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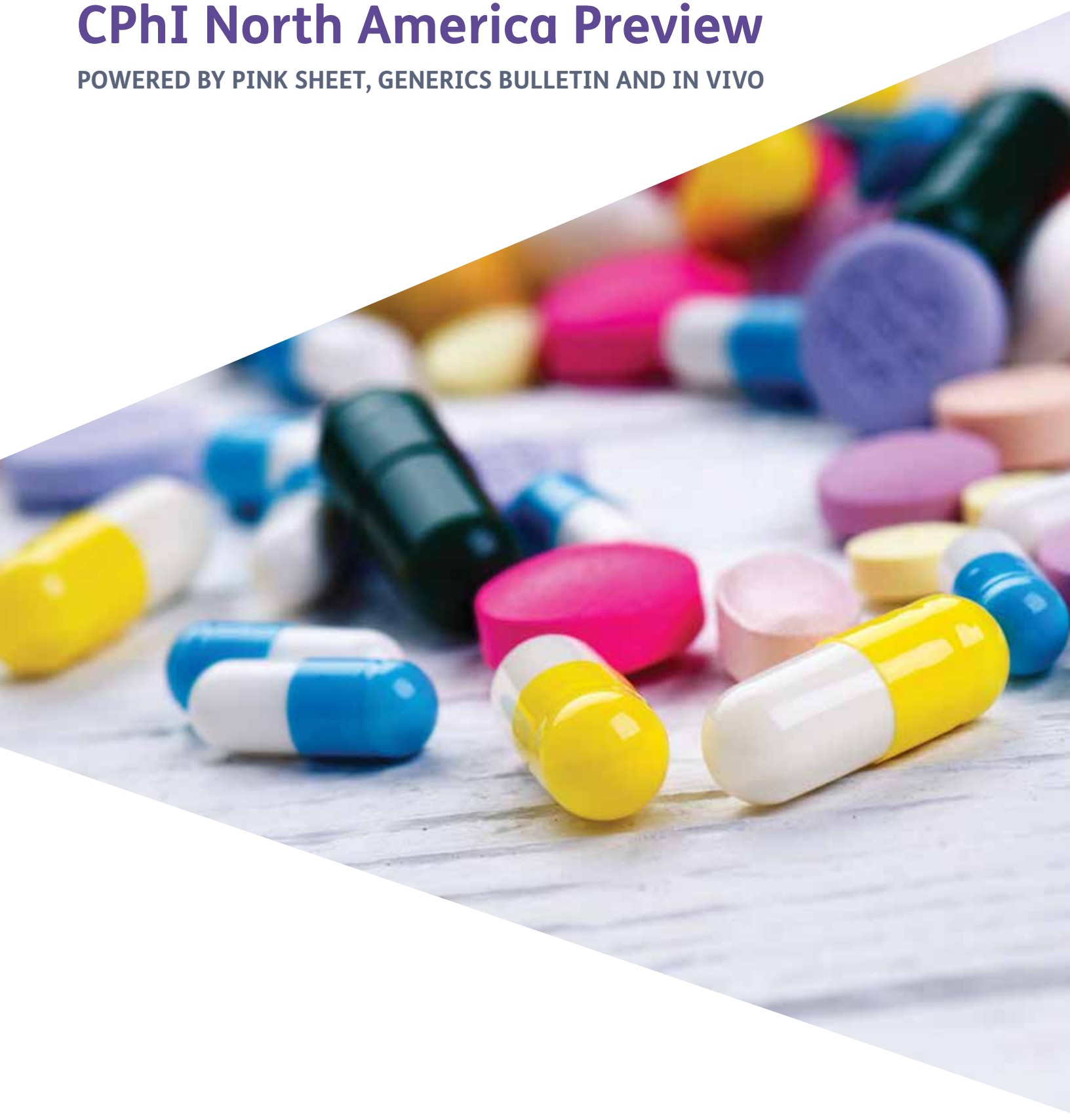
# CPhI North America Preview

## POWERED BY PINK SHEET, GENERICS BULLETIN AND IN VIVO



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# Contents





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# Pure Drug Nanoparticle Production With Advanced Polymeric Milling Media

Poor aqueous solubility, which affects up to 70% of new chemical entities (NCEs) in development, continues to pose significant formulation challenges for the pharmaceutical industry. The more insoluble a drug is – generally defined as aqueous solubility of less than 1 mg/ml – the more difficult it is to successfully navigate the development process. Most NCEs are designed to be lipophilic, with affinity for dissolving in oils, fats or lipids rather than water.

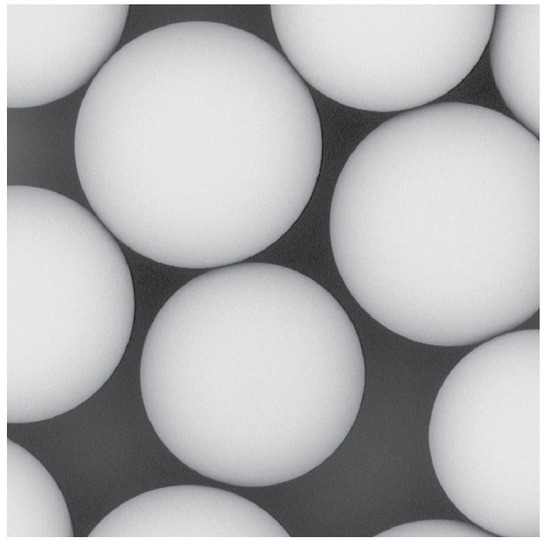
While researchers have explored a multitude of novel formulation technologies to address poor solubility and problems with bioavailability, the use of pure drug nanoparticles is now commercially validated and regarded as a universal formulation approach, applicable to all routes of drug administration. Newly commercialized advanced technologies, such as milling with polymeric milling media, present an ultra-pure, top-down approach to creating nano-based delivery systems.

## Making Nanoparticles

Pure drug nanoparticles are pure solid drug particles with a mean diameter of less than 1,000 nm. They are typically crystalline but can be partially or completely amorphous, stabilized by the physical adsorption of substances such as surfactants and/or polymeric stabilizers. It is generally accepted that for BCS (Biopharmaceutical Classification System) Class II molecules (i.e., with low solubility/high permeability) intended for oral administration, low bioavailability is directly associated with slow dissolution velocity and low saturation solubility.

Presentation of these molecules in a nanoparticulate state – with sizes below 1,000 nanometres (nm) – can accelerate *in vivo* dissolution and even increase saturation solubility in the case of extremely small nanoparticles (<200 nm). Improved drug dissolution and solubilization invariably enhances the rate and extent of oral absorption. Nanoparticles can reduce food effects, hasten onset of action and enable dose reduction to minimize adverse side-effects.

That amounts to a better safety, delivery and efficacy profile that favors both therapeutic outcomes and patient compliance. From a commercial perspective, nanoparticles can facilitate the path to approval and help make NCEs commercially viable. They also present an opportunity to repurpose marketed compounds with alternative drug-delivery platforms, as a component of pharmaceutical lifecycle-management strategy. However, sizes significantly smaller than 1,000 nm are needed to achieve safety and effectiveness in several dosage forms, including parenterals and inhalables.



**"PuroMill™ is a wear-resistant bead-form polymeric milling media purified under cGMP guidelines for the production of pure drug nanoparticles.**

## Poorly Soluble Injectable Drugs

Formulating poorly soluble drugs intended for injectable administration (IV, IM, SC), where the intent is either systemic circulation or depot release, can be particularly challenging. Typically, IV administration requires nanoparticles of <1,000 nm – much smaller even than red blood cells which are in the range of five to eight microns. However, traditional solubilization techniques, including the use of co-solvents, surfactants and complexing agents, are often associated with low drug loading, instability and undesirable toxicities.

Formulating injectable drugs as pure nanoparticles, stabilized by GRAS (Generally Regarded As Safe) surface stabilizers, overcomes these problems and provides a universal pathway for the delivery of poorly soluble parenteral agents. Beyond oral and injectable applications, drug nanoparticles also bring significant benefits in the administration of poorly soluble drugs via pulmonary, nasal, ocular, topical and other routes.

## Micronization vs. Nanonization

In drug development, every NCE needs to be evaluated independently to establish optimal performance. Historically, micronization techniques, such as jet milling, dry grinding, microfluidics or homogenization of active pharmaceutical ingredients (APIs), have been the preferred method of particle-size reduction to address solubility challenges.

However, micronization of crystalline APIs is limited to producing particle sizes in the 5 – 10 µm range, which for poorly soluble APIs is insufficient to maximize the dissolution rate and achieve improved saturation solubility. Moreover, micronized particles are completely unacceptable for IV applications or other routes of drug administration where large particles might present safety risks to patients.

Over the past two decades, a new class of "nanonization" technologies has emerged to enable production of pure drug nanoparticles. The most widely adopted technique, now incorporated into multiple drug products approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency, is high-energy media milling.

## Milling Media and Equipment

For decades, high-energy media milling has been the preferred production process for industrial nanoparticles used in paints, pigments, imaging and electronic applications. With high-energy media milling, nanoparticles are generated via physical fragmentation of larger particles when milling beads, subject to high-velocity agitation within the media mill, collide either with each other or the internal agitator.

Besides producing smaller nanoparticles, high-energy media milling can generate pure nanocrystals with very low concentrations of surface stabilizer. That enables much higher drug loading than with other technologies, thereby helping to minimize dosage sizes.

Since the advent of pure drug-nanoparticle applications, media mill equipment manufacturers have invested heavily in developing pharmaceutical-grade milling equipment. This is now suitable for all pharmaceutical dosage forms, including aseptic processing of parenterals. It can also accommodate very small grinding media – with bead sizes down to a couple of hundred microns – that enhance milling efficiency and produce even smaller nanoparticles to optimize solubility.

**"PuroMill™... is the only commercially available current Good Manufacturing Practice (cGMP) -certified milling media for reducing API particles to the nano scale in pharmaceutical and biotechnology applications."**

The emergence of pharmaceutical-grade milling equipment has also driven innovation in milling media. Many industrial applications, where there is less concern about potential contamination, typically rely on ceramic media. However, ceramic media is not generally compatible with the stainless-steel equipment prevalent in pharmaceutical manufacturing, due to metal contamination resulting from excessive abrasion of stainless steel during high-energy agitation within the mill.

