be consistency in standards, including materials of construction and end products—this has to apply across the globe to be most effective. There cannot be large variations, and characterization and global agency alignment have started to play a larger role in help overcome this challenge.

Bulpin (MilliporeSigma): Change management can cause challenges for both suppliers and end-users. A large majority of single-use components are comprised of polymeric materials, and despite the high growth rates for single-use technologies over the past decade, they still make up a very small piece of the plastic consumables business. Although it's improving, single-use suppliers still don't have much control over raw material changes from the plastic suppliers, which means we are faced with a higher number of changes than we'd like. The volume, complexity, and cost of qualifications can be burdensome for both the single-use sup-

plier and the end-user. With new requirements for extractables and other testing, the time associated with the assessment and qualification of changes is increasing, which makes it more challenging to manage supply risks throughout the duration of the change.

Managing change is challenging in a rapidly growing market with continuous evolving guidance that requires a smart risk-based approach. One size does not fit all. We have extensive knowledge of our customers' processes so we can strategically evolve their manufacturing process to fit their growth plans.

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SUSTAINABILITY IN DISPOSAL OF SINGLE-USE SYSTEMS

Single-use systems for biopharmaceutical manufacturing are, as their name implies, used once and then disposed of, unlike traditional, stainless-steel equipment, which is cleaned and re-used. Although single-use components might seem at first glance to be less sustainable than reusable ones, single-use systems actually have a lower environmental impact, primarily due to the high environmental impact of the high purity water and heat needed to clean and sterilize traditional systems, notes Jeff Carter, strategic project leader at GE Healthcare Life Sciences. The company performed a lifecycle assessment (LCA) study in 2016–2017 (1) as a more detailed follow-up to its 2010–2012 LCA study, and the new LCA showed that end-of-life impacts were small compared to use and supply-chain impacts. Disposal, however, is still an issue to be considered. Options include landfill, waste-to-energy (WtE) incineration, or recycling.

"One should be aware that every solution to the problem has its own limitations and its own environmental impact. Waste management is complex from a societal, technological, and regulatory perspective. As such, this issue is one that demands a cooperative and collaborative effort," says Carter.

The first challenge for disposal of single-use components is that components that are in contact with biological materials are classified as bio-hazardous. A user will typically treat the waste at their site by autoclave, before sending it out through local waste management vendors that will bury the waste in a landfill, says Andrew Bulpin, head of Process Solutions at MilliporeSigma. Another option is incineration with cogneration. "WtE has been an acceptable practice for many users, as it offers an efficient way to collect and dispose of the waste, while converting the energy released by the burning of the plastic to electricity and/or steam used in heating municipal resources," explains Bulpin. "However, not every region has WtE facilities near their site, and not every WtE facility will accept single-use materials if they have been classified as bio-hazardous. In some areas, such as the United States, an appropriate WtE facility can be more than 250–400 miles away, and in some regions it could be well over a thousand miles away." In Western Europe, more facilities may have access to local WtE capabilities, but recycling is being considered because of its potential benefits for contributing to reducing the use of plastics to make new products. "There are many different options available to users based on where they are located geographically and what works best for their corporate culture and commitments," says Bulpin.

"The solution of recycling should be contextualized into the common sustainability mantra: reduce, reuse, and recycle, in that order," suggests Carter. "Effort should first be aimed at reducing waste generation in the first place, for both the product and the packaging, as well as transportation. Reusing doesn't get a lot of traction with single-use equipment, although there is discussion of reusing pallets that are used in the transport of the equipment. Lastly, there is recycling."

In addition to the biohazard classification, a significant challenge for recycling is that single-use systems used in biopharma are typically made up of different types of plastic materials that are difficult to separate. An alternative is to use the mixed plastic waste to make durable products, such as pallets and plastic boards, notes Carter, who says there is also some discussion of recycling the magnets used in the impellers of mixers and bioreactors.

In the eastern part of the US, MilliporeSigma has partnered with Triumvirate Environmental to offer the Biopharma Recycling Program, which allows manufacturers using single-use devices and systems to recycle the plastic into industrial-grade construction materials. "The process, which has been fully permitted to accept bio-hazardous materials, as well as other plastic-containing devices, can safely sterilize and manufacture recycled plastic lumber under one roof," says Bulpin. "This program has been operating since 2015 and has recycled approximately 22% of the waste generated by single-use facilities along the East Coast. There are currently 18 manufacturing sites using the program, and while this is the first of its kind, there is hope that this program will help to increase investigation into other technologies that can further reduce the environmental impact of single-use systems."

