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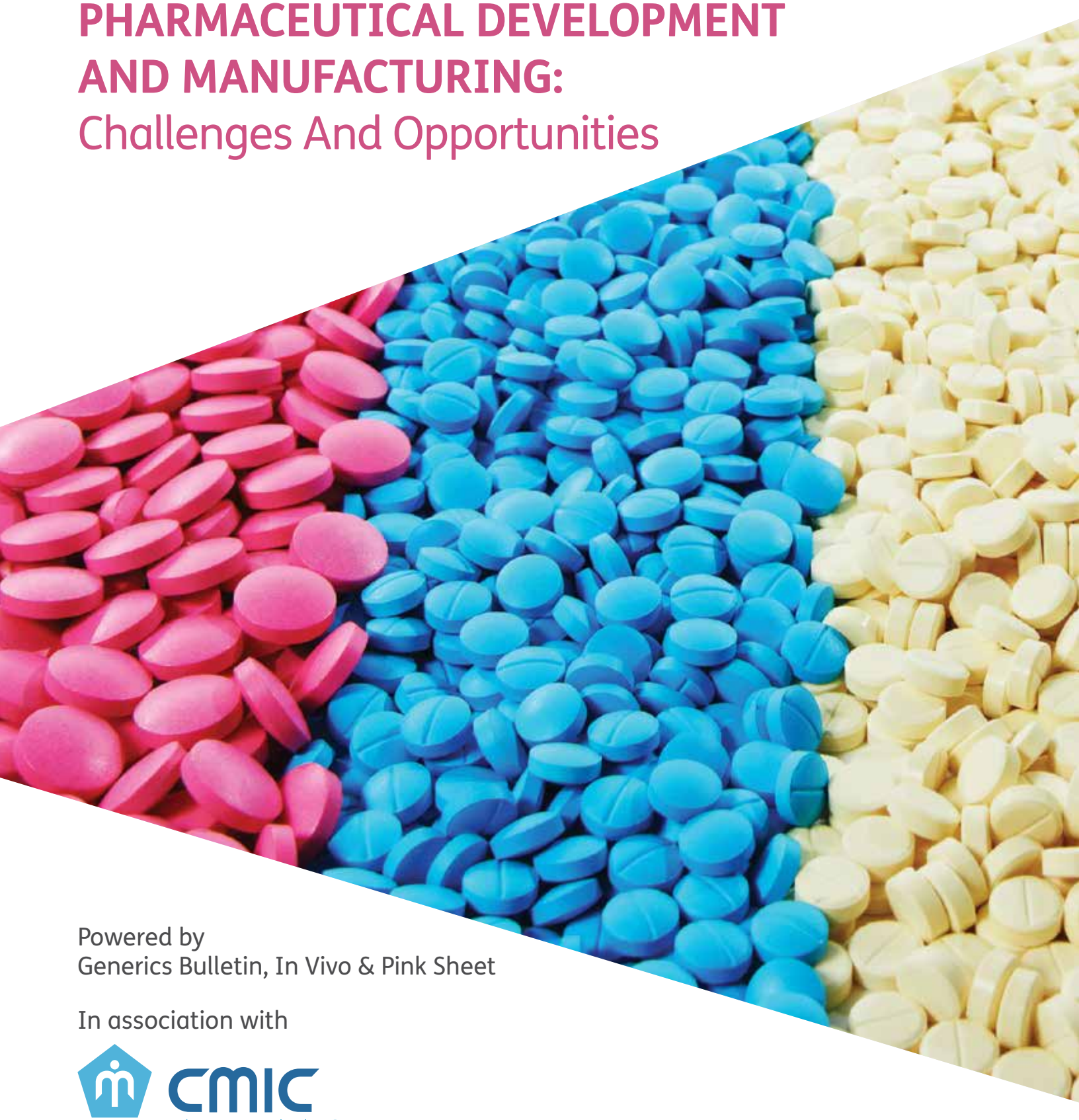
PHARMACEUTICAL DEVELOPMENT AND MANUFACTURING:
Challenges And Opportunities



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Contract manufacturers are right at the center of the transformation that is reshaping the pharmaceutical and biotech industry. Their central position brings opportunities and challenges that keep them striving to stay on top of quality, technological innovation and safety and regulatory considerations. The flip side of this is working strategically to ensure the right business decisions are made, managing costs and astutely investing in technology.

The demand for manufacturing expertise continues to increase and, in the US, promoting domestic manufacturing is a feature of FDA budget requests for both 2019 and 2020, with the US Center for Drug Evaluation and Research (CDER) expected to receive the largest share of funding.

There is a recognized need for manufacturing guidance, particularly for new manufacturing technologies relating to large and small-molecule development, end-to-end continuous manufacturing and continuous manufacturing of solid oral dosage forms. Draft guidance on quality considerations for continuous manufacturing has been published by FDA. The document covers small-molecule oral solid-dosage forms regulated by the CDER. Interested parties have been asked to submit comments and suggestions.

Furthermore, solubility and bioavailability remain a challenge for small-molecule oral drug development. There has been an increase in 505(b)2 filings using existing drugs in new combinations for new indications. Thus, API compatibility or non-compatibility needs to be considered and can pose challenges for formulation and delivery technology. In order to support pediatric, geriatric and psychiatric use, there is an increasing focus on taste-masked APIs for use in orally disintegrating tablets (ODT). There are also challenges and opportunities in topical formulation, which is the third most popular route of delivery behind injectables and oral delivery (see page 24).

It is clear that CMOs need to act wisely when finalizing contracts with sponsors to avoid over-investing in new technology areas that are not yet proven in terms of efficiency and ROI. In this environment of change where pharma is adopting new business models, taking a flexible approach and learning from commercial and regulatory experiences is key to making achievable strategic and business decisions that lead to manufacturing, healthcare and financial success based on quality, consistency and cost.

This e-book tackles these issues head-on and provides tips for meeting good manufacturing practice standards.

Lucy Sha
Senior Vice President
Corporate Development & Corporate Marketing
CMIC HOLDINGS Co., Ltd.

TABLE OF CONTENTS

Having It Both Ways: CMIC's CDMO Supports US And Japan Pharma Solutions

CMIC CMO is a joint venture of CMIC Holdings, the first and largest clinical contract research organization (CRO) in Japan, and the Development Bank of Japan Inc. CMIC's contract development and manufacturing organization (CDMO) business provides expert drug development and high-standard investigational product and commercial manufacturing in the US, Japan and South Korea.

QUESTION : In 2007, CMIC acquired a manufacturing plant in New Jersey. That early acquisition became CMIC CMO USA, a contract service provider for oral solid drug manufacturing. What has changed for the US part of the company?

MAKOTO MATSUKAWA: The original purpose of CMIC CMO was to support US-based pharma companies. For the small to mid-sized pharmaceutical companies interested in product development for the US and the Japanese markets, it is preferable to connect with a CDMO operating in both the US and Japan. This geographic advantage plus CMIC's Japan market solutions also benefit US-based pharmaceutical companies that wish to carry out clinical trials in Japan.

Since 2007, CMIC New Jersey facilities have been supporting both branded and generic drug development and manufacturing. The demand for drug development and manufacturing capacity has been increasing. Thus, we decided to invest more than $10m in two years to expand the New Jersey facility to enhance our drug formulation development capabilities, triple our analytical testing capacity and double our commercial manufacturing capacity. We can continue to support our US customers. At the same time, commercial manufacturing in the US helps reduce risk for our Japanese pharmaceutical customers who wish to enter the US market. It is much easier for Japanese companies to connect with a Japanese CDMO in the US because of the language and culture fit.