In line with these trends, Purolite developed PuroMill™ Pharmaceutical Grade milling media as an integral component of the nanonization process for pure drug nanoparticles. It is the only commercially available, current Good Manufacturing Practice (cGMP)-certified milling media for reducing API particles to the nano scale in pharmaceutical and biotechnology applications. Additionally, PuroMill™ has a Drug Master File registered with the U.S. Food and Drug Administration.

PuroMill™ Pharmaceutical Grade media is compatible with all media mill equipment platforms and enables production of ultra-pure, ultra-fine drug nanoparticles. Narrow particle-size distribution provides a more uniform milling

Jacob Brodie, Global Vice-President and President – Americas Division at Purolite

process with, for example, less risk of catastrophic events such as clogging of the mill screen. It also gives regulatory agencies the assurance of improved batch-to-batch consistency with the final product.

### Avoiding Contamination

Product contamination in nanoparticle milling can occur due to leaching of unwanted chemical compounds from the milling process, or to media attrition and equipment abrasion. PuroMill™ Pharmaceutical media is a styrene-divinylbenzene co-polymer-based media, formulated to minimize the risk of product contamination traditionally associated with high-energy media milling.

Compared with using conventional ceramic media in stainless-steel milling equipment, PuroMill™ Pharmaceutical media effectively eliminates physical wear of equipment and attrition of media surfaces. It is highly purified to prevent potential leaching and extraction of soluble materials, including solvents and monomers, during the milling process.

PuroMill™ Pharmaceutical media is also stable with respect to steam sterilization or autoclave processes, and chemically and biologically inert to avoid undesirable chemical reactions and composition changes. Among other advantages, PuroMill™ Pharmaceutical's low density of 1.07 g/cc enables high media loads and agitation speeds during milling, to maximize reduction in particle size while avoiding the scale-up inefficiencies associated with centrifugation of more dense media.

### A New Standard

Launched in 2017 and available worldwide directly through the manufacturer, Purolite, PuroMill™ Pharmaceutical Grade media comes in sizes ranging from 50 – 1,000 µm, with stringent proprietary and compendial specifications for the highest quality assurance in producing the full range of drug-dosage forms.

"This process and technology for manufacturing PuroMill is in our wheelhouse of producing co-polymers and polymer media," notes Jacob Brodie, Global Vice-President and President – Americas Division at Purolite. "It's what we have done for 36 years. We also have a long tradition and history in the pharmaceutical market, so the FDA regulatory and GMP processes are very familiar to us."

Companies can conduct feasibility studies with PuroMill™ Pharmaceutical by contacting a pharmaceutical-grade mill manufacturer or contract development and manufacturing organization that utilizes mill technology – or by using their in-house equipment – to test-run the media with specific products or in different sizes of mill.

In an ever more competitive marketplace, pharmaceutical companies must strive to remove bottlenecks at every stage of drug development, and to deliver drug pharmacokinetics that will drive meaningful outcomes in the clinic.

PuroMill™ Pharmaceutical Grade media represents a new standard in pharmaceutical milling media for the production of pure drug nanoparticles. It can help companies confidently overcome the challenges associated with poorly water-soluble drugs, removing obstacles to drug development and ultimately improving therapeutic options for patients.

Purolite®





# FDA Insists Its Quality Controls Are Up To The Task

▶ By David Wallace


Allegations of substandard quality controls are not a new phenomenon for the generics industry. However, it is rare for an industry regulator to produce as comprehensive and pointed a response to such criticism as has just been published by the US Food and Drug Administration (FDA).

In a lengthy statement – apparently positioned as a rebuttal to media coverage suggesting deficiencies in the FDA's quality oversight for generics facilities, both foreign and domestic – Scott Gottlieb and Janet Woodcock have maintained that the agency's quality controls are sufficient, insisting that "at the FDA, protecting patient and consumer health is our highest priority".

Articles published by *Bloomberg* recently questioned the agency's quality enforcement in the wake of a record numbers of generics approvals in 2018, asking "Is the fast-tracking of those approvals coming at the expense of oversight that's supposed to ensure that drugs already on the market are safe and effective?"

*Bloomberg* also suggested there had been "a drop-off in inspections in many places and, in some cases, the softening of penalties" for generics companies demonstrating quality deficiencies.

### Gottlieb And Woodcock Hit Back At 'Flawed' Reporting

Commissioner Gottlieb and center for drug evaluation and research (CDER) director Woodcock acknowledged that "recently, there have been reports in the press calling into question the quality of our nation's drug supply and specifically, asserting that certain generic drugs are of a lesser quality than brand drugs", with "some of these reports claim[ing] to be based on data analysis".

"We believe these interpretations are seriously flawed and do not account for the full picture of our global vigilance over generic drug manufacturing," the pair contended.

"We recognize that our statement, in part directly responding to a news report, is not customary; we nonetheless feel

obligated to provide a substantive response given the public health issues at stake."

## Mitigating Risks Is 'At The Heart' Of FDA's Activities

"Assessing and mitigating risks is at the heart of everything we do across our vast portfolio," Gottlieb and Woodcock explained. "Sometimes the actions we take are visible, like warning letters or recalls. At other times, our actions to protect consumers are less discernable, but equally vital."

Maintaining that analyzing and addressing potential risks was a "complex effort based on data and grounded in science", the FDA executives said such activities were "at the center of our consumer protection mission and underpin our efforts to ensure the quality and safety of medical products".

Moreover, they attested, "our rigorous standards and inspections apply equally to generic and brand drugs – whether the medicines are being manufactured in Shandong, India, or Indiana".

Reiterating that generics were as safe and effective as their equivalent brands, Gottlieb and Woodcock pointed out that the FDA "continually monitors brand and generic drug products to make certain the medicines at all levels of the supply chain, from active pharmaceutical ingredients (APIs) to drug products being sold to consumers, are safe, effective, and high quality".

They also maintained that reports of adverse effects were responded to with appropriate changes to how both brands and generics are used or manufactured, noting that "we closely analyze reams of data to ensure the quality and safety of manufacturing throughout a product's lifecycle."

## Review Process Ensures Quality

Pre-approval reviews of drug applications – including "a robust review of manufacturing information" – were "a cornerstone of our current regulatory framework", the pair explained, allowing the agency to "perform a careful analysis and assessment of the drug product and manufacturing quality".

"We also, where needed, conduct pre-market inspections of manufacturing facilities for the product to ensure compliance with good manufacturing practice (GMP) regulations and other quality requirements before it is ever marketed."

For generic drugs in particular, Gottlieb and Woodcock observed, "this includes all the assessment activities conducted by our office of generic drugs (OGD) as part of their multi-disciplinary review of all generic drug applications".

"As a result of the FDA's rigorous review of manufacturing information, many drugs are not allowed to be marketed because, based on our careful review and analysis, they do not meet the standards for approval," the pair pointed out.

Furthermore, "before and after marketing of a drug product, manufacturers are also required to notify the FDA of any changes they make to their manufacturing process or facilities". And after marketing begins, they summarized, FDA pharmacovigilance activities helped to evaluate adverse events and safety data.

## Robust International Footprint

Turning to criticism of international inspections, Gottlieb and Woodcock insisted that "the FDA's inspectional footprint is robust, particularly in China and India".

Explaining fluctuations in inspection frequency – including a decline in surveillance inspections in China during the agency's 2017/18 financial year, at the same time as a substantial increase in Indian inspections – the pair explained that "the number of inspections in any given country reflects our risk-based prioritization of our inspections and improvements in our targeting; our increasing ability to leverage inspectional work done by trusted partners, especially in Europe; and a higher number of pre-approval inspections".

"Our policy for prioritizing and scheduling drug manufacturing inspections at higher risk facilities for quality-related surveillance is based on a facility's compliance history, recall trends, time since last inspection, inherent risk of the drug being manufactured, processing complexity, and other factors, which are all carefully weighed and considered."

"When you look at the full force of our inspectional resources," Gottlieb and Woodcock observed, "the FDA is maintaining global vigilance by concentrating inspections on higher-risk facilities. As global compliance trends change – and standards in some sectors improve – we should expect to see an evolution in these trends."

## Strong Compliance And Enforcement Actions Taken

"While the numbers of inspections have varied over the past few years, compliance actions, including warning letters, have increased," the executives noted. In fact, they pointed out, warning letters to human drug manufacturers regulated by the CDER had steadily increased in recent years, with the CDER issuing "nearly five times as many warning letters to human drug manufacturers" as four years ago.

"We don't believe this reflects a growing problem in drug quality," Gottlieb and Woodcock acknowledged. "On the contrary, the FDA's improvements to targeting inspections and in evaluating recommendations for enforcement action mean more attention is being given to higher-risk facilities than ever before."

"By better focusing our inspectional resources on higher risk facilities," they said, "we can identify potential quality problems that have the most impact on consumers."

"Overall, our inspections find that most companies are in compliance with GMP and other regulations. But the reality is that we're looking in the riskiest places. So, we're better able to spot problems and take action when needed. Our approach appropriately allows for companies to provide a plan for how they'll address issues identified during an inspection, which encourages a culture of quality within manufacturers, supported by smart and efficient regulation."

## All Manufacturers Meet The Same Global Standards

Importantly, Gottlieb and Woodcock emphasized, "the FDA's standards and inspections for generic manufacturers are the same around the globe".

"Pharmaceutical manufacturers, no matter where they're located, are responsible for ensuring that high quality products reach US patients. The FDA's role is to provide sufficient oversight – through application reviews and inspections – to ensure that companies fulfill their responsibilities and to take appropriate action when they do not. In addition to our pre-market steps, this oversight also includes testing selected finished drug products and APIs after they're on the market. This testing affirms that the potency, quality, and consistency of generic medicines meets the standards established for the specific drug."

For example, they indicated, when the FDA tested 323 products from around the world – including more than 100 from India – to determine if foreign manufacturers had a higher incidence of product failure, all 323 samples met US market quality standards.