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—Jennifer Markarian

Challenges with Successful Commercialization of Biosimilars

Anurag S. Rathore, Arnold G. Vulto, James G. Stevenson, and Vinod P. Shah

This article presents some key differences between the US and European regulation of biosimilars, including naming conventions and pharmacovigilance of biosimilars, and the impact of biosimilars on commercialization and affordability of biotherapeutics.

Anurag S. Rathore is professor, Department of Chemical Engineering, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi, India. **Arnold G. Vulto** is a professor, Dept. of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands and Dept. of Pharmaceutical and Pharmacological Sciences, Catholic University Leuven, Belgium. **James G. Stevenson** is a professor, Department of Clinical Pharmacy, University of Michigan College of Pharmacy, USA. **Vinod P. Shah** is a pharmaceutical consultant.

Commercialization rights for novel therapeutic products are protected for a finite period by patents and other measures. After expiration of patents and other exclusivity rights, other manufacturers are allowed to make copies of these products, referred to as generics in the case of small-molecule pharmaceuticals and biosimilars in the case of biopharmaceuticals (1). Biosimilars are biological products that are highly similar to and have no clinically meaningful differences from an existing approved reference product (1). They offer improved affordability and are thus expected to have major impact on accessibility of biotherapeutics, including in developing and emerging economies. The global market value of biosimilars is expected to reach $36 billion by 2020 (2).

Biosimilars are defined by the European Medicines Agency (EMA) as biological medicines that are highly similar to another already approved biological medicine (the 'reference medicine') (3). They are approved according to the same standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines. There are some key differences between the production of biosimilars and that of the traditional small-molecule generics. Capital investments, as well as operating costs associated with manufacturing of biosimilars, are significantly higher than that for small-molecule generics, along with the associated risk of failure. The heterogeneities are a result of the size and complexity of the molecules themselves, as well as activities in the host cell that is used to express the product, the bioreactor conditions under which the cells are grown, and the purification process utilized for generating the final product.

The correlations between the clinical safety and efficacy of a biologic product and its product quality attributes are generally quite well known, however with residual uncertainty. The regulatory

process is designed to address this residual uncertainty (4). In both the United States and Europe, limited clinical data have been required so as to enable evaluation of safety and efficacy of the biosimilar drug in comparison to the original drug. EMA, for ethical reasons, is exploring ways to reduce the clinical testing to a minimum to avoid extensive and thereby expensive clinical trials.

The success of biosimilars has been somewhat muted, in particular in the United States, though certainly picking up with time. The reasons for this are several including the complexity of biopharmaceutical processes and products as well as the inherent heterogeneity of these products, which makes it difficult if not impossible to maintain identical purity even by the innovator itself. For this reason, both in the US and in Europe, new regulatory pathways have been developed for the assessment of copies of biological medicines after expiration of market exclusivity (1). Europe has been a leader in creating the regulatory framework for approval of biosimilars, and as a result, more than 50 biosimilars of 15 innovator biotherapeutics have been approved by the EU as of April 2019 (3). This is a sharp contrast with the US, where only 17 biosimilar products related to nine innovator biotherapeutics have been approved and only 10 were available on the market at the time of writing (5).

In this 42nd article in the Elements of Biopharmaceutical Production, the authors present a perspective on challenges with successful commercialization of biosimilars. Aspects that have been explored include common principles in biosimilar development and assessment, key differences between the US and EU regulations, and the role of pharmacovigilance in biosimilars.

Development and characterization of biosimilars

The design of a biosimilar is mostly an art of reversed engineering (6). A biosimilar company may purchase 10–20 different batches of the product they seek to copy and perform an analytical characterization exercise. The number of batches used needs to be justified to the regulator. A selection of attributes that are often examined as well as the numerous analytical techniques used in the assessment can be found in Kwon *et al.* (4).