What do you see as the contract manufacturing market trends in the industry?

Pharmaceutical customers need industry partners who can provide advice to make decisions earlier in the process, so that they find the most appropriate technologies and flexible manufacturing solutions to deliver the right treatments. Dose form is increasingly important, as well as patient acceptance.

Solubility and bioavailability are still challenges for small-molecule oral drug development. There has been an increase in 505(b)2 filings using existing drugs in new combinations for new indications. Thus API [active pharmaceutical ingredient] compatibility or non-compatibility needs to be considered and can pose challenges for formulation and delivery technology. To support pediatric, geriatric and psychiatric use, there is an increasing focus on taste-masked APIs for use in orally disintegrating tablets [ODTs]. For certain therapeutic areas, a diverse patient population needs self-individualized dosing options. To meet this need, we use new manufacturing processes to create a dosage form that offers easy and accurate dose flexibility.

You mentioned orally disintegrating tablet [ODT] technology for drug development. Can you tell us more about the technology and your services?

ODT technology is commonly used in both the US and Japan. In the Japanese market, it accounts for 7% of the revenue of all oral tablet drugs. ODT technology can be used for new drug development as well as product lifecycle management. The ODT dose form is ideal for administering to pediatric and geriatric patients, as well as to patients who have trouble swallowing pills. It can also help minimize dosage errors and improve compliance. ODT is very convenient as it can be taken without water. Our CDMO business currently offers third-generation ODT technology for drug development and commercial manufacturing from our New Jersey, US, and Shizuoka, Japan facilities. The third-generation technology provides better tablet hardness and stability, while providing good taste-masking at the same time.

Who are your customers?

We have found our niche in serving Japanese companies and small to mid-sized US pharmaceutical companies in both US and Japanese markets. We are a large organization with mid-sized CDMO speed and flexibility. We provide a high standard and convenient service to help our customers bridge their needs in US and Japanese markets.

With our drug development and manufacturing sites in the US and Japan, we are able to support new product clinical development projects in both countries. We can serve as a company's In Country Clinical Caretaker [ICCC] in Japan for its Japan clinical trials, and help in drug formulation development, clinical trial batch manufacturing and/or clinical trial management in Japan and Asia. CMIC is a Marketing Approval Holder [MAH] in Japan and provides a wide range of dose form commercial manufacturing and packaging solutions. CMIC is also a contract sales organization [CSO] in Japan with 500-plus sales professionals. We can help US and European pharmaceutical and biotech companies to take their product to the Japanese market via licensing, commercial product registration and selling.

How do you maintain your quality standards between the sites?

Our drug development teams in the US, Japan, and South Korea work collaboratively to support our customers with high-quality product design for a global market. We integrate our sites under one quality standard, ensuring our manufacturing meets specific quality standards. Training is also of the utmost importance. In addition, when we manufacture a US product at our US site, we are prepared for FDA inspections, as well as for ensuring we have quality standards that meet or exceed the standard across all systems and processes.

Where do you see CMIC CDMO business growing over the next few years?

Just recently, we announced the planned transfer of the Nishine, Japan, plant from Astellas to CMIC CMO. Combining the drug development experiences, high quality control capabilities and technological capabilities of the Nishine plant with the existing sites of CMIC CMO, we will be able to serve our global customers better.

In addition, we are potentially interested in acquiring a US-based CMO, depending on the candidate. The US remains a key area of potential growth: CMIC intends to strengthen its business portfolio through alliances and increased development opportunities.

About Mr. Makoto Matsukawa

Mr. Matsukawa is the Representative Director and CEO of CMIC CMO Co. Ltd., a company focusing on CDMO business in CMIC Group. He started the first 15 years of his career at pharmaceutical and medical device companies, such as Baxter Healthcare. Mr. Matsukawa joined CMIC Group in 2012 as an Executive Officer for Corporate Planning and IPD Business. He continues to expand the CDMO business with his broad experience and expertise.

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US FDA Budget Boost Would Increase Domestic Drug Manufacturing By Better Regulating New Technologies

▶ Bowman Cox

A theme of promoting domestic manufacturing that debuted in the US FDA's fiscal year 2019 budget request has reappeared in the request for FY 2020, which seeks yet more money and agency staff positions under the rubric of helping to convince global pharmaceutical manufacturers to put down more roots in the US.

Meanwhile, previously initiated efforts to help advance US drug manufacturing excellence would continue under the Trump administration's proposal. For example, activities under the 21st Century Cures initiative would continue to support research and development on continuous pharmaceutical manufacturing technologies.

The proposed investments in domestic drug and biologics manufacturing, along with an effort to advance a fledgling outsourcing facility sector *(Also see "FDA Again Proposes To Advance Outsourcing Sector With Center Of Excellence" - Pink Sheet, 28 Mar, 2019.)*, account for more than $50m, or at least 14% of the $362m in new appropriated non-user fee spending the Trump administration is seeking in FY 2020 for FDA.

The budget document calls attention to several areas where it says CDER guidance on new manufacturing technologies is urgently needed.

Despite the way it's labeled in the budget request, congressional budget justification documents show that the money earmarked for domestic manufacturing would go primarily toward developing and explaining regulatory approaches for novel manufacturing technologies. FDA would review applications for products to be manufactured using these new technologies in the same manner, whether applicants planned to use the technologies in the US or abroad.

By saying that the increase is for domestic manufacturing, the FDA budget document reflects a signature initiative of the Trump administration and a rallying point for voters in the Rust Belt, where the past decade of globalization has accelerated an economic decline. *(Also see "US FDA 2020 Budget Request Is Parting Gift From Commissioner Gottlieb" - Pink Sheet, 15 Mar, 2019.)*

Nearly $40m More

The request includes $38.5m for domestic manufacturing that's divided among FDA's centers for drugs, biologics and toxicological research, with a little for agency headquarters.

That's down from the $58m increase for domestic manufacturing that had been requested in the administration's budget proposal last year. It's not clear whether the omnibus FY 2019 spending legislation Congress approved Feb. 14 included this money.

FDA explains in the FY 2020 request that it plans to promote domestic manufacturing with these funds by developing efficient regulatory pathways for advanced manufacturing technologies for drugs and biologics.

The agency goes on to assert that "these technologies have great potential to accelerate new, more targeted therapies, enhance product quality, allow the vaccine supply to be more easily ramped up on short notice, and bolster stability in the US drug supply to meet domestic and global needs."

CDER Would Get Lion's Share

The $25m portion of the domestic manufacturing increase FDA sought for its Center for Drug Evaluation and Research in FY 2020 is smaller than the $35m CDER plus-up requested for FY 2019.

For promoting domestic biologics manufacturing at its Center for Biological Evaluation and Research, the agency is seeking $10m, down from $38m for FY 2019.

FDA also requested another $2m for its National Center for Toxicological Research to help with promoting domestic manufacturing. This center is expected to help by developing a science-based framework for evaluating new manufacturing technologies and by funding research, development and testing of the new technologies.

Another $1.5m is for FDA headquarters to use in promoting domestic manufacturing by enabling its Office of Laboratory Safety to oversee the quality of the agency's laboratories, according the FY 2020 request.

How CDER Would Spend The Increase

The budget document's narrative goes into more detail on how the $25m for the agency's drug center would promote domestic manufacturing.