"We recognize that the US market for pharmaceuticals has changed dramatically in recent years. In 1990, generic medicines only accounted for 33% of retail prescriptions. Today, generics account for 90%. Supply chains have also expanded globally. This has created new complexities, and new opportunities for novel risks. Our program has evolved to meet these new challenges, and we continue to implement policy measures to address emerging threats."

## Press Scrutiny Is Part Of The Process

"We welcome discourse about our process through public comment and a constructive dialogue with all partners and stakeholders, including the press," Gottlieb and Woodcock attested. "We welcome the scrutiny of our programs. We welcome the accountability inspired by a free press. This dialogue is part of how we advance our public health mission."

However, they insisted, by maintaining "global vigilance" over the generic manufacturing industry, in close collaboration with international regulatory partners, the FDA was "maintaining the quality of these medicines while helping patients and payers realize more of the benefits from high quality, low cost generics".

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*Published online in Generics Bulletin, 26 Feb 2019*



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# Company Overview

### About Purolite

Purolite is a premier manufacturer and innovation leader for resin-based separation, purification, extraction and catalysis technology. With production plants and advanced research labs across the globe, we provide effective solutions—including ion exchange resins, APIs, excipients, agarose and synthetic chromatographic resins, catalysts, adsorbents, enzyme carriers and advanced specialty resins—that improve the quality of almost every consumer product that exists today.

Supporting pharmaceutical, healthcare and life sciences customers for over 30 years, Purolite is dedicated to developing, manufacturing and commercializing resin technologies to support research, development and production-scale applications in pharmaceuticals, bioprocessing, food production, fine chemicals, personal care and other related markets.

### Global Manufacturing and Innovation

Purolite products are made in our ISO certified facilities in the UK, Romania, China, and the USA. Our API and pharmaceutical milling media products are manufactured in dedicated cGMP, FDA inspected facilities in Romania. With an R&D Centre of Excellence in the U.K. and R&D labs in China, Moscow, Romania and the U.S.A., our scientists address the industry needs of today and the challenges of tomorrow.

### Exemplary Service

We are an expert team of chemists, engineers, scientists, researchers and support specialists providing extensive technical, optimization and customization services. With over 40 global offices and 6 application laboratories, we have one goal—to provide the best solution for your application.

For further information on Purolite products and services, visit www.purolite.com and www.purolitelifesciences.com or contact your nearest Technical Sales Office.

### Exceptional Products

Purolite's broad portfolio of products are designed to meet your research, formulation and process demands.

- **PuroMill™**
  Polymeric Milling Media for the creation of pure drug nanoparticles
- **Purolite®**
  Pharmaceutical APIs and excipients
- **Praesto®**
  Agarose Resins for affinity and ion exchange chromatography
- **Lifetech™**
  Enzyme Carriers and ready-to-use Immobilized Enzymes
- **PuroSynth™**
  Resins for solid-phase peptide synthesis
- **PuroPhase™**
  SPE Reverse Phase adsorbents for solid phase analyte extraction
- **Chromalite®**
  Synthetic chromatographic resins for biomolecule and organic molecule separations in analytical, preparative and industrial applications


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# PuroMill™

Pharmaceutical milling media

## Enhance solubilization of small molecule APIs with advanced polymeric milling media.

PuroMill™ is the only commercially available cGMP pharmaceutical-grade milling media for reducing API particles to the nano scale and is an essential element for the development of pure drug nanoparticles through milling technology.

Made of advanced copolymer beads, PuroMill enables the creation of pure drug nanoparticles for the development of oral, injectable, pulmonary, ophthalmic and other dosage forms, while facilitating the delivery of insoluble compounds.

The benefits of PuroMill for nanonization of pharmaceutical molecules include improved formulation success and enhanced drug efficacy, safety and patient compliance—which ultimately results in better patient health.

Compatible with all conventional high-energy media milling equipment, Puromill minimizes the risk of process-related impurities associated with nanoparticle milling such as leachables/extractables and attrition from bead and equipment surfaces.

- **Non-porous, non-adsorptive micro surface minimizes contamination**
- **Monodisperse size improves flow properties**
- **Non-reactive and biologically inert beads ensure formulation integrity and biocompatibility**
- **Creates nanoparticles < 100 nm**
- **Enables high milling efficiency and scalability**
- **Conforms to USP specifications**
- **Autoclavable / steam sterilizable**
- **Drug Master File registered with the U.S. FDA**

Purolite®

**Available from 50 µm – 1,000 µm**

**Mill With Confidence.**
**www.purolite.com**

# **CLINICAL TRIALS IN 2019:** Is Biopharma Ready To Tackle The Iron Triangle of Time, Cost and Quality?

▶ By William Looney

Ken Getz, director of sponsored research and associate professor at Tufts University School of Medicine's Center for the Study of Drug Development (CSDD), discusses how information and technology advances, stakeholder education, and system reforms focused on service integration are finally transforming the patient experience in clinical trials. Combined, these three trends carry the potential for improving the bottom-line performance of this most costly component of the new drug product cycle.

Making a 20th century trial model fit-for-purpose into the third decade of the 21st century is a strategic necessity as drug discovery attracts a more diverse set of players and expands to complex areas of science with vastly higher price tags. According to Tufts CSDD research, these biotech products, often developed by smaller companies with fewer resources than the typical big pharma, now comprise a third of all US novel drug approvals.

**IN VIVO: Clinical trials are central to the mission of biopharma in developing new drugs to treat disease. Because humans are involved, the process is imperfect. How is the industry progressing in its task to raise the efficiency of trials by delivering results that are relevant to regulators and productive for patients?**

**KEN GETZ:** Reducing the time and cost of clinical trials is the endless, unresolved challenge facing every biopharma company. In 2019, however, we see three broad trends that are game changers with the potential to reverse this stalemate as we move forward into the next decade.

The first relates to use of data and analytics: companies are getting better at integrating information that historically has been very siloed. Data is emerging as a tool to drive cross-functional decision-making. To see operating functions – procurement, site management and patient recruitment – aggregating and sharing summary data with clinical teams represents real progress. Its creating that direct line of sight into protocol performance. It may be a baby step, but it paves the way for artificial intelligence, machine learning and other cutting-edge technologies that exist today but cannot be applied effectively to trials due to the hidebound organizational culture of most big pharma today. Before you can leverage the high volume of diverse data, you must integrate the data. That is the stage we are at now.

The second trend is the patient engagement movement. This is also transformative because it is forcing companies to revise their standard procedures and practices in developing a drug for registration and launch. Companies are soliciting input from patients and patient advocacy groups when building their development plan. And patients are helping sponsors to determine clinically relevant protocol design endpoints, and improve trial feasibility and participant convenience. The US Food and Drug Administration and the European Medicines Agency are looking to encourage these collaborations by requiring companies to report clinical trial results in language understandable to patients. I am optimistic this will soon be standard practice in every clinical trial. In fact, engagement is extending beyond the patient to include outreach to payers and providers too. Taken together, this has a positive influence on the overall delivery of care while simultaneously focusing resources to better execute against plan.

The third trend is linked to the two I've just cited: the convergence of clinical research and care delivered at the clinic setting. If you harvest the data and analytics, integrate the information in the trial protocol, and then use it to more effectively engage the patient, then the result is trials that are easier to recruit for and less expensive to conduct. The National Academy of Sciences is promoting an initiative called Learning Health Systems, which uses data from patient responses both to investigational and commercial medical therapies to incentivize broader changes in the way care is delivered to patients in the real-world setting. Essentially clinical research data contributes to the patient's medical record and informs clinical care throughout the patient's lifetime. Learning Health Systems represent a shift in thinking whereby research and accessible medical data will become embedded in a much leaner operating model supported by wearable and mobile technologies, flexible personnel staffing like telemedicine and other virtual communications. It is all about having infrastructure that reaches out to meet the patients, where they can most easily share their experiences and data, rather than the reverse. Embedding those contacts should address a stark statistic explaining why the trial status quo needs to change: we estimate that upwards of 80% of patients in a clinical trial never learn if their participation resulted in an approved drug.

**What about disruptive changes in the trial space that could slow or complicate these three positive transitions you've just outlined?**

There are several – though instead of disruptions I'd prefer to describe them as curveballs. One issue that stands out is the predicament of many smaller companies whose innovations now tend to dominate the development landscape in biopharma. What the FDA calls the "emerging sponsors" group accounts for nearly two-thirds of all active drugs and biologics in R&D today. Their economic footprint is different, most notably because these innovators cannot fund the sizable trials typical of a big pharma. Another issue is the continued proliferation of rare and stratified disease drug candidates in company pipelines. This is a major curveball, because to progress a trial in this space you have to work with relatively more complex protocols and a smaller number of patients. Sponsors must look far and wide for eligible trial participants, all while educating a provider community that often has no exposure to clinical research for the literally thousands of rare conditions vying for attention. And you don't have the scale efficiencies that you get when working with the much larger population groups in chronic disease.

Taken together, the concern is that such curveballs will delay the positive structural changes I have laid out that promise to enhance patient experience and engagement. The importance of the science coming from these two segments of the biopharma business demands we make the transition to a leaner, more efficient operating model for drug development, reducing the cost of trials with

## OTHER 2019 PREDICTIONS: PREP FOR THE VALUE WAVE

Information is the currency of value in biopharma, and, as data analytics capabilities explode, competitive advantage will accrue to those companies able to master the logistics and operational challenges in making this bounty of knowledge useful to the business. Julie Locklear, *In Vivo* editorial advisory board (EAB) member and managing director of the end-to-end evidence consultancy **Genesis Researc**h, weighed in on the topic of managing and utilizing data for value-based contracting success.

"Making the pursuit of value part of your business model doesn't just happen. We've found that successful companies recognize early on that the transition to value contracting can't be accomplished entirely in-house. It's not about setting a metric like recruiting a fixed number of additional FTE's. Instead, a flexible, hybrid approach – relying on a mix of internal and external resources – is required to address the new realities of budget limitations, the growing diversity of payer expectations, and real time access to vast amounts of data to speed decision-making. Bottom line: to prove its mettle in commercial negotiations, a value-based approach depends on partnering. Strategic external engagement is critical, especially in getting the analytics behind the transaction right. With multiple stakeholders in play, the approach to data has to be agnostic, so it pays to cast the net widely.