The biosimilar manufacturer attempts to define the critical quality attributes (CQA) that are responsible for mode(s) of action on one side but also for side effects (like immunogenicity) on the other. In addition, the variability in the CQA between batches of the reference product is defined, as the biosimilar is required to stay within these boundaries. According to FDA, "although the scope of ICH [International Council for Harmonization] Q5E is limited to an assessment of the comparability of a biological product before and after a manufacturing process change made by the same manufacturer, certain general scientific principles described in ICH Q5E are applicable to an assessment of biosimilarity between a proposed product and its reference product. However, demonstrating that a proposed product is biosimilar to an FDA-licensed reference product manufactured by a different manufacturer typically will be more complex and will likely require more extensive and comprehensive data than assessing the comparability of a product before and after a manufacturing process change made by the product's sponsor. A manufacturer that modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established

controls and acceptance parameters. By contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product" (1).

Subsequently, the amino-acid sequence is cloned in a suitable producer cell and then the tedious work of selecting such a clone of cells that produce as close as possible the reference product and also in commercially viable quantities (7). Once the cell line has been chosen, the cell culture process followed by the purification process and the formulation are developed. The expressed or secreted biosimilar candidate is exhaustively scrutinized for resemblance to the reference product using a variety of sophisticated chemical, physical, and pharmacological techniques (4). Once close resemblance has been established, a minimum of three clinical batches are produced under GMP-conditions suitable for starting the clinical pharmacological testing program. This program starts with a Phase I pharmacokinetic (PK), and whenever possible pharmacodynamic (PD) trial in human volunteers or patients to assess similarity with respect to exposure to the different preparations. The reason for this is that for several reference products there are geographically different manufacturing sites, and small differences between EU and US reference products have been observed (such as for etanercept and infliximab).

Once the results from preclinical studies have shown that the biosimilar candidate has completed all requirements for the similarity exercise, it is common practice to perform a Phase III trial in patients. However, this is not a strict requirement for the EU. One of the first approved biosimilars—a biosimilar of a granulocyte colony-stimulating factor from Sandoz (Zarzio, approved in EU in 2008)—was not tested in patients, but only underwent extensive PK/PD trials in human volunteers (8).

The conditions for the pivotal biosimilar trial deserve special consideration. The objective for this study is not to prove safety and efficacy but rather demonstrate absence of clinically meaningful differences as compared to the reference product. This has important consequences for the choice of patients and indications and the choice of endpoints. The choice has to be based on scientific advice from regulatory agencies to maximize the chance of finding any clinically relevant difference. For TNF-alfa inhibitors, for instance, psoriasis is a sensitive indication with a relatively clear endpoint (with mean PASI change as readout). Alternatively, rheumatoid arthritis is a good disease model, with the ACR-20 the most sensitive indication. And here a second principle of biosimilar development is eminent, that of indication extrapolation. The scientific justification of extrapolation is based on the similar mechanism of action, target/receptor interactions, and molecular signaling; product structure interactions with the target or receptor; PK, expected toxicities; and information based on mechanism of action. All of these factors are examined in the biosimilar application. Any differences in these factors can be addressed in the context of the totality of the evidence supporting a demonstration of biosimilarity. The principle of extrapolation can result in substantial cost-savings in the development of biosimilars.

Once the clinical studies have been completed, the marketing license application is submitted to

the regulatory agency. In Europe, it takes an average of 12–13 months to obtain a positive recommendation from the Committee for Medicinal Products for Human Use (CHMP), the body that advises the EU commission on market approval. The approval process is quite transparent, and after approval, EMA publishes a European Public Assessment Report (EPAR) that includes all the details of the scientific assessment. If there are residual uncertainties, these are incorporated in the post-marketing surveillance program imposed by the regulator. Once regulatory approval has been received and market exclusivity of the reference product has expired, the products become available for use by patients. In most EU countries, there is no hurdle for biosimilars to obtain full reimbursement (or with a small co-payment), and so patients have quick access to the licensed more cost-effective alternative.

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The US Biologics Price Competition and Innovation Act (BPCI Act) of 2009 provided an abbreviated pathway for FDA approval of a biosimilar product. FDA recommends use of a stepwise approach for the development of biosimilar products: analytical studies, animal studies, clinical PK/PD studies, clinical immunogenicity assessment, and additional clinical studies. At each step, the sponsor should evaluate the level of residual uncertainty about the biosimilarity of the proposed biosimilar product to the reference product and identify the next step to address remaining uncertainty. If there is a residual uncertainty about biosimilarity after conducting structural analyses, functional assays, animal testing, human PK and PD studies, and a clinical immunogenicity assessment, then additional clinical data may be needed to adequately address that uncertainty. A clinical study should be designed to investigate whether there are clinically meaningful differences between the biosimilar product and the reference product.