CDER would accomplish this by the way it evaluates proposed use of innovative manufacturing technologies such as continuous manufacturing approaches for small- and large-molecule drugs and biologics.

The center would create "a robust scientific base to define the impact of these new technologies on product quality, safety and effectiveness."

CDER would go on to use this "improved analytical framework ... to develop clear scientific standards, guidance and policy to support effective and efficient regulatory evaluation of advanced manufacturing technologies."

The budget document calls attention to several areas where it says CDER guidance on new manufacturing technologies is urgently needed.

In an apparent allusion to single-use systems and portable manufacturing pods, the document mentions "modular or plug-and-play type manufacturing equipment design with reusable, flexible or interchangeable parts" that could enable "different types of continuous manufacturing process integration."

There also are needs for guidance on end-to-end continuous manufacturing that integrates production of active ingredients and drug products, as well as on process analytical technologies, advanced control systems and enhanced process modeling.

The center is developing guidance on continuous manufacturing of solid oral dosage forms, the document says.

How FDA Says It Would Promote Domestic Manufacturing

While it's clear that these activities would promote advanced manufacturing, it's not clear that they would favor domestic over foreign manufacturing.

The difference, the document says, is that FDA would be "simultaneously encouraging the industry to relocate drug manufacturing to the United States."

The agency also asserts, in a section on the budget for compounding pharmacy regulation, that "the more FDA can do to foster innovation, the more likely it will be that new technologies – and new jobs – will take hold in the US."

CBER Would Clarify Regulatory Approaches

The request would add $10 for CBER to promote domestic manufacturing, mainly by developing a science-based framework that makes it clear how the center would evaluate plans to use new technologies for manufacturing biologics, including vaccines and cell and gene therapies.

This "can help reduce the cost and uncertainty of adopting these new manufacturing platforms, essentially de-risking them for adoption by industry," the agency explained.

ORA To Focus More On Outcomes

The budget document said the Office of Regulatory Affairs – FDA's field organization – is moving ahead with plans to switch from outputs to outcomes as performance measures.

The office has added measures in FY 2019 that it will track on a three-year rolling basis for:

Continuous Manufacturing Cures

The request also includes $15m for the 21st Century Cures Act, which can be used for developing emerging technologies such as continuous pharmaceutical manufacturing.

The budget document notes that FDA used Cures Act funding for grants to the University of Connecticut, Rutgers, Georgia Tech and MIT for the study of continuous manufacturing in 2017 and 2018.

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Performance-Based Conditions Could Ease Post-Approval Changes For Process Analytical Technologies, Experts Say

▶ Joanne S. Eglovitch

Pharmaceutical industry officials recently explored how a performance-based approach to defining the established conditions for manufacturing processes outlined in the International Council on Harmonization's draft Q12 guideline could open the door for more use of process analytical technologies.

The performance-based option could provide a more efficient way to manage post-approval changes by reducing the number of changes that need to be reported to regulators, proponents said March 5 at a meeting sponsored by the International Forum and Exhibition on Process Analytical Technology (Process Analysis & Control), or IFPAC, in North Bethesda, Md.

There was also discussion on some of the barriers hindering greater adoption of PAT technologies, including lack of familiarity with data analytics generated by these technologies among industry and regulators, and on the need for more training in this area. Examples of PAT methods include near infrared spectroscopy (NIR) to understand and design a blending process and on-line sensors to batch performance. Some officials also expressed skepticism that regulators would accept the use of PAT in the post-approval area given the pushback they are receiving in the pre-approval area.

Sonja Sekulic, senior director of Pfizer's analytical group, said that "I think we are a pivotal point with respect to ICH Q12 and we should consider carefully where we're going because this will determine where we go over the next 20 years. There is also a great opportunity for the pharmaceutical industry to utilize advanced methods and models."

'Marry' The Concepts of Performance-Based Approaches and PAT

Christine Moore, Merck's global head of CMC policy, said that the purpose of the IFPAC session, called "ICH Q12 as an Enabler for Pat and the Digital Revolution" was to "marry the concepts of performance-based approaches and process analytical technologies, to put the concepts that are emerging in regulatory guidelines specifically through ICH Q12 with some of the emerging technologies related to PAT."

The draft ICH Q12 guideline was issued on Nov.16, 2017. The deadline for public comment was Dec. 18, 2018.

The draft guideline outlines three approaches for defining established conditions for reporting regulatory changes: a parameter-based approach in which product development provides a limited understanding of the relationship between inputs and resulting quality attributes and will include a large number of inputs; an enhanced approach that can be focused on input parameters as well as outputs; or a performance-based approach that focuses on control of operation outputs. Established conditions are legally binding information considered necessary to assure product quality. Any change to ECs necessitates a regulatory submission to health authorities.

At the IFPAC meeting last year, US FDA and industry officials touted the benefits of performance-based established conditions, as described in the draft ICH Q12 guideline. *(Also see "FDA And Industry Officials Tout Benefits Of Performance-Based Established Conditions In ICH Q12" - Pink Sheet, 16 Feb, 2018.)*

Trying To Shape The Landscape

Moore said that while not explicitly stated, the draft Q12 guideline opens the door to using PAT as one way to meet the performance-based approach for analytical methods.

In the section on ECs for analytical procedures, the draft states that "when there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method-specific performance criteria (e.g. specificity, accuracy, precision) rather than a detailed description of the analytical procedure."

This sentence, said Moore, "lays the foundation for what we are talking about today." She added, though, that "there really is no detail in the draft to say how to use it and how much development information do you need. ... That may change before the final guideline comes out. This lays the foundation and provides an opportunity for us to have a conversation in trying to shape that landscape."

Moore offered an example of how the performance-based approach could work for analytical methods: for a standard high-performance liquid chromatography (HPLC) column the manufacturer would focus on the performance of the method. For example, it would focus on the method's specificity, accuracy, linearity and range, precision/repeatability and robustness. This differs from parameter-based ECs that would focus on the method inputs such as the type of analysis, the type of column, the mobile phase composition, flow rate and gradient.

Moore said that the benefit of using a performance-based approach for analytical methods is that changes to the output can be managed within the pharmaceutical quality system rather than being reported to regulators. Changes made under the parameter-based approach that focus on inputs would necessitate prior approval from regulators.

"Under the parameter approach there is a long list of inputs that are expected in your dossier on how the method performs. In a performance-based approach, a lot of those inputs would go away and there would be more of a focus of the performance of that PAT model."

Moore said that industry and regulars will "have to work together" to move this idea forward.

Novartis: Making The Business Case For PAT

Lorenz Liesum of Novartis further elaborated on how PAT technologies can be used within the context of performance-based established approaches in Q12.

He said that "the new allies for PAT are continuous manufacturing, pharma 4.0 and ICH Q12." Industry 4.0 is the fourth industrial revolution involving new digital technologies; at the IFPAC meeting last year, industry representatives explored how industry 4.0 can be leveraged for the pharmaceutical industry.

Liesum said that the typical areas for changes for solid oral dosage forms are batch size, because at the time of filing there is uncertainty about counts and volumes; changes in

the API; changes in the excipient; changes in the analytical method; and site transfers.

Under a performance-based approach "we would like to shift criticality from a process parameter, like for instance a blending step, the batch size, the number of rotations, the equipment, to shift criticality from process parameters to a control method, which would enable you to use PAT."