The second mandate we see coming in 2019 is more focus on the details of value-based transactions. The most important is to address the auditing of contracts contingent on specific outcomes like pay for performance. Discounts demanded by payers are going to increase, in turn raising the bar on the scope, reliability and integrity of the audit role –clearly, this function is vital as a confidence-builder for both biopharma and the payer community. In some therapeutic areas, like oncology, where verifiable data on progression-free survival is hard to come by, especially at the point of care, a consensus on auditing terms will be difficult, and, due to these data constraints, expensive too.

One possible solution to variant perceptions of data reliability is the emergence of a new class of vendors offering data management as an independent, third-party service, to work on behalf of payers who lack the internal expertise or resources to register outcomes.

The third mandate biopharma would be wise to follow in the months ahead is to recognize the growing institutional clout of third-party HTA review bodies, especially the Institute of Clinical and Economic Review (ICER), which now has a formal advisory role in the formulary listing decisions of high-profile pharmacy payers like **CVS Heath Corp**. and the US Veterans Administration Health Service. One practical step is for drug makers to take the initiative in modeling the ICER QALY-based methodology as part of their early-stage work to establish a compound's value proposition with payers and other key stakeholders."

more focus on patient-centric care. We all want to realize the promise of transformative, precision medicine as quickly as possible.

**Are internal company cultures, standards and practices "fit for purpose" in accelerating the operational transformation you reference?**

The industry is continuing to pursue multiple and often inconsistent strategies on policy issues like open sourcing of data and trial transparency. At the company level, we see a disconnect between what senior management identifies as a strategic opportunity and the execution of that opportunity down through the ranks. An example is a corporate decision that is commonly made to choose a single or limited number of preferred external providers for contract services on clinical trials. But that decision gets upended when it is time for individual clinical teams to select who they want to work with. It is all mix and match – some part of the operation adheres to management's preference for a single service provider, while others, for various reasons, choose to go their own way. The result just perpetuates inefficiency and inconsistent performance. There are countless additional examples of this type of behavior. Fixing organizational incoherence is a priority for big pharma, but change is hard. It takes time to adapt.

**What specifically are you predicting for the clinical trial environment in the coming year?**

Developments in this space tend to unfold slowly. The most important thing to expect in 2019 is that the CRO community will prioritize the introduction of advanced data and analytics to drive efficiencies in trial design, recruitment and execution. They are not going to leave it to the companies to muddle through any longer. We will see some compelling new examples of how that data is being integrated across the entire drug development spectrum. Specifically, information will be applied more robustly to identify and recruit investigators with the right credentials as well as to accurately target the best study volunteers.

**Tufts CSDD has a robust research program covering all aspects of the drug development cycle. What's on tap for 2019?**

Tufts CSDD typically works on 15 or so research projects simultaneously each year; some of it is sponsored by individual organizations (e.g. foundations, industry, and government agencies), with others done on a multi-sponsor basis. We work closely with most of the top 50 biopharmaceutical companies and the top 10 CROs, whom we survey frequently to capture emerging trends in policy and practice. My current work centers on a number of areas, including the evaluation of protocol design practices and their impact on drug development performance and cost; and benchmarks and trends in functional area practices such as outsourcing, site management, data management and patient recruitment. My team also looks at the impact of new operating solutions and innovations – patient engagement, single-source manufacturing, predictive analytics – on the expected net present value of drug development programs.

One example of projects we are currently working on is evaluating the use of machine learning and other forms of AI in clinical trial management, where we identify major areas this technology could be applied for performance improvement and demonstrable cost savings. Another is assessing study volunteers' participation in clinical trials to better understand the burden borne by patients. Specifically, we are developing a methodology to routinely measure the burdens that patients face from procedures as well as the simple cumulative inconveniences of patient participation. The results will show companies where they need to modify protocol design to make participation more convenient for enrollees, enhancing study feasibility and volunteer retention rates -- ultimately delivering a better cohort of patients and a higher quality of clinical research data to support registration.

An upcoming project for 2019 will quantify study volunteer diversity (e.g. gender, race and ethnicity) in new drug and biologic approvals. Hard and credible baseline measures are lacking right now. If you were to ask me for the number of black patients enrolled in trials for new diabetes drugs last year, I could not tell you. We have received a large grant to conduct this benchmark assignment based on evidence from clinical trials conducted over the past several years. Clearly, there is no shortage of drug development inefficiencies and improvement opportunities ripe for scholarly research. Our goal must be to apply this work to actual changes in the way trials are conducted – to establish precedents for patients, backed by evidence and astute observation.

*Published online in In Vivo, 7 Jan 2019*



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# US Must Rethink Biologic Naming Suffix, Says IGBA

▶ By David Wallace

Citing a "growing global consensus" against the use of product-specific suffixes to non-proprietary names to distinguish biosimilar medicines from their brand biologic counterparts, the International Generic and Biosimilar medicines Association (IGBA) has called on the US Food and Drug Administration (FDA) to rethink its use of such a mechanism given its status as a "notable outlier".

The call follows Health Canada's recent decision to not add suffixes to non-proprietary names for biologics – including biosimilars – leaving the US as the only major territory to operate such a convention. *(Also see "Canadian Decision On Biological Names Leaves US As The Outlier" - Generics Bulletin, 19 Feb, 2019.)*

"Health Canada's decision supports quality use of medicines, including safe prescribing and dispensing practice, by avoiding the complexity and potential confusion that would be associated with the introduction of a non-memorable suffix-based system," said IGBA chair Jim Keon, who is also president of the Canadian Generic Pharmaceutical Association (CGPA).

"The IGBA urges the FDA to reconsider its divergent approach to biologic naming and align with its regulatory partners in Europe, Canada, Australia, and other jurisdictions."

## Canadian Decision Aligns With Other Territories

Last year, Australia's Therapeutic Goods Administration (TGA) was praised by the IGBA for its decision not to use specific identifier suffixes as part of naming conventions for biologics. *(Also see "Australia praised after rejecting biologic suffix" - Generics Bulletin, 2 Feb, 2018.)* The IGBA noted that Australia's policy "aligns with the EU, which has approved the highest number of biosimilar medicines worldwide, and has acquired considerable experience of their use and safety".

Moreover, the World Health Organization (WHO) in 2017 suspended its proposal for a 'biological qualifier' that would have applied a random four-consonant code to the non-proprietary names of both biosimilars and brand biologics.

Meanwhile, Japan's approach to biosimilars uses the non-proprietary name followed by the word "biosimilar" and a sequential number, rather than adding a suffix to the name.

The US approach has been criticized by the international generics and biosimilars industry before *(Also see "Drop biologic suffixes IGBA urges US FDA" - Generics Bulletin, 31 Aug, 2018.)*, as well as by industry stakeholders within the US. *(Also see "Broad alliance queries FDA's suffixes stance" - Generics Bulletin, 5 Oct, 2018.)*

## No Improvement Demonstrated In US

"There is no data available that demonstrates that added non-memorable suffixes in the US have improved, or will improve, the US pharmacovigilance system," Keon claimed. "The IGBA continues to oppose any measures which have the potential to hamper public health and patient access to medicines."

Health Canada's decision to identify all biological medicines, including biosimilars, by their unique brand name and non-proprietary or 'common' name – without the addition of a product-specific suffix – was made following a domestic consultation process with stakeholders.

Welcoming the Canadian decision as "a strong choice for patient safety", the IGBA said the move "highlights a growing global consensus against the use of a product-specific suffix, as seen in long-standing EU experience and the Australian government's decision to also reject this approach".

"Additionally, the decision aligns with the WHO's approach for nomenclature of biological medicines and the WHO's decision to put on hold any further discussions of a biological qualifier."

## US Is Now A 'Notable Outlier'

"The decision draws attention to the US as a notable outlier diverging from this growing global consensus," the IGBA said. "The recognition that product-specific suffixes pose an unnecessary degree of complexity is highlighted as a core consideration in Health Canada's decision."

The IGBA also pointed to a recent European academic and regulators study on pharmacovigilance systems that found that 96.7% overall product identification was achieved across 10 classes of biologic products, including biosimilar medicines, sharing the same international non-proprietary name (INN).

"There are over 700 million patient days of safe clinical experience with EU-approved biosimilar medicines alone, based on shared INNs with their respective reference products," the association emphasized.

*Published online in Generics Bulletin, 27 Feb 2019*



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# Canadian Decision On Biological Names Leaves US As The Outlier

▶ By David Wallace

Health Canada will not impose suffixes on non-proprietary names for biosimilars and brand biologics, the regulator has announced, in a move that has been welcomed by the Canadian Generic Pharmaceutical Association (CGPA).

"Following internal and external stakeholder consultations and analysis of related issues, Health Canada has decided that biologic drugs, including biosimilars, will be identified by their unique brand name and non-proprietary – common – name, without the addition of a product-specific suffix," Health Canada announced.

"Both the brand name and non-proprietary name should be used throughout the medication use process so that biologics that share the same non-proprietary name can be distinguished by their unique brand names."

The consultation had included among its options the suggestion of appending a "unique, meaningless four-letter suffix" to the non-proprietary name, similar to that imposed in the US, with guidelines developed to align with the US Food and Drug Administration's (FDA's) approach "as much as possible".

But Health Canada said that during the consultation, "numerous healthcare system stakeholders, including prescribers, pharmacists, patients, and drug information systems providers, indicated that unique brand names are a key component for readily distinguishing among biologic drugs".

In particular, the regulator noted, its chosen approach "avoids any potential perception that different suffixes indicate clinically meaningful differences between a biosimilar and its reference biologic drug".

"All biologics, including biosimilars, will continue to have a unique drug identification number (DIN)," Health Canada pointed out. "The DIN distinguishes key characteristics of a drug product, including the brand name, manufacturer name, medicinal ingredient(s), strength(s), dosage form, and route of administration."

The decision leaves the US as the only major territory to implement a suffix system for biological naming.

## Distinguishes Without 'Regulatory Burden'

Health Canada said its naming convention:

- Will serve to achieve the objective of distinguishing among biologics in prescribing, dispensing and pharmacovigilance in the Canadian context;
- Was the most favored option among respondents to the stakeholder consultation;
- Does not impose unnecessary regulatory burden, and;
- Avoids the complexity associated with implementation of a suffix-based naming convention with retroactive application to previously authorized biologics.