FDA requires US-Reference Listed Drug (RLD) for comparability studies—analytical, clinical PK/PD—to demonstrate biosimilarity. For a PK/PD clinical study, the most sensitive dose to detect and evaluate differences in the PK and PD profiles is suggested. FDA has also established an additional approval classification called an "interchangeable biosimilar". To achieve this designation, the biosimilar manufacturer must demonstrate that an interchangeable product is expected to produce the same clinical result as the reference product in any given patient. Also, for products administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product must have been evaluated. The FDA guidance for the interchangeable biosimilar designation was published in 2017. The consequence of the interchangeable biosimilar designation is that pharmacists in the US would be permitted to automatically substitute the interchangeable biosimilar for the reference product without the prior approval of the prescriber (similar to small molecule generic products). Thus far, none of the

biosimilars currently approved in the US have this designation.

Challenges in development and commercialization of biosimilars

The two major concerns with respect to approval and use of biosimilars are the efficacy and safety of the biosimilars in comparison to the original drug. The foundation for establishing this is to demonstrate product comparability (9).

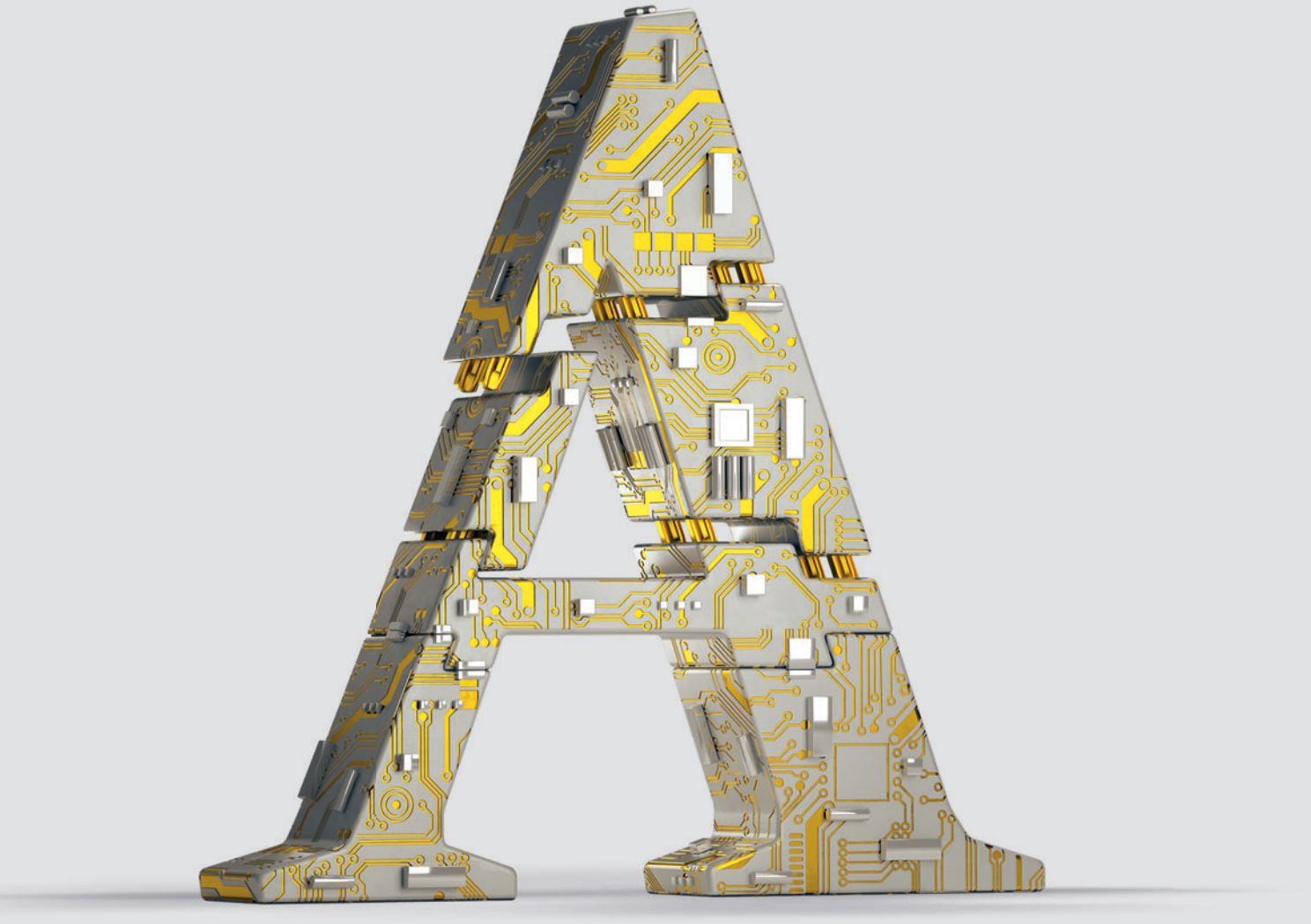
Quality of biotherapeutic products is known to be significantly impacted by the manufacturing process used to produce them as signified by the oft mentioned adage "The Process Defines the Product" (10). A biosimilar manufacturer has to demonstrate their capability to control the process so as to manufacture product of consistent quality (11) and follow it up by a thorough comparison between the biosimilar and the innovator's product based on extensive analytical examination, stability studies, non-clinical studies (such as receptor-binding studies and cell-based assays), and clinical studies (for pharmacokinetic, pharmacodynamic, and immunogenic behavior) as mentioned previously. In most likelihood, the biosimilar product may differ from the innovator's product in a subsection of the quality attributes, although it is not allowed to impact on clinical efficacy and safety (12,13,14).