This would give manufacturers more flexibility to change the blending parameters or the blending size or blending time without reporting the change to regulators. "In the solid world if you want to change the blending parameters or the blending time … you would be able to file a range for batch sizes and it would give you more flexibility and better optimization of the method." In addition, manufacturers would be able to use on-line sensors with multivariate/batch statistical process control (MSPC) to evaluate batch-to-batch variation.

He also discussed how to sell this idea to senior management.

Liesum said that manufacturers can make a strong business case to senior management that adopting PAT within the post-approval change environment can save companies money. For example, every year Novartis "makes thousands of regulatory-related changes" at a very high costs, with the biggest portion of this cost related to submission fees, and a smaller percentage related to internal administration and stability studies.

This money he said, could be "better spent on developing new drugs. … This is a huge business opportunity to reduce the cost of these changes."

Yet Liesum said that this idea is still evolving and has not yet been articulated in ICH Q12. "There needs to be homework and more development done in terms of how to file and how to frame this in submissions."

He said that in his ideal vision, the emerging digital technologies that support PAT are contained in new models that are automatically updated and changed and processes are self-running processes.

Vertex: Lots Of Questions On Real-Time Release

Yet despite the business case of having performance-based parameters tied to PAT, there was some skepticism on whether regulators would accept post-approval changes based on use of PAT methods.

Stephanie Krogmeier of Vertex discussed the company's experiences in dealing with regulators in their submission of two applications for drugs products on a continuous manufacturing line using real-time release methods; the drugs were Orkambi and Symdeko. FDA's first approval of a continuously manufactured drug came in July 2015 for Orkamai to treat cystic fibrosis. Symkedo was approved later as another treatment for cystic fibrosis in February 2018. *(Also see "Vertex Eyes Triple Glory After Hat Trick of CF Approvals" - Scrip, 13 Feb, 2018.)*

She said that regulators are still on a learning curve with these technologies, as is industry, particularly for in-process testing. This unfamiliarity was noticeable in Vertex's applications to FDA and the European Medicines Agency.

The PAT tools used to support real time release were loss in weight feeders and two NIR points for measuring potency and water and a NIR used for final blend, as well as used quantitative NIR to make real time release calculations.

Many Questions On RTR

Krogmeier said that there was a "high degree of interest" for real time release among regulators in reviewing Vertex's two applications for continuous manufacturing. She told the audience that if they file for real time release, "you are going to get a lot of questions."

For Orkambi, the NDA was 231 pages, with 75 pages devoted to answering regulators questions on real time release testing, while five addressed continuous manufacturing and eight were concerning QbD.

There was similar high interest in real time release from EMA. In the 552-page filing to EMA for Orkambi, 74 pages of the submission addressed regulators' questions on real time release testing, 21 addressed continuous manufacturing and 14 addressed quality by design.

In the 234-page filing for Symkedo filed in the US, 23 pages covered real time release testing, six addressed continuous manufacturing, four addressed QbD. In the 352-page filing for Symdeko filed in the EMA, 27 pages addressed real time release, 26 pages addressed questions related to continuous manufacturing and 22 addressed QbD.

The reason why the number of questions related to Symdeko dropped was that Vertex had a meeting with both the EMA and FDA to discuss the filings before submission.

Krogmeier said that "there are different ways to look at this and we think at a high level there will be a lot of questions and there will be a lot of scrutiny. This is new for them and it is new for us. We are all learning together and that is OK, that is a good thing."

In a panel discussion, Krogmeier also expressed some skepticism on whether ICH Q12 will confer regulatory relief when adopted. "We are at a critical point with ICH Q12 in that industry needs to see value in this. At Vertex there is a healthy skepticism on Q12. We invested in QbD and invested in design space yet there was not a ton of benefit to this. It is up to industry to interpret this to our advantage. But really quickly we have to see something come from it or else it will shrivel away.

Workforce And Regulators Need Training

During the discussion at the end of the session, speakers were asked to address some of the opportunities as well as the challenges in implementing PAT within the context of ICH Q12. Many of the speakers focused on the challenges in implementing PAT and attributed this to a lack of regulatory and industry experience in using these technologies. They offered some potential solutions.

Moore said, "I wonder if we are seeing a vicious circle here where we are seeing lack of experience leads to conservative approaches which leads to less utilization which leads to lack of experience."

Krogmeier responded that "there is a lot of hesitation with going and asking for advice from EMA because they are often very conservative so a lot of time companies will take the approach to beg for forgiveness rather than ask for permission so we are not having those conversations because we are still burnt by their conservative advice and findings and that is a huge deterrent. I am constantly battling subject matter experts."

Speakers also said that the workforce as well as regulators need better training in data analytics.

Pfizer's Sekulic said, "I think there is a really big challenge. We are trying to take analytical instruments and moving them into the production environment, and we have made a lot of progress. I think where there are still challenges is that we do a lot of measurements and we generate a lot of data. It is the analysis side of the data where I feel we are still playing catch up on. What we are asking people to do now is to focus on numbers and look at variances and data correlations and that is not something that is taught extensively in chemistry."

She said that at Pfizer, three sets of people work in the analytical area: analysts, engineers and modeling experts. Pfizer is trying to "cross-pollinate" so that people with experience in data analytics can share their skills with others.

Abigail Moran of the UK's Medicines and Healthcare Regulatory Agency also agreed that there is a lack of data analytic skills among regulators. "We have a similar issue. We have assessors from all backgrounds but very few are experts in data analysis."

Sekulic also stressed the importance for regulators to become more familiar with data analytics so they understand how to evaluate applications that use PAT technologies. If not, industry will not want to submit filings based on PAT technologies.

"There is a shift that we're seeing in our operations. There has been an up-skilling of operators to accommodate these activities and the same activities need to be mimicked in the inspectorate as well so that we have a commensurate level of understanding so that we can have these cogent conversations. It is no good to have all this great science and then it comes to a screeching halt because someone does not have the science, so you have all that good science and no submission."

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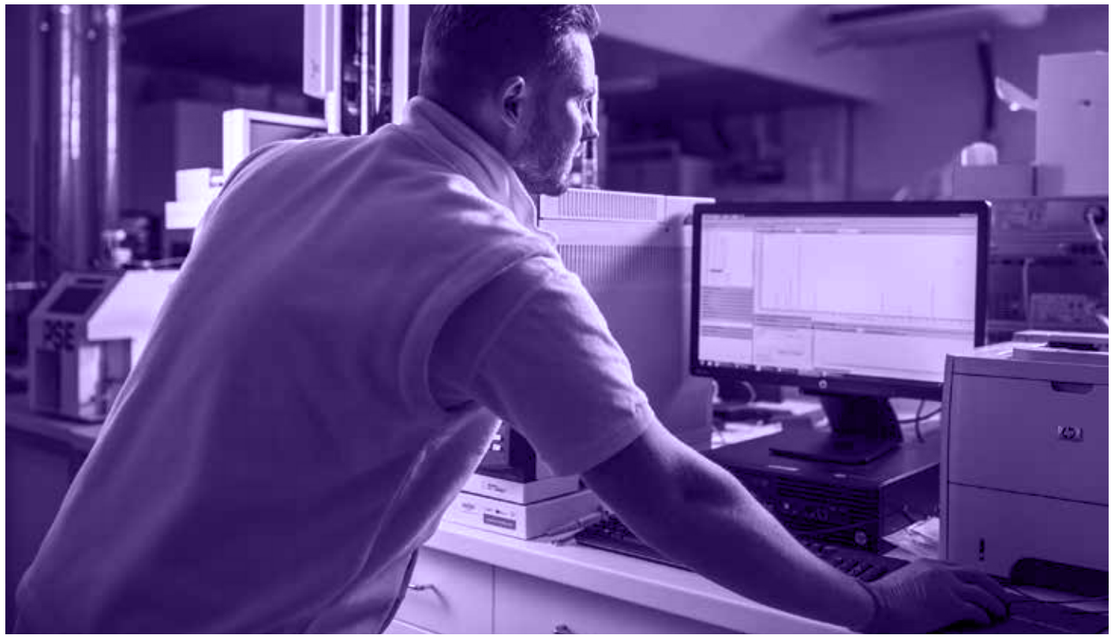
Proponents Of Quality Control Multi-Attribute Methods Tackle Adoption Challenges

▶ Bowman Cox



A new way to characterizing biopharmaceuticals that development laboratories have enthusiastically adopted faces an array of challenges as proponents look to bring the mass spectrometry-based technology to quality control laboratories for use in release and stability testing of commercial product.