In reaching its decision, Health Canada said it had considered the fact that brand names were "consistent with current biologics naming practice, and are already recognized and in use".

"All biologics authorized in the last 20 years that are within scope of the biosimilars guidance document have a unique brand name," Health Canada pointed out, noting that the product DIN was already used to specifically identify products in Canadian healthcare system databases.

"There is no internationally adopted naming scheme to distinguish among biologics that, based on active ingredient, will be assigned the same international non-proprietary name (INN) by the World Health Organization (WHO)," the regulator pointed out.

Reporting by brand name was "largely successful in achieving accurate product-level attribution of spontaneously reported adverse events for suspected biologics", Health Canada said, citing an analysis of adverse drug reaction (ADR) reports from its own Canada Vigilance database.

However, the regulator acknowledged that the traceability of biologics primarily used in hospital settings had been identified as "an area for improvement".

"Activities are underway to implement mandatory reporting of serious ADRs and medical device incidents by healthcare institutions," Health Canada said, emphasizing that "encouraging ADR reporting by brand name and/or DIN would have program-wide pharmacovigilance benefits for both biologic and pharmaceutical drugs".

## Implementation Involves Education

To implement the naming convention, Health Canada said it would update related guidance documents as well as making a regulatory amendment "to ensure that the current practice of sponsors submitting unique brand names for biologics is adequately supported".

Stakeholder communications will also be provided "on the importance of recording both brand and non-proprietary names throughout the medication use process – as well as other product-specific-identifiers, such as DIN and lot numbers where appropriate – to help ensure product-specific identification and traceability of biologics".

To bolster pharmacovigilance efforts, Health Canada said it would update ADR reporting forms and instructions to support reporting of brand and non-proprietary names as well as other product-specific identifiers, as well as educating stakeholders on how to improve ADR reporting practices "with communications reflecting key messages about the importance of providing product-specific identifiers in ADR reports".

## Follows European And Australian Approach

Last year, Australia's Therapeutic Goods Administration (TGA) was praised by the International Generic and Biosimilar Medicines Association (IGBA) for its decision not to use specific identifier suffixes as part of naming conventions for biologics. *(Also see "Australia praised after rejecting biologic suffix" - Generics Bulletin, 2 Feb, 2018.)*

The IGBA noted that Australia's policy "aligns with the European Union, which has approved the highest number of biosimilar medicines worldwide, and has acquired considerable experience of their use and safety".

The WHO in 2017 suspended its proposal for a 'biological qualifier' that would have applied a random four-consonant code to the non-proprietary names of both biosimilars and brand biologics.

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The US approach has been criticized by the international generics and biosimilars industry *(Also see "Drop biologic suffixes IGBA urges US FDA" - Generics Bulletin, 31 Aug, 2018.)*, as well as by industry stakeholders within the US. *(Also see "Broad alliance queries FDA's suffixes stance" - Generics Bulletin, 5 Oct, 2018.)*

*Published online in Generics Bulletin, 19 Feb 2019*



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# Conflict Management Strategies And Dispute Resolution Clauses – Ensuring Your International Contract Will Be Enforced

▶ By Dorothee Schramm

Last month, the focus was on tips for protecting business deals against three common contract failures through smart drafting. But nothing can make a contract "100% future proof," so you need a plan B in case things go wrong. Without an effective dispute resolution clause, your efforts negotiating your contractual rights may be wasted.

For example, imagine you are a US-based company concluding a supply agreement with a Chinese company. Even if you have the best contract rights possible, the chances of actually enforcing them may not be rosy if you agreed to have disputes resolved by Chinese courts in your contract partner's hometown. In contrast, if you have a robust and effective dispute resolution clause (for example an arbitration clause), the prospect of having contract breaches appropriately sanctioned and remedied will instill a certain discipline in your contract partner and incentivize it to find a reasonable solution to any disagreement.

## Choose The Right Dispute Resolution Strategy

The current trend is for medtech companies to establish a dispute resolution system that is used for all contracts and, if you are part of a group of companies, often harmonized globally.

Your basic options for resolving disputes are:

- finding a **win-win**, through structured negotiations (e.g., by senior management) and/or mediation;
- getting a **final resolution of the dispute**, either through litigation or arbitration; or
- combining both approaches in a multi-step, or **multi-tier**, approach.

The choice between these basic options is driven by commercial and strategic considerations. The following key points provide a starting point when addressing this issue for your individual company.

## Finding A Win-Win

For medtech companies, finding a win-win is typically the preferred option as it tends to be faster and less costly than litigation or arbitration. Win-win options are best suited to save the business relationship, to focus on your business needs and interests, and to find a sustainable solution for the future. For example, in a scenario where former co-development partners are in dispute over patent ownership rights, win-win solutions could include a new cooperation to work on technology improvements, or rights to a broader patent portfolio, depending on the interests at stake. This, of course, goes well beyond what arbitration or litigation can achieve, which are focused on resolving the specific issues in dispute.

Often win-win options consist, as a first step, in escalating any dispute to a named position within senior management. This can remove the heat and open the door to solutions. Alternatively, or as a second step, mediation can be a valuable tool to find a win-win solution. Mediation is an informal procedure in which a neutral mediator assists the parties in reaching a contractual settlement, often through separate meetings with each side in which the mediator understands the business interests, points out weaknesses and shows possible solutions, without being able to impose any decision.

Finding a win-win often works best between companies of similar strength or with ongoing common business interests. It requires parties to cooperate and compromise – and to have the authority and support within their organizations to do so. If this is not the case, trying to find a win-win risks dragging the process out, wasting time and money instead of saving it.

## Your Safety Net

Even if you agree in a contract to first negotiate or mediate, you need to decide on the **dispute resolution mechanism** if no settlement can be found. Will the dispute be resolved by a state court or by a private arbitral tribunal? The familiarity of state courts with international medtech disputes differs from country to country (and even within a country), but they all have in common the fact that you cannot choose your judge. This is different in arbitration, which minimizes the risk of having a decision maker who does not understand your business.

In international contracts, the increasing trend with medtech companies is to opt for arbitration. In a nutshell, these are the reasons why:

- **Neutrality:** If you and your contract partner are in different countries, neither of you wants to litigate disputes on the other's home turf. This is a key reason why companies agree on arbitration in a third and neutral country, for example Switzerland.
- **Choice of arbitrator:** Many arbitral tribunals consist of three arbitrators, which enables each party to freely choose one arbitrator and to have an impact on the choice of the presiding arbitrator. This ensures that you feel comfortable with the decision maker and gives you a say on the expertise and industry knowledge present in the tribunal. You have no such influence in court litigation.
- **Confidentiality:** You can obtain full confidentiality of arbitration proceedings, either by choosing arbitration rules that contain a confidentiality clause or by separately agreeing on confidentiality. In comparison, excluding the public from state court proceedings is, in many countries, more difficult and less predictable.
- **Saving the relationship:** Arbitration is typically perceived as a more consensual process than court litigation, which can help to save the business relationship. Arbitration proceedings are often more civilized in tone, and with experienced arbitration counsel there is typically a great degree of procedural cooperation between the parties.
- **Time:** Arbitration is usually quicker than court litigation. Medtech arbitrations typically last between six months (e.g., in case of a $1 million dispute regarding outstanding payments for supplies) and two years (e.g., in case of complex and high-value disputes involving IP rights). If you choose your place of arbitration wisely, the final award is not subject to prolonged appeals. For example, in arbitrations in Switzerland (often chosen for its neutrality and reputation), you can expect that any challenge against the award is decided by the Supreme Court within six to seven months. In comparison, there are typically one or more layers of appeal in court litigation, which can bring the duration of court litigation well beyond that of arbitration. As a practical matter, parties and arbitrators normally agree on the full procedural timetable of the arbitration from the outset, which makes the duration predictable and facilitates your planning.
- **Cost:** The cost of legal counsel accounts for the majority of both arbitration and litigation cost. As a rule of thumb, the longer the proceedings (including appeals) the higher the counsel cost. Arbitration has the advantage that you can use the same counsel for all of your disputes, regardless of the place of arbitration. This gives counsel more familiarity with your business and enhances efficiency, plus you are in a better position to negotiate volume discounts.
- **Know-how and tools:** You can chose arbitrators with specific industry knowledge and a good understanding of business realities, which is not the case for all state court judges. You may also have more freedom to use visual tools, quantum tools, and other forms of evidence that help the arbitral tribunal understand technically complex issues, beyond the means traditionally used by some courts. This enhances the ability to appropriately resolve complex commercial or technical questions.
- **Enforceable decision:** While court decisions can be difficult to enforce abroad (at least outside the European Union), there is a UN convention in arbitration (called the "New York Convention") under which arbitral awards rendered in a contracting state must be recognized and enforced in 159 contracting states around the globe. This includes almost all of the world's largest economies, including the US, China, India and Russia.While enforcement under the New York Convention is still subject to country risk (for example in China, India or Russia), it is easier than enforcing a court decision in the absence of any strong enforcement treaty.

That being said, court litigation can be a better choice for your company in cases where a reliable court forum is available and where the amounts at stake are small, where you need to establish a legal precedent, or where third-party rights are involved and cannot be accommodated in arbitration.

Should you opt for **arbitration**, you need to choose (1) a place of arbitration, and (2) the arbitration rules outlining the arbitral process, which are typically issued by an arbitration institution that supports the process and minimizes the risk of obstruction. These are important choices involving different practical and legal aspects. As a rule of thumb, you are well advised to opt for an internationally reputable and "arbitration-friendly" place of arbitration (*e.g.*, Geneva or Zurich in Switzerland, Paris, London, Hong Kong, Singapore, New York) and a major, internationally recognized arbitral institution (*e.g.*, International Chamber of Com-



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merce, Swiss Chambers' Arbitration Institution, London Court of International Arbitration, Hong Kong International Arbitration Center, Singapore International Arbitration Center, World Intellectual Property Organization Arbitration and Mediation Center). As there are significant practical differences between these seats and institutions, you may want to get help from arbitration counsel to choose the right dispute resolution system for your company. If you do so, make sure you ask an experienced multi-jurisdictional team to avoid a lawyer's natural inclination towards his or her home jurisdiction.