A key aspect that needs to be understood as well is the relationship between the product and the clinic. Biotech products tend to be complex and subject to potential modifications. For this reason, all these qualities are scrutinized with advanced analytical techniques.

Role of pharmacovigilance in commercialization of biosimilars

The complexity of biologic molecules and the associated manufacturing processes mean that these products have the potential for immunologic reactions, which could result in a decrease in efficacy (neutralizing antibodies) or adverse reactions (antidrug antibodies). Regulatory pathways employed by EMA and FDA place greater emphasis on findings from analytical assessments and reduce the need for comparative clinical trial data. While this is efficient in bringing biosimilar products to market, it also means that there is limited clinical exposure to the product at the time of market entry. Therefore, it is important that an effective and well-designed post-marketing pharmacovigilance program is in place to detect potential product-related problems that would likely not be observed during the biosimilar development. The example of pure red cell aplasia that occurred with the use of a particular epoetin alfa product in Europe (Eprex, Johnson & Johnson) in the late 1990s and early 2000s demonstrated that small manufacturing changes have the potential to cause clinically significant immunogenic responses (15). While the potential for immunogenic reactions is possible given that there will inherently be small structural differences between the reference product and the biosimilar due to the complexity of the molecules and manufacturing processes, in practice there have not been any significant issues related to immunogenicity reported throughout the experience with biosimilars in Europe (over a decade) or the US.

Approaches to post-marketing pharmacovigilance are often categorized as passive surveillance or active surveillance methods. Passive



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surveillance is primarily the reliance on spontaneous reports from healthcare workers such as physicians or pharmacists. Passive reporting systems for adverse drug reactions exist in Europe (EudraVigilance, EMA) (16) and in the US (MedWatch, FDA) (17). Active surveillance generally involves examination of databases or patient registries to identify potential adverse events. In both cases, one of the keys to the success of a pharmacovigilance program is to be able to differentiate between similar products produced by different manufacturers (e.g., biosimilars). This has focused attention on the naming conventions that are used to distinguish these products in clinical practice.

Naming conventions

While in Europe the convention is to use brand names to identify and differentiate products, the situation in the US is quite different. There has been much debate over the preferred method of naming biosimilars in order to both facilitate effective pharmacovigilance and also to encourage the adoption of biosimilars to control costs and improve patient access. Some organizations in the US advocated for the reference product and the biosimilar to share the same US Adopted Name (USAN). The argument was that this would facilitate the adoption of biosimilars and would provide some confidence that the products were in fact expected to produce the same clinical effects. However, in the US there is a high reliance on the use of the USAN and not on brand names in electronic systems. Many argued that sharing a common USAN would not facilitate accurate and effective pharmacovigilance. In order for spontaneous reporting systems and active surveillance systems to be effective, there must be a reliable means of correctly identifying the specific product that the patient received.