Proponents are taking different approaches to expanding the ways their companies use these new methods, but they worry about resistance not only from regulatory authorities around the world, but also from their own quality control laboratories.

Fear of losing quality control jobs is one factor some proponents of multi-attribute methods say they must overcome to replace conventional methods for release and stability testing of biopharmaceuticals with this powerful new approach, participants said in a wide-ranging discussion at the 2019 CASSS WCBP Symposium in Washington.

There has been a great deal of excitement around liquid chromatography-mass spectrometry (LC-MS) multi-attribute methods, or MAM for short, both for use in developing biopharmaceutical manufacturing processes and potentially in controlling those processes during production operations and demonstrating commercial product quality.

A growing number of biopharmaceutical companies and instrument vendors participate in a group called the MAM Consortium – as does the US FDA – that aims to make MAM methods successful for process development and QC release testing.

But there are challenges to adopting MAM for manufacturing quality control, and fear of job loss is just one of the issues that came up in a frank discussion at the symposium, which is attended primarily by biopharmaceutical analytical laboratory personnel.

Too Much For QC?

One participant who works for a major pharmaceutical company said she worries that "putting this high-end, expensive mass spec in a QC environment could in the end create more trouble than convenience."

That said, she added that "it's a wonderful tool and we use it on a daily basis for process development."

She said it's great for establishing structure-function relationships and ion exchange variants, for example.

But by the time the firm must choose specifications for quality control, it's clear which attributes are important and must be monitored, she said. "In a QC environment, you want to do very targeted analysis. You probably don't need high-resolution mass spec."

One Assay To Replace All?

This participant said her firm nevertheless is piloting the use of LC-MS in quality control and co-validating conventional QC data sets.

"But what we're doing is not one assay replaces all," she said. "Because if you're trying to tell your QC colleagues or the QC VP that you're going to be out of a job, mass spec's coming in, one assay replaces all, that's the end of the conversation."

Beyond that, she asked the other participants to consider the regulatory commitment involved in switching to a single assay for everything. "This better be the most robust, most reliable assay, because patient safety is relying on the output of a single assay. Just think about it."

Her firm's approach is instead to look for ways to complement the traditional QC release package. So, for example, it's promoting the use of mass spec for the identification assay, which is harder to do with the traditional high-performance liquid chromatography (HPLC) or capillary electrophoresis (CE) approaches.

Other areas of focus include analyzing glycans and monitoring oxidation.

Getting Peptide Mapping Experts Involved

As a prelude to establishing MAM for quality control, one major pharmaceutical company brought in a couple of peptide mapping experts who work in its QC groups "to give input as we've started to establish systems suitability criteria, assay acceptance and method performance. And that's been really helpful in moving things along."

Another participant said his firm's focus is on developing a mass spec method to replace a peptide map it's using for a release test. The problem is the QC lab must burden the development lab with the task of running the peptide map method to get product released.

Regulatory Successes – And Challenges

There were a few participants in the packed room willing and able to discuss regulatory interactions.

One said her major pharmaceutical company has launched a demonstration program and invited members of the Emerging Technology Team in FDA's Office of Pharmaceutical Quality to see how the company can use MAM in its QC laboratory, and how it compares to traditional methods.

Another said that as part of her firm's phase-based approach that starts with clinical materials, "we have engaged with other regulatory agencies around the world and have not received any concerns."

However, one participant raised concerns about the viability of rolling out MAM methods globally for QC testing. "It's a huge capital investment," she said. Her firm has a drug product that's approved in 77 countries, many of which require batch release testing to be repeated in country. There's the cost of installing the equipment in all the countries, along with the challenge of educating all of the regulatory authorities about it and training all of the QC analysts on how to perform the testing.

The equipment is challenging enough for experts with PhDs to operate, she said. "For QC scientists, many of

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them just have bachelor's degrees. And they're busy. They're actually running so many different assays for so many different products. Expecting them to be able to filter through all of this and come up with a reliable conclusion and also explain to QA colleagues what those tiny peaks mean is quite a challenge."

A Better Way To Use MAM For QC?

A participant with a major biotech firm suggested a different approach for relying on MAM in the commercial environment. His firm uses MAM as an in-process test to make sure the product is good and that it will pass conventional release tests. Then it runs all the conventional release assays on robotic platforms to meet the acceptance criteria "applicable to all the countries in the world."

With this approach, he said, "the incremental cost is almost zero to your process and you have zero risk because you already know through your mass spec data it's going to pass."

He noted as well that this approach can allow a firm to streamline its release testing process "because now you can forward-process all of your batches without all the conventional release testing because you know they're good."

What About A Myriad Of New Impurities?

One participant expressed concern that MAM and high-resolution spectrometry would be so powerful that if it's used in the quality control laboratory, it would find all sorts of minor impurities that would have to be investigated.

He wondered if there should be a cutoff limit in terms of what additional impurities found by such new methods should be reported to the regulatory authorities.

Another participant said there's a way to prevent such a sensitivity increase of testing methods from spurring investigations.

Recalling advice from Steven Kozlowski, director of the Office of Biotechnology Products in FDA's Office of Pharmaceutical Quality, this participant said to "always go back, look at samples that you've had from previous product that you've been using. Was it in there? You're probably going to be OK then."

Background On MAM

A January 2018 AAPS Journal article provides background on what MAM is all about.

Biopharmaceutical critical quality attributes typically include product- and process-related impurities, the article notes.

Unlike MAM, conventional purity assays used for lot release and stability testing are often too narrow in focus and limited in resolution to identify product-related impurities resulting from post-translational and chemical modifications, sequence variants or hydrolysis during storage, it goes on to say.

MAM's enhanced capabilities make it useful for distinguishing which product quality attributes are of critical importance, particularly when used along with structure-function studies. It also could simplify product lifecycle management.

Conventional assays "have served as surrogate measures, often capable of only assessing global rather than site-specific chemical modification at the amino acid level," the article explains.

"Peptide mapping coupled with mass spectrometric analysis" is great for identifying the quality attributes of monoclonal antibody therapies, and QC labs already use peptide mapping for identity testing, the authors note.

MAM relies on software to compare thousands of chromatography peaks in reference and test samples that rise above set thresholds. By automating the search for new peaks that signify impurities, MAM avoids the manual labor, as well as the false positives and missed co-eluting peaks that are associated with conventional peak detection, the article says.