In practice, medtech companies increasingly opt for multi-tier clauses with a **combination of structured negotiation, mediation and arbitration**, and often prepare a "cheat sheet" for their contract negotiation teams with preferred and alternative clauses, depending on the type of contract and contract partner.

### Five Tips For Drafting Dispute Resolution Clauses

These five tips for drafting and agreeing dispute resolution clauses help avoid the most common pitfalls:

1. **Use the written form.** Agree the dispute resolution clause in writing and make sure each party's consent is evidenced in written form. For example, if your dispute resolution clause is contained in standard terms and conditions, refer to them in writing, maintain a record of sending them to the contract partner (e.g., by saving the cover e-mail) and obtain the contract partner's written acceptance (e.g, by e-mail).
2. **Keep things simple.** Use the standard clause issued by the chosen mediation or arbitration institution and do not change it more than absolutely necessary. Resist the temptation of agreeing on any timelines for the arbitration. You do not know today what a dispute might look like in a year's time. Contractual arbitration timelines often turn out to be inappropriate for a specific dispute and may put an unreasonable burden on the availability of your own witnesses (e.g., if they have left the company in the meantime).
3. **Mind confidentiality.** Pay attention to whether the chosen arbitration rules contain a confidentiality provision (for example, the WIPO Rules, the Swiss Rules, and the Rules of the London Court of International Arbitration do, while those of the International Chamber of Commerce do not). If necessary, include a confidentiality provision in your arbitration clause.
4. **Be clear about multi-tier.** When combining structured negotiation, mediation and arbitration, you should do the following to limit the risk of obstruction by the counterparty: (1) be clear about whether the parties "shall" or "may" go through the negotiation and/or mediation phase; (2) provide for clear time limits and procedures for the negotiation and/or mediation phase; and (3) make sure you do not block the possibility of obtaining protective interim relief and initiating arbitration/litigation (e.g., to interrupt a limitation period) while going through the negotiation and/or mediation phase.
5. **One clause to rule them all.** Avoid conflicting dispute resolution clauses, especially if a contract is made of different documents and term sheets. Also, avoid submitting different types of disputes to different dispute resolution clauses (e.g., do not send IP-related disputes to litigation and other contractual disputes to arbitration).Often, disputes span across different aspects of contract, and you do not want to find yourself fighting several small battles in different fora at the same time or caught up in years of litigation over which forum has jurisdiction over certain aspects of a dispute.

The dispute resolution clause may be the most underestimated provision of your contracts, but it can prove to be amongst the most important. Thus, do not make the fundamental mistake of letting this clause escape your attention, and instead make a conscious decision on how to enforce your rights if things go wrong. Beyond the basic tips and measures outlined above, further advice and trends aimed at saving time and cost in dispute management will be discussed in an upcoming article.

*This article has been prepared for informational purposes only and does not constitute legal advice. This information is not intended to create, and the receipt of it does not constitute, a lawyer-client relationship. Readers should not act upon this without seeking advice from professional advisers. The content therein does not reflect the views of the firm.*

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*Published online in In Vivo, 4 Feb 2019*





# WHEN THE TRIAL SITE IS A LIVING ROOM: Pharma Explores Virtual Research Options

▶ By Emily Hayes


Today, roughly 75% of Americans own a smartphone, up from 35% in 2011, and acquisition by older adults and those with lower incomes has been increasing in recent years, according to the Pew Research Center. Furthermore, 70% use social media, up from about 50% in 2011.

For many people, interacting with devices is a big part of life, said Noah Craft, CEO and co-founder of the mobile clinical trials and technology company **Science 37**.

Speaking from the stage during **MedImmune LLC***Patient-Centric Drug Development in the Digital Era* meeting on Oct. 9, 2018, Craft admitted that he had been afraid to leave his own cell phone at his front row seat, instead bringing it with him in his pocket. "We all have this as part of our body," he said.

Craft and others at the meeting believe that it is only a matter of time before the mobile device revolution disrupts the way pharma conducts clinical trials. There has been growing recognition of the potential use of new technologies, including apps on cell phones and other handheld devices, to build connections between trial sponsors and patients, feeding back data points, real-world experience and reports on participant satisfaction directly to pharma. *(Also see "Adherence Issues Add Weight To Digital Trials Push" - Scrip, 24 Nov, 2017.)*

Management consultancy Arthur D. Little found that increasing demands from payers and providers around the delivery of better outcomes "provide a strong driving force for pharma companies to more actively engage in the opportunities arising from the digital revolution and patient-centered care," according to a 2016 report. *(Also see " Digital Health: Does Pharma Need To Change Its Business Model To Make It Work? " - Scrip, 24 Feb, 2016.)*

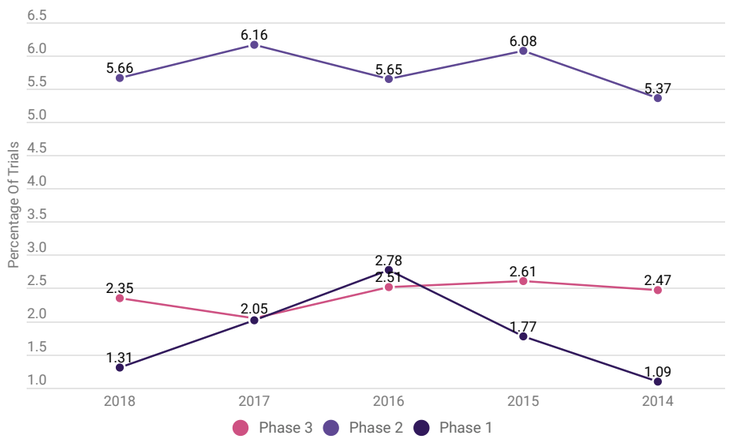
Virtual, or decentralized clinical trials (DCTs), operate remotely outside the traditional clinical site model, using telemedicine and other information technology services. For the companies, this promises to make clinical trials shorter and improve diversity in trial populations. For patients, it means access to new therapies through clinical trials. "The empowered consumers will drive change in this industry, just like they did in banking, investment and transportation," Craft said.

### The Site Is Your Living Room

A 2017 survey of 12,427 people conducted by the US nonprofit Center for Information and Study on Clinical Research Participation found that 75% of respondents were willing to take part in a study. However, only 30% were knowledgeable about how to do so. Factors that ranked as "very important" in a decision to participate included risks and benefits (83%), purpose of the study (75%), physical location of the research site (60%) and potential costs and reimbursement (57%).

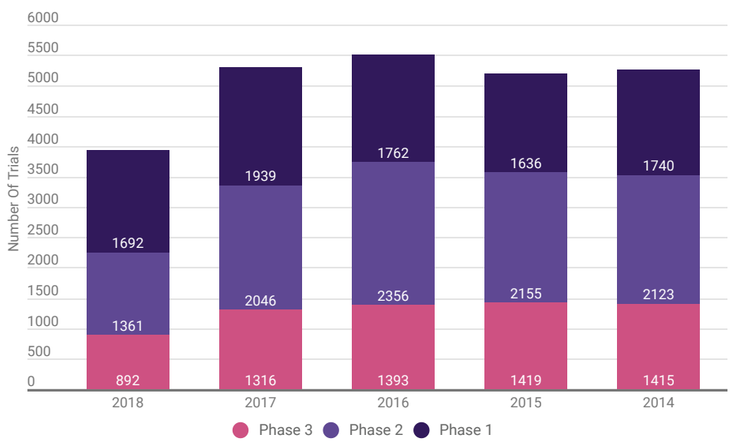
According to data from Trialtrove, more trials are terminated in Phase II because of enrollment issues than in other development phases. Though the percentage of trials terminated due to poor enrollment in each phase (Phase I, Phase II and Phase III) has remained fairly flat over the last few years.

**Exhibit 1: Percentage Of Trials Terminated Due To Poor Enrollment Vs. Total Trials Completed, 2014-2018**




*Source: Trialtrove®, January 2019*

**Exhibit 2: Trial Numbers Per Phase That Completed In 2014-2018**




*Note: Trial numbers were corrected for reporting time bias*

*Source: Trialtrove®, January 2019*

The number of trials completed in 2018 also appears to be lower than previous years. Even when factoring in reporting time bias, Trialtrove data reveals that in 2018 less than 4,000 trials completed, compared with more than 5,000 trials in the previous four years.

Craft said that common reasons for lack of participation in clinical trials are lack of knowledge that the studies exist and challenges getting to trial sites for geographic/logistical reasons. Science 37 developed a technology platform for virtual trials called NORA (Network Oriented Research Assistant) that facilitates moving trials into the virtual world. The company has a tech headquarters in Los Angeles – but patients are at home and doctors are wherever they want to be.

Patients are recruited through more than 100 different online channels – including Facebook and Google ads. The company also records everything electronically, including informed consent. Science 37 ships a NORA-loaded Apple *iPhone* to enrollees. "It means it doesn't matter what color you are or what insurance you have or what phone you have or what plan you have – you can participate in our trials," Craft explained.

Drugs are shipped to the participant's residence and tests may also be done by local health professionals, for example, blood draws. "The site is in your living room," Craft said.

With funding from **Genentech Inc.**, Science 37 launched in 2014 with a research project in pemphigus vulgaris, a rare and deadly autoimmune skin condition. The company created a telemedicine-based site that was part of Genentech's Phase III PEMPHIX study of infused *Rituxan* (rituximab) versus oral mycophenolate mofetil in treating adults with active pemphigus vulgaris. The infused medication was administered by a mobile phlebotomist.

Science 37's site was one of over 60 in Genentech's study. For this population, patient recruitment through a Google ad proved effective – 10 patients were enrolled in nine months, which Craft said is a lot considering the rarity of the disease and that most sites enrolled zero over a period of years. Two years later, 100% were still in the study. Rituxan was approved for an additional indication in pemphigus vulgaris in June 2018. *(Also see "Keeping Track: Mylan Wins First US FDA Approval For Neulasta Biosimilar, But Lands A CRL For Insulin Glargine; Genentech Nabs Broad Full Approval For Venclexta, PV Indication For Rituxan" - Pink Sheet, 8 Jun, 2018.)*

Most patients who find Science 37 do so through their cell phones, and they are a particularly engaged set of people, Craft noted. For a Phase IIb "site-less" study of AOBiome's live bacterial therapeutic AOB101 in acne vulgaris, the company used Facebook almost exclusively for recruitment. It screened 8,000 people to enroll 272 patients, 41% of whom were not Caucasian, in seven months.