To assure pharmacovigilance and also in an attempt to avoid any perception of superiority or inferiority of the reference product and biosimilars, FDA has proposed a naming convention that entails assigning a unique suffix to every biological product. Biologics of the same therapeutic type would share a common "core name", but biosimilars would have a unique four-character suffix that is "devoid of meaning" or reference to the manufacturer (18). The use of a suffix was preferred because it would still allow products with the same core name to be grouped together in electronic databases and systems for ordering, dispensing, and administering medicines.

There has been concern raised about this approach by FDA. One concern is that the use of distinct names will create the impression that the products may not produce the same clinical effects in patients (19). The second concern is around the use of a suffix that is "devoid of meaning". The use of a "non-memorable" suffix is expected to make it difficult for patients and healthcare workers to be clear about which specific products that patients are receiving, thereby benefiting the originators. Confusion or ambiguity in the communication of the specific product could lead to inadvertent switching and could actually harm overall pharmacovigilance efforts. One approach to reduce the likelihood of wrong product selection errors in the US would be to include brand names as well as the USAN for biologics into electronic systems and when communicating with patients, as is the case in Europe where the brand name is used as the unique identifier.

Benefiting the patient: Access to biosimilars

European healthcare systems are based on solidarity, which means that there is a collaborative effort to provide patients access to medicines at the lowest possible cost. Each year the European Commission organizes an open forum for all stakeholders to report on the progress of this objective (20). An indirect but significant benefit of biosimilars is that post their introduction, typically the corresponding innovator company also offers considerable rebates to patients of sometimes 50% or more (21). For some smaller proteins such as short acting filgrastim, the cost has gone down by as much as 80%. It is critical to note that uptake of biosimilars in itself is a naïve parameter, as it overlooks where innovator products have been able to stay in the market at prices similar to those of biosimilars. As a result of the leadership exhibited by the EU, savings for healthcare systems and patients are now billions of Euros each year.

Some countries, such as Denmark, Norway, Poland, and Hungary, have chosen for a centralized top-down decision system to tender for biologics and implement the outcome as the only alternative (22). Across Europe in the more open healthcare systems such as UK, Germany, and The Netherlands, the following are four key factors that in close coherence appear to be critical for acceptance by prescribers and patients of biosimilars as an alternative for the sometimes outrageous expensive reference products (23):

- Multi-stakeholder approach: Get everyone involved, prescribing doctors, pharmacists, supporting staff and hospital management, and third-party payers.
- One voice principle: The whole medical team should be educated to talk the same language to avoid the so-called nocebo-effect (a negative not pharmacology-related negative therapeutic outcome like side-effects or perceived loss of efficacy) (24).
- Shared decision making: Involve the patient in the discussion when medication is being shifted toward a biosimilar, avoid ignorance and confusion (which may again induce a nocebo-effect).
- Gain sharing: Introduction of biosimilars takes time, transitioning patients from innovator product to a biosimilar requires careful instruction, etc., and there should be some benefit for the local healthcare community.

The EU—in collaboration with EMA—has produced information materials to inform healthcare professionals and patients in many languages (25). In several countries, there are local initiatives to support hospitals to educate all stakeholders on the great value biosimilars can have for the access and sustainability of medical care.

Summary

While the EU and the US regulatory systems have so much in common, they are different in their approach toward making biosimilars available to patients. The EU Commission launched initiatives to this end in the early 2000s, and as a result an abundance of available biosimilars and impressive cost-savings for patients has been achieved. Patent litigation, political turmoil, and a profit-driven healthcare system have denied US patients access to the same benefits. Even FDA is appalled by the

lack of progress (21). In Europe, there may be 70 biosimilars by 2020, and then a second wave of patent expirations will widen the available armamentarium.

With the biosimilars marketed in Europe and the US, the record of safety and efficacy has been excellent thus far. It can be surmised that so far, the regulatory process has appeared to be robust enough to prevent clinical issues, even across use of biosimilars by millions of patients. This bodes well for the future of biosimilars.

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