Additional QC, Process Control Capabilities

MAM can readily monitor charge heterogeneity or size variants associated with post-translational or chemical modifications and can facilitate monitoring of risky host-cell proteins, the article says.

It's widely used in monitoring for potency-reducing oxidation, deamidation or isomerization events, and in associated expiry dating.

By enabling quantitative attribute measurement at the molecular level, MAM "enables us to establish a direct link between product quality attributes and clinical performance," the paper says.

The method can enable improved control for lot release and stability testing based on biologically relevant specifications.

This can involve prediction and self-correction of critical process parameters for critical quality attributes at critical control points, which in turn can set the stage for possible use as a real-time release testing method.

With its three- or four-hour data turnaround time, MAM can be used at line as a process analytical technology for numerous attributes.

Challenges Noted

The article noted several challenges to the use of MAM for advanced control and cGMP testing of biotherapies.

There are technical issues such as ensuring robustness of hardware and software for new peak detection.

There are regulatory and compliance worries, mainly around acceptance by regulators, technical understanding in quality control labs, and possible increases in out-of-specification findings and associated investigations.

Opinions vary on replacing conventional assays with MAM; some favor keeping them. The paper observes in this regard that "the notion of having conventional assays in addition to MAM is a barrier to broader implementation for most companies."

That said, it could be challenging to demonstrate the correlation between MAM and conventional assays that would be needed to justify replacing them.

Meanwhile, there is some dual testing underway for product release and stability with the idea of helping regulatory agencies get comfortable with the idea of switching to MAM.

Global regulatory acceptance poses additional challenges due to what the article refers to as the "diverse regulatory environment."

One strategy the article advocates is for firms to use MAM for release testing and stability testing for clinical trials and incorporate it into the eventual applications.

Ultimately, the article said, "MAM offers the opportunity to platform a global release strategy that can improve the safety and efficacy of these therapeutics for the patient."

Published online in Scrip, 29 Mar 2019

GENE THERAPY'S NEXT BIG CHALLENGE: Manufacturing

▶ By Amanda Micklus

Commercialization of modern-day gene therapies is now a reality. Next-generation modalities such as chimeric antigen receptor T-cell (CAR-T) therapies are fully in launch mode in the US, where **Novartis AG** and **Gilead Sciences Inc.** are banking on the success of their one-time hematological cancer treatments *Kymriah* (tisagenlecleucel) and *Yescarta* (axicabtagene ciloleucel), respectively. Final approval of those CAR-T therapies has also occurred in the EU, with funding arrangements in place in the UK. In addition, the first *in vivo* gene therapy for an inherited disease is now available in the US, by way of **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec - rzyl), and the EMA is currently evaluating what could be the next approval in the market, bluebird bio's *LentiGlobin* (lentiviral beta-globin gene transfer) for transfusion-dependent beta thalassemia.

Presently, there are 25 unique gene therapies that have reached Phase III or have been filed for approval. Approximately 33 individual Phase III trials involving these therapies are ongoing (open, closed, or temporarily closed) across a broad range of diseases, led by various cancer types, hemophilia and other rare disorders. The Phase II gene therapy pipeline is even larger, totaling 150 products right now with nearly 100 ongoing Phase II studies being conducted. Given overall pharmaceutical industry attrition rates, many of these therapies will fail, but the large number of candidates overall suggests that there will be several, at the very least, that will advance and gain approval, moving toward commercialization.

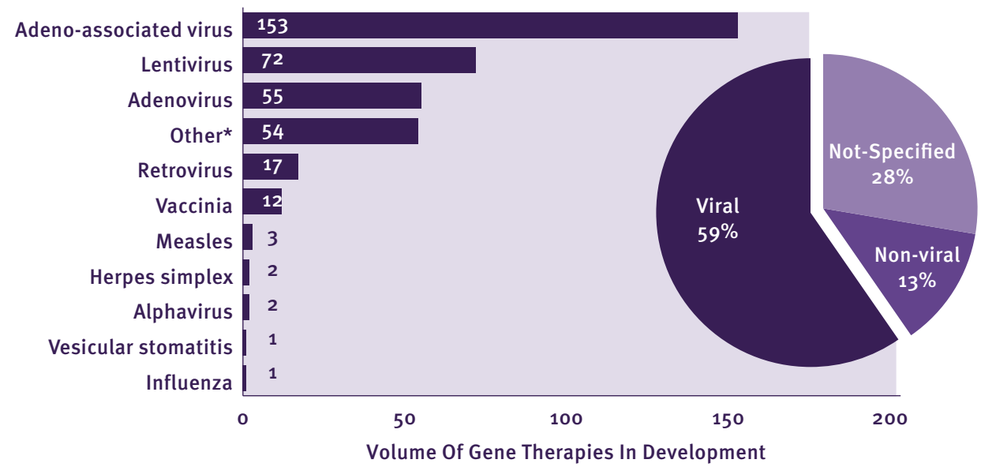
Supply May Not Meet Demand

The vector used in a gene therapy is a critical component, as it acts as the delivery vehicle for the gene into the target cell. Its role as a carrier allows for genetic material to enter and be taken up by the cell, whether it is *in vivo* or *ex vivo*, where the genetic instructions are provided to express or block the function of a gene. In the current gene therapy pipeline, viruses are most often called upon as gene delivery vectors. More than half, or approximately 59% of the candidates in development are delivered via a viral vector, while only 13% are administered by a non-viral vector, such as a plasmid (there is also a 28% proportion of the pipeline where the vector type cannot be determined because it is not publicly known). As a gene delivery vehicle, viruses, which are typically modified so that viral genes are removed to prevent replication in the host cell, offer many advantages, such as enabling efficient gene transfer and long-term or transient transgene expression. The adeno-associated virus (AAV) has emerged as the most actively used vector by gene therapy developers, followed by lentivirus and adenovirus (*see Exhibit 1*).

Sponsors of gene therapies will require a stable supply of vectors for their products. For many, this may not be an issue now as they treat smaller patient populations in clinical trials. As these firms move from smaller-scale trials, though, to larger studies and then mass production for commercialization, the supply of vectors becomes a mission-critical issue. "Right now, viral vector manufacturing is probably one of, if not the single biggest limitation in the cell and gene therapy space," says Bruce Thompson, former senior scientific director, therapeutic products program at Fred Hutchinson Cancer Research Center, and "could ultimately affect those therapies about to come onto the market." [*Editor's note: Thompson has since moved to* **Lyell Immunopharma** *as vice president of manufacturing.]*

Further, manufacturing of the vectors used to deliver these gene therapies has been an expensive and time-consuming endeavor, and more of a custom process at this point. US FDA Commissioner Scott Gottlieb has highlighted vector production as a big concern, noting that approximately 80% of the standard review time for gene therapies is spent on manufacturing and quality concerns. He says the FDA is working internally and with partners on initiatives to improve the yield of cell lines used to produce gene therapy vectors. In 2018, the FDA announced a new initiative, called the INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER producTs) program, which will include cell-based regenerative medicines and gene therapies, and encourage those sponsors to set up formal meetings with the FDA at the early or preclinical stage of development to discuss chemistry, manufacturing, and controls (CMC) issues related to clinical trials, much like discussions sponsors who have received the regenerative medicine advanced therapy (RMAT) regulatory designation do have. Major academic