**Novartis AG**has also been collaborating with Science 37 and owns a stake in the company. In a cluster headache study, Science 37 found the target patient population did not respond to Facebook, so it partnered with a patient advocacy organization in Lombard, IL, called ClusterBusters to forward information about the study by email, and that did the trick. Novartis and Science 37 announced in March 2018 that they were expanding the collaboration to launch up to 10 trials with increasing decentralization over three years, "scaling up to the 'site-less' model." *(Also see "Interview: Novartis Takes Virtual Route To Transform Clinical Trial Paradigm " - Scrip, 7 Mar, 2018.)*

## MedImmune Tests Virtual Waters

It is hard to determine the exact number of decentralized clinical trials that are being done today, but the trend has "certainly increased over the past few years," said Pamela Tenaerts, executive director of the Clinical Trials Transformation Initiative (CTTI), a public/private partnership co-founded by Duke University and the US Food and Drug Administration.

Several companies are actively working on DCTs on behalf of sponsors and some large traditional contract research organizations (CROs) have launched virtual studies.

Tustin, CA, remote research platform company Thread Research's chief product officer John Reites told *In Vivo* that numbers across industry have not been published yet. But, he added, since the first of these studies was launched in 2012, there has been a steady increase in the number conducted. "The last two years has seen the most growth with nearly every top 40 pharma and top eight CRO exploring, piloting or designing a strategy for virtual research," Reites said.

"We feel this is a trend that is coming, and we need to explore how well it works," Ann Taylor, vice president of clinical development at MedImmune, said in an interview. MedImmune is currently working with Science 37 on an undisclosed study design.

In rare diseases where there may only be one patient in a whole state, industry cannot justify setting up a site to find that one person, who needs to travel eight hours to get there, Taylor pointed out. With trials of rare diseases, it may be less expensive to have a traveling nurse rather than fly patients to a site. "That's a perfect setting for using a model like this, where instead you have a roving practitioner," Taylor said.

Taylor commented that she expects, at least in the near term, everybody will move toward the decentralized model, but probably mostly a hybrid version that includes virtual aspects but also involves patients coming to a site for visits.

Many things can be done at home with devices – such as continual glucose monitoring for diabetes patients – but there are still a lot of assessments that can't be done at home, like MRI scans, she said.

Although decentralization of trials is a strong trend of the future, today it's still more or less in the pilot phase, Taylor stated. Whether the model will work will depend on how sick a patient is and how easy it is to understand procedures. "I think we are going to learn a lot as we get there and there will be times where it's better and times where it's not," she added.

## Variety Of Approaches Possible

Thread Research's Reites said he is a big proponent of a fully virtual clinical trial but hybrid models that bring trials to

patients and also involve site visits allow sponsors to crawl before they can walk. “Not everybody in the industry is really ready to put every study in a virtual model,” he pointed out.

For example, sensors and wearables can capture information in between visits. Some visits may be done through two-way video conference. It’s possible to convert some visits to a virtual model and keep others onsite, Reites explained. Consent and patient satisfaction surveys, for example, may be done virtually. The journey through telehealth “has not been a one-size-fits-all approach,” he said.

On Sept. 26, the CTTI published new recommendations that it says are intended to support the growing use of a variety of hybrid models for DCTs in clinical research and the potential advantages, including improved recruitment and retention, greater diversity and a more comfortable and convenient research experience. “In a single trial, some participants may be enrolled at traditional clinical trial sites, while others may be enrolled or managed in a decentralized or remote manner,” the CTTI document states.

The CTTI document also advises conducting DCTs in therapeutic areas that have already incorporated telemedicine, such as dermatology, psychiatry, cardiology and radiology, to streamline processes and increase the chance for success.

## New Model = New Problems

Still, there are some barriers and challenges to implementing virtual models. The legal issues are complex – for example, shipping products directly to patients and using telehealth professionals across state lines.

The CTTI advises sponsors to keep abreast of the “complex and varying legal landscape of applicable state laws,” by tapping into policy organizations that specialize in telemedicine law.

Cost is an important consideration. Science 37’s Craft said that his company doesn’t promise a cheaper study, though it may be cheaper depending on the study design and indication. “Shipping costs drive our budget through the roof,” and mobile nurses cost a fair amount more than a nurse onsite, Craft continued. The trials are typically shorter, however, which can save time and money for pharma sponsors, whether the study is successful or not, as it could result in an earlier assessment of futility.

The true value of DCTs lies in improved recruitment of geographically more dispersed participants, retention of participants and greater convenience and comfort for participants, CTTI’s Tenaerts told *In Vivo*. “Decreasing recruitment barriers and running more efficient trials decreases clinical trial costs, but, as with the introduction of any new technology, initial investments may be needed when first designing a DCT,” she said.

Another potential barrier is that research teams may be wary of the virtual model. In those cases, Reites advised telling them they are not the first to do it and that this is the direction industry is taking.

“This is an inevitability; this is what patients and consumers are asking for and it also fits the business model sites are moving toward. This is something we have to get our heads wrapped around and have to build business models for in clinical research today,” Reites said.

The biggest barrier to using DCTs could be the simple fact that they are relatively new and fairly complex, Tenaerts said. Many sponsors and CROs may see a DCT as a daunting undertaking, but in reality running a DCT is not an “all-or-nothing” approach – there is a broad continuum of hybrid approaches.

By early 2019, the CTTI plans to release new recommendations on patient and investigator engagement in the use of mobile technologies in clinical trials.

Asked at the MedImmune meeting about whether virtual trials will fly with the FDA, executives cited the agency’s involvement in the CTTI as a strong sign of buy-in. Craft also said that his company has half a dozen separate conversations going on with the FDA. Areas of inquiry relate to authentication of patients, reliability of tests and oversight of nurses across state lines. It will be necessary to navigate these at the FDA one division at a time, but top leadership is clearly supportive, Craft asserted.

“The leadership there is crystal clear: they – like you all and we all – want this innovation to work,” Craft said.

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*Published online in In Vivo, 21 Jan 2019*





# Teva, Sandoz, Mylan, Pfizer…Who Sees Value In The US Biosimilars Market?

▶ By Dean Rudge

“This feels like the inflection point for the industry. The investment has been made, but the return – at least in the US market – is delayed. Over the next two years, the US biosimilar industry will either get better, on more affordable/predictable US requirements and gradual adoption; or morph into a European Union- (EU-) focused business, without material US presence.”

This was the view of Bernstein analyst Ronny Gal, made in a note last July per our sister publication *Scrip*, summing up the concerns and frustrations of many biosimilars players that had seen barriers to market access in the US.

In the decade since the Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated approval pathway for ‘similar’ biological products, 17 biosimilars have received US Food and Drug Administration (FDA) approval, spanning 10 molecules.

Despite this, less than half – seven – have been launched; and of these seven, four have been on the market since July 2018; representing the hurdles, largely intellectual property- (IP-) related, biosimilar manufacturers have faced in order to realise any kind of return on their investments.

One could also argue that four biosimilar launches in the space of six months – in chronological order, Mylan and Biocon’s Fulphila (pegfilgrastim-jmdb); Pfizer’s Nivestym (filgrastim-aafi) and Retacrit (epoetin alfa-epbx); and Coherus’ Udenyca (pegfilgrastim-cbqv) – represents good progress, and indication of the “inflection point” of which Gal spoke.

And only weeks into the new year the FDA has approved the first biosimilar of 2019: Samsung Bioepis’ Ontruzant (trastuzumab-dttb) biosimilar to Herceptin *(Also see “Samsung Bioepis’ Trastuzumab Biosimilar Is Third Cleared By FDA – But The Market Hasn’t Formed Yet” - Generics Bulletin, 21 Jan, 2019.)*.

## Technical Challenges, High Costs And IP Hurdles All Serve As Barriers

Nevertheless, concerns remain; particularly over the ‘patent families’ amassed by originators like AbbVie, which can boast more than a century of patents shielding its Humira (adalimumab) original; as well as rebating and discounting incentives offered by branded sponsors that are allegedly strangling the market uptake of biosimilars.

Pfizer, wholesalers and retailers and purchasers are currently embroiled in an antitrust suit against Johnson & Johnson on this issue, concerning the disparate market shares of the former’s Inflectra (infliximab-dyyb) biosimilar and the latter’s Remicade (infliximab) original.

J&J maintains a 93% share of the infliximab market by volume, the originator has just reported, indicative of the uphill task infliximab biosimilar players are facing *(Also see “Teva, Sandoz, Mylan, Pfizer…Who Sees Value In The US Biosimilars Market?” - Generics Bulletin, 25 Jan, 2019.)*.

There are also the exorbitant development costs to factor in, a particular problem for start-ups without revenues coming in the door that are almost entirely dependent on financing; as well as the technical challenges to develop and manufacture a biosimilar, evidenced by the glut of complete response letters (CRLs) dished out by the US Food and Drug Administration (FDA).

## FDA’s Gottlieb Has Taken Action

Biosimilar sponsors can at least take comfort in the fact that FDA Commissioner Scott Gottlieb is taking seriously steps to rectify and better the nascent biosimilars market.

Of the FDA’s many recent actions to foster market access, it rolled out several key guidance documents, including measures to address the abuse of Risk Evaluation and Mitigation Strategy (REMS) programs; as well as transitioning products such as insulin and human growth hormone into the biologic framework *(Also see “FDA’s Gottlieb Rolls*

*Out A Raft Of Biosimilar Reforms" - Generics Bulletin, 14 Dec, 2018.)*.

Against this backdrop, some biosimilar sponsors have acted to curtail their investments for the US market; either to focus on other developed markets that have thus far better engendered biosimilar share – namely the EU – or to pour research and development dollars into other areas of their business.

Others, however, are pressing ahead with biosimilars in the US, eyeing the sizeable gains to be made on smashing multi-billion-dollar biologic monopolies, if reasonable market shares can be obtained.

Ahead of companies publishing financial results and updated corporate strategies in the days and weeks ahead, *Generics Bulletin* looks at where some of the major players stand in terms of their investments and expectations in the US biosimilars market.

## Teva

Teva shelved a joint-venture with Lonza targeting biosimilars in July 2013 when under the stewardship of Jeremy Levin, the former Bristol-Myers Squibb executive.

Despite being the largest generics player by value in the US, Teva's interests in the biosimilars market to date have not resulted in the company pursuing any disclosed programs in the US.

Instead, its biosimilars interests currently stretch to a commercialization agreement signed with Celltrion in October 2016 covering the Korean firm's Truxima (rituximab-abbs) and Herzuma (trastuzumab-pkrb) biosimilars; which were approved by the FDA in November and December 2018 respectively.

Teva and Celltrion late last year settled with Genentech over Truxima, providing an undisclosed entry date in the US.

President and chief executive officer Kåre Schultz told attendees to the recent J.P. Morgan Healthcare Conference that he thought the market was slowly changing for the better, following an initial period of "not much success." *(Also see "US Pricing Pressures Have Stabilized, Insists Teva Chief" - Generics Bulletin, 9 Jan, 2019.)*

Referring to the Truxima and Herzuma approvals, Schultz said that he was "very optimistic" about Teva's future launches in the market.

## Sandoz

A pioneer and key player in the industry, Sandoz received approval for in March 2015 and subsequently launched the first biosimilar in the States, its Zarxio (filgrastim-sndz) biosimilar of Amgen's Neupogen.

Sandoz' approved portfolio also includes Erelzi (etanercept-szzs), which it is yet to launch following approval in August 2016 due to IP issues, marking the only FDA-approved competition to Amgen's Enbrel; and Hyrimoz (adalimumab-adaz), which Sandoz has agreed not to launch until September 2023 under the terms of a licensing agreement with AbbVie.

Looking further into the future, Sandoz a year ago announced a global collaboration with Biocon on 'next-generation' biosimilars, under which it will lead commercialization efforts in North America *(Also see "Sandoz and Biocon strike global biosimilars alliance" - Generics Bulletin, 26 Jan, 2018.)*; and finished the year by announcing a commercialization and supply agreement for insulin biosimilars with Gan & Lee *(Also see "Sandoz Forms Insulin Biosimilars Deal With Gan & Lee" - Generics Bulletin, 19 Dec, 2018.)*.

Nevertheless, Sandoz last November announced that it would no longer chase FDA approval for its GP2013 rituximab biosimilar following an agency request for further data in relation to a CRL, despite holding an EU-wide marketing authorization for the product.

Stefan Hendriks, global head of Sandoz' Biopharmaceuticals, said the company believed "the patient and marketplace needs in the US will be satisfied before we can generate the data required."

Company head Richard Francis recently told *Generics Bulletin* that he thought development times were "going to come down significantly," while costs "will probably shrink a bit, but will still be around US$150 million, plus or minus a bit. We will have fewer US$300 million-plus development projects."

## Mylan

Deciding, like Teva, against pursuing biosimilars alone, Mylan's partnership approach has thus far spawned alliances with Biocon and Momenta; albeit with wildly contrasting fortunes.

Covering, across the globe, 11 biologic and insulin products co-developed by the parties, Mylan's partnership with Biocon bore fruit midway last year with the approval and launch of their Fulphila biosimilar at a 33% wholesale acquisition (WAC) discount to Neulasta *(Also see "Biocon confirms US Neulasta rival launch" - Generics Bulletin, 3 Aug, 2018.)*.

This built on the FDA approval for the firms' Ogivri (trastuzumab-dkst) biosimilar in December 2017; which was not launched in light of Mylan settling litigation with Herceptin sponsors Roche and Genentech on undisclosed terms earlier in 2017.

Mylan's Head of Biologics, Chrys Kokino, told *Scrip* last year that while the company believed the Fulphila launch had been a success, the commercial expectations in the US needed to be reset; he described as "unrealistic" expectations that "new biosimilar will enter the market and quickly take a big share of a blockbuster branded biologic's revenues."

Momenta, on the other hand, announced plans at the end of last year to largely pull-out of the partnership covering the so-called 'third wave' of biosimilars, concluding that it would focus efforts on its novel programs instead.

Under their alliance formed in January 2016, Momenta and Mylan agreed to jointly develop and commercialize six biosimilar products. But following a strategic review, Momenta last October said it would seek to drop development of five Mylan-partnered biosimilar programs, including the M834 Orencia (abatacept) candidate. The firms' M710 biosimilar of Eylea (aflibercept) survived Momenta's cull.

Momenta is currently pursuing its own Humira biosimilar but announced plans last December to delay filing its application, with costs in mind. The firm also desires a commercial partner to shoulder the financial burden of bringing biosimilars to market *(Also see "Momenta Delays on Adalimumab In A Bid To Save On Costs " - Generics Bulletin, 7 Dec, 2018.)*.

## Pfizer

With three biosimilars on the market and five in mid-to-late stage development, Pfizer is among the leading players.

The US-based player assured *Generics Bulletin* that recently-announced plans to axe development of five pre-clinical biosimilar programs, in order to fund innovative products, were not reflective of its overall commitment to biosimilars *(Also see "Pfizer Axes Staff And Five Pre-Clinical Biosimilars To Fund Late-Stage Innovative Programs" - Generics Bulletin, 15 Jan, 2019.)*.

By taking control of Hospira in September 2015, Pfizer has thus far received approval for and launched Retacrit and Nivestym; launched partner Celltrion's Inflectra; and grabbed approval for, but held off launching for strategic reasons, its own infliximab biosimilar, Ixifi (infliximab-qbtx).

Last year, group president of Pfizer's Essential Health business, Angela Hwang, commented that the company was "excited" about breaking into oncology biosimilars in the US, given the oncology market's "different dynamics" that typically result in higher and faster biosimilar uptake.

This year, Pfizer is facing FDA action dates on three cancer-treatment biosimilars: trastuzumab, bevacizumab and rituximab, in that order. Pegfilgrastim and adalimumab biosimilars complete Pfizer's pipeline.

Going into 2019, industry awaits the verdict in Pfizer's antitrust suit against Johnson & Johnson, after a court in August refused the originator's motion to have the case dismissed.

## Amgen

"We have talked in the past about this being a potentially multi-billion-dollar business unit for us," Amgen's chairman and chief executive officer Bob Bradway reminded investors during the company's third-quarter earnings call last year, when asked about the company's biosimilar expectations *(Also see "Amgen has plans for biosimilar infliximab" - Generics Bulletin, 9 Nov, 2018.)*.

Bradway was speaking about the entire Amgen biosimilars offering, which has so far made inroads in the EU with several launches. In the US, Amgen holds approval for two biosimilars: Amjevita (adalimumab-atto) and Mvasi (bevacizumab-awwb) the latter being the only FDA-approved biosimilar of Avastin. Neither have been launched thus far.



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Under its alliance with partner Allergan, Amgen expects to file applications for the firm's ABP 710 infliximab biosimilar in both the US and Europe by the end of the first quarter of 2019; while global alignment on the Phase III study design for the company's ABP 959 biosimilar of Alexion's Soliris (eculizumab) rare diseases blockbuster had also just been achieved by Amgen, and the firm was now in start-up activities for that trial.

The firms' latest development, Amgen And Allergan have just announced positive top-line results from a Phase I/III clinical study of the firm's ABP 798 rituximab biosimilar candidate in patients with moderate-to-severe rheumatoid arthritis

### Coherus BioSciences

A company that clearly sees the value in the US, Coherus has made clear its intentions to prioritize its Udenyca in the market ahead of the European Union (EU); despite holding one of the few pan-European marketing authorization approvals for the Neulasta biosimilar.

Coherus rolled out Udenyca in the US at a 33% WAC discount to Neulasta on 3 January, supported by a suite of patient and reimbursement services and a fully-fledged commercial team *(Also see "Coherus BioSciences Outlines 'Very Different Approach' And Raises Another US$75m To Launch Udenyca" - Generics Bulletin, 11 Jan, 2019.)*.

Chairman, chief executive officer and president Denny Lanfear described recently the launch of Udenyca as "a full-on pharma launch in a branded fashion. This has never been done before with a biosimilar," he insisted.

### Samsung Bioepis

Through partner Merck Sharp & Dohme, the Korea-based joint venture of Samsung Biologics and Biogen has offered further competition to infliximab via the Renflexis (infliximab-abda) biosimilar that was rolled out in July 2017.

Samsung, meanwhile, holds the latest approval dished out by the FDA, for its Ontruzant trastuzumab biosimilar that will also be commercialized by Merck upon market entry.

On the other hand, Merck confirmed last year that it would not commercialize its own version of Sanofi's Lantus (insulin glargine) in the US, despite holding a tentative approval from the FDA.

A "comprehensive assessment of the current and future market environment for insulin glargine, which included an assessment of anticipated pricing and cost of production" had led the company to the decision, Merck said.

### Boehringer Ingelheim

Boehringer confirmed reports to our sister publication *Scrip* last December that its biosimilars business was going to focus on the US market only moving forward; and was pulling the plug on plans to develop biosimilars in the rest of the world.

The German group said this while holding an approval from both the European Commission and FDA for its Cyltezo (adalimumab) biosimilar, which it says will not be sold by itself in Europe.

Boehringer has set itself apart from the competition in the biosimilar Humira space by announcing in July 2017 the initiation of an interchangeability study for its BI 695501 adalimumab candidate, to demonstrate that it is interchangeable with the US-marketed formulation of Humira. "This is the first study in the US to investigate an interchangeability designation for an adalimumab biosimilar candidate," the German player underlined.

Boehringer has also previously terminated development of Avastin and Rituxan biosimilars.

### Outlook Therapeutics

The New Jersey-based player, formerly known as Oncobiologics, dropped development of biosimilars altogether per a strategy unveiled at the turn of 2018, adopting the new name Outlook Therapeutics and pledging to focus solely on a novel intravitreal bevacizumab product.

Previously, Outlook had biosimilars to Humira and Avastin in its pipeline.

*Published online in Generics Bulletin, 25 Jan 2019*

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