Exhibit 1: Gene therapy pipeline by vector category and viral vector type



Source: PharmaProjects

manufacturing centers, where many vectors are produced for clinical trials, all have longwaits, of somewhere between 12 months and probably 18–24 months, says Thompson. *(Also see "BIO Notebook Day 4: Gottlieb Seeks Early Engagement On Gene Therapy; Ireland's Brexit Opportunities; AMAG's Bremelanotide Strategy; Alzheimer's 'Learnings' " - Pink Sheet, 7 Jun, 2018.)*

Contract Organizations Emerged With Gene Therapy Capabilities

The demand for manufacturing will provide lucrative opportunities for contract manufacturing organizations (CMOs) or contract development and manufacturing organizations (CDMOs) in the specialized market of cell and gene therapy, but that demand will likely exceed the supply. There is only a select group of companies currently with these capabilities (*see Exhibit 2*), which are considered highly specialized, and it is likely that new CMO/CDMO players will emerge as well to address this demand, says Morrie Ruffin, co-founder and senior advisor at the **Alliance for Regenerative Medicine** (ARM). The demand, along with the potentially enormous cost, is cause for concern, and for this reason, there is worry about the sustainability of such a model. **Lonza's** head of cell and gene therapy, Thomas Fellner, agrees this is a major roadblock: "If they [late-stage gene therapy companies] all needed to outsource manufacture of their products at the same time, for example, the CMO sector might not be able to cope. *(Also see "Cell Therapy Manufacturing: Challenges Remain" - In Vivo, 14 Dec, 2016.)* Lonza, which is a big player in the custom development and manufacturing of active pharmaceutical ingredients, in fact, might be best equipped for the challenge. In April 2018, it opened a 300,000-square foot manufacturing plant in Pearland, Texas, for cell and gene therapies, said to be the largest yet in the world. The facility will be responsible for development activities from concept through preclinical testing, clinical trials, and commercialization.

Besides Lonza, other CMOs have built up vector manufacturing capabilities in the gene therapy market. **MilliporeSigma**, for instance, has been involved in viral vector manufacturing for decades, contracting with not only industry players but also academia and hospitals. The company, which was acquired by **Merck KGAA** in 2010 and integrated with **Sigma-Aldrich** (also later bought by Merck KGaA; and previously known as Sigma Aldrich Fine Chemicals [SAFC]), offers these services under the BioReliance brand. MilliporeSigma says its manufacturing plant

located in Carlsbad, California has been greatly expanded in recent years to advance the quality requirement and regulatory output, including 16 modulatory viral bulk manufacturing cleanroom suites. *(Also see "How Merck KgaA's Life Science Unit Is Riding The Crest Of The Gene Therapy Wave" - Scrip, 2 Mar, 2018.)*

When shopping for CDMOs/CMOs, industry clients should keep in mind the potential for contamination of products, especially if multiple gene therapy companies are contracting with the same CDMO/CMO. Denise Gavin, of the Gene Therapies Branch of FDA/Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies, advises sponsors to ensure their partners have strong cleaning and segregation procedures and good quality control to reduce the risk of contamination of, for example of random plasmids or adventitious agents getting into a product. *(Also see "FDA's CMC Guidance For Investigational Gene Therapies Reflects Broader CMC Evolution" - Pink Sheet, 11 Jul, 2018.)*

Securing Stable Vector Supply Through In-House Build-Out Or External Capabilities

While many gene therapy developers will indeed contract with CMOs or CDMOs, some have also built out their own manufacturing capabilities, or are in the process of doing so, as they prepare for commercialization. Key advantages to doing this include mitigating the risk of demand exceeding the supply, and avoiding the reliance of vector manufacturing on an external vendor. Having an internally controlled facility allows sponsors to maintain control over the manufacturing process, according to ARM's Ruffin. The reliability of supply that comes with a company's own manufacturing is important as it advances through the clinical development process. Another potential benefit, says Ruffin, are the future uses for such facilities, including meeting commercial demand and post-approval requirements. According to a 2018 survey conducted by KNect365 of cell and gene therapy players, nearly half of the companies (48%) said they planned to conduct manufacturing in-house, with another 32% making their products both through internal means and through contract manufacturers.

Industry sponsors have the choice to build their own plant, contract out, or employ a combination of both strategies. There is not necessarily one correct approach, says Ruffin, and it will largely depend on an individual company's needs and requirements, and the therapeutic programs involved, including the size of the trial, target indication, and patient population. "As the sector matures, we will see companies opting for both solutions [building and contracting]." Ruffin believes that it is unlikely that there would be a scenario in which all gene therapy companies are utilizing their own facilities. An important benefit to employing the "build and buy" model in manufacturing, using both internal and external (through a CMO/CDMO partner) capabilities, is the capacity to run projects in parallel, says Bruce Thompson. This model will likely work better in smaller companies who are mostly or solely dedicated to gene therapy with smaller pipelines.

Bluebird Bio Developed Both Internal And External Capabilities

bluebird bio Inc.is one such company that has taken manufacturing into its own hands, and for good reason. In December 2015, bluebird bio disclosed that responses in a small study of its ex vivo gene therapy LentiGlobin for severe sickle cell disease were not adequate due to the lower-than-expected vector copy number (VCN), which is a measurement of the average number of vectors in a modified cell population. Bluebird bio modified the manufacturing process by adding in enhancers during the procedure in which cells are transduced to increase the proportion of successful transductions, and, thus, boost the VCN. The results look promising, with updated data showing stable VCNs, and signs of improving effectiveness in a small group of patients in terms of anti-sickling threshold. LentiGlobin is now being reviewed by the EMA under accelerated assessment, and the therapy has a 70% likelihood of approval, 10% above average, according to Biomedtracker.

In late 2017, bluebird bio executed on its manufacturing efforts and acquired a partially completed complex in Durham, North Carolina for $11.5 million. The 125k-square-foot facility will produce the clinical and commercial supply of lentiviral vectors for not only LentiGlobin, but also Lenti-D (human ABCD1 gene), in Phase III for cerebral adrenoleukodystropy, plus other products. To ensure it has a stable supply of vectors on top of what it can produce in house, bluebird bio also has contracts in place with many of the CMOs that specialize in gene therapy. In 2017, the company executed a number of deals with Lonza, apceth, Brammer Bio, Novasep, and SAFC (now MilliporeSigma).

Exhibit 2: Select Group Of Contract Development And Manufacturing Organizations With Gene Therapy Vector Supply Capabilities

Manufacturer Name	Gene Therapy Manufacturing/Vector Capabilities
apceth	Manufacturing platform for genetic engineering of allogeneic mesenchymal stem cells using viral vector system; facilities in Munich (Ottobrunn and Großhadern) involve GMP manufacturing and quality control for multiple types of advanced therapies
Brammer Bio	Dedicated clinical and commercial supplier of viral vectors for in vivo and ex vivo therapies; manufacturing facilities located in Cambridge, Massachusetts and Somerville, Massachusetts that handle early- and late-stage gene therapy manufacturing process technologies
Fujifilm Diosynth Biotechnologies	80k-square-foot flexibility manufacturing facility in College Station, Texas; clinical and commercial production
Lonza	300k-square-foot manufacturing plant in Pearland, Texas, reportedly the largest in the world, for cell and gene therapies
MilliporeSigma (Merck KGaA)	BioReliance services, including viral vector manufacturing from small scale/clinical to commercial scale; manufacturing plants located in Carlsbad, California and Glasgow, Scotland
Novasep	Experience in manufacturing attenuated or wild type viruses and viral vectors, focusing on AAV, adenovirus, and lentivirus; capabilities ranging from process development to clinical trial material manufacturing
Paragon Bioservices	Offers manufacturing services for recombinant AAV production
VGXI	Expanding manufacturing site in Texas by 5k-square-feet to add two flexible-use GMP production facilities to handle demand for gene therapies, including plasmid raw materials for viral vector production of AAV and CAR-T therapies
Yposkesi	Industrial platform (reportedly the largest in Europe) for the GMP manufacture of viral vectors for cell and gene therapies

AAV = adeno-associated virus; CAR-T = chimeric antigen receptor T-cell; cGMP = current good manufacturing practices; GMP = good manufacturing practicesSource: company websites

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- Among top 5 largest CDMO in Japan
- Largest regulatory consulting and medical writing team in Japan with 120+ experts
- No.1 capacity for stability testing in Japan

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Contract Manufacturers Cautioned On Allure of Novel Cell and Gene Therapies

Meanwhile, Monoclonal Antibodies Remain Where It's At In Recombinant Biopharmaceutical Manufacturing

▶ By Bowman Cox

A McKinsey & Company partner Sept. 17 cautioned biopharmaceutical contract manufacturers against diving into the emerging markets for novel treatment modalities like chimeric antigen receptor T cells.

He and another industry consultant also suggested that the comparatively staid monoclonal antibody manufacturing market segment, already quite large and poised for significant growth, perhaps merits greater attention

Many organizations are responding to the promise of cell and gene therapies by trying to play catch up, despite the risk of disruption, McKinsey's Gerti Pellumbi told the Pharma & Biopharma Outsourcing Association's second annual meeting in North Bethesda, MD.

"I think a lot of our clients right now that are also your clients are way over-correcting. I think people feel left behind on these [novel] therapies and they're over-investing in them," he said.

The CDMO sector could be caught in the middle. Imagine, he said, if a contractor meets the supply chain challenge for an autologous CAR-T cell therapy, only to find that a competitor like **CRISPR Therapeutics AG** develops better, cheaper allogeneic options, and the markets for autologous therapies and their elaborate supply chains collapse. That's just one scenario that many seem to be discounting in their efforts to get in on the action with new treatment modalities.

For new treatment modalities, "the growth has been at neck-breaking pace," Pellumbi said. The number of companies that have new modalities has increased from 160 just 10 years ago to 284 today. "That is a stunning number, especially if you think about the size and the scale you're required to participate in some of these."

It makes sense for large pharmaceutical companies with their substantial balance sheets to compete in this area, he said. "But if you're talking 284 companies, where did the other 200 companies come from? Where did they find the funding?"

He reminded the audience of contract development and manufacturing organizations that when the financial crisis hit a decade ago, a lot of biotech clients halted clinical trials and manufacturing activity "and you all felt it because you had these great biological or other programs that just immediately went belly up."

CDMOs that jump onto the new modalities bandwagon could face similar risks, he suggested. "It just feels like there's way too much focus and money that's going into these."

Although it's important for contractors to develop new manufacturing technologies to help them continue to serve their customers, there are some questions to consider, he said. "How much of this is fluff? And how many of these will be really successful, versus how many of them will really flake out in the future?"

Another consideration is that firms venturing into novel modalities may be looking to offload some of the risks. Pellumbi observed that "one of the reasons why they work with you is they pass on third-party risks to you."

Even the successful ventures may not provide such great opportunities for contract manufacturers, given that high-price cell and gene therapies are not likely to generate high volumes of manufacturing activity. The emerging sector may not grow to such a scale as to support a large contract manufacturing base. Pellumbi said new modalities accounted for 13% of the pipeline in 2017 compared to 9% in 2011. Certainly, it has increased, he said, "but in six years that's not a fundamental shift."

It's A MAb, MAb, MAb, MAb World

Meanwhile, Pellumbi said, "if you look at what drives the majority of the growth, it's [monoclonal antibodies]. It's technologies that, once again, many of you in this room support and develop from inception all the way through to manufacturing. So it's sort of the true and tried."

Patricia Seymour, principal consultant with **BioProcess Technology Consultants Inc.**, agreed that MAbs "is a big growth area, and has been and will continue to be for the foreseeable future."

She shared some highlights from BPTC's bioTRAX database, which predicts how much production will be required to meet sales projections for recombinant biopharmaceuticals.

The firm is tracking 700 molecules that are in Phase II through commercialization, as well as 1,100 molecules that are preclinical through Phase I.

BPTC also tracks supply capabilities at some 165 sponsor and contract companies that manufacture in nearly 260 locations.

The firm forecasted 18 metric tons of MAb production for 2017, and Seymour called attention to a "huge queue" of MAbs now at the approval stage.

Today, 201 product companies and CMOs have 3.7M liters of production capacity, up from 2.5M liters five years ago, she said. Industry will add another 1.8M liters of capacity over the next five years – a 50% increase – for a total of 5.6M liters, the firm predicts. "So you can see people and companies and investors are really gearing up to meet this wave of demand and making sure the capacity is available to manufacturing these products."

Despite the allure of cell and gene therapies, the bigger prize for contract manufacturers appears to remain with monoclonal antibody therapies.

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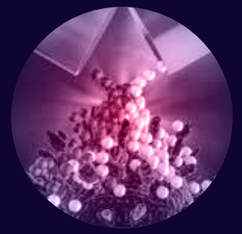
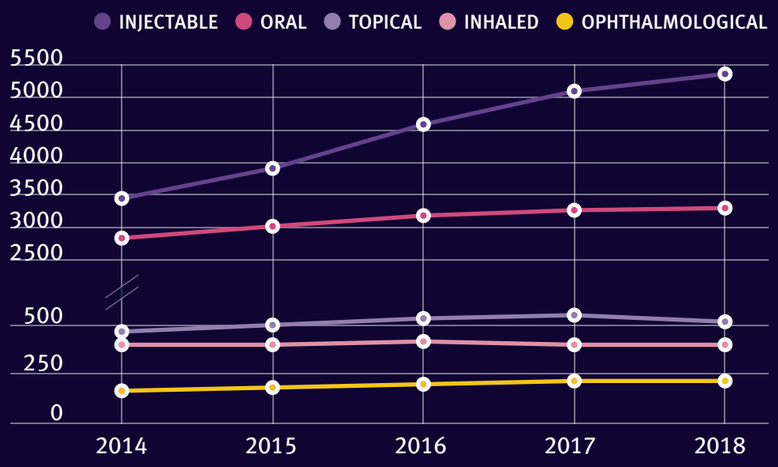
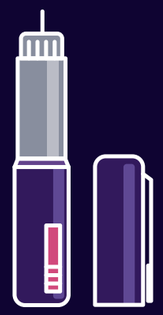


DRUG DELIVERY

Exploring route of administration, mode of action, clinical trial and therapy area trends across the biopharma pipeline.

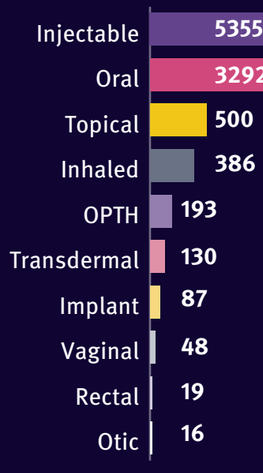
Top Five Treatment Delivery Routes For Investigational Pharma Pipeline





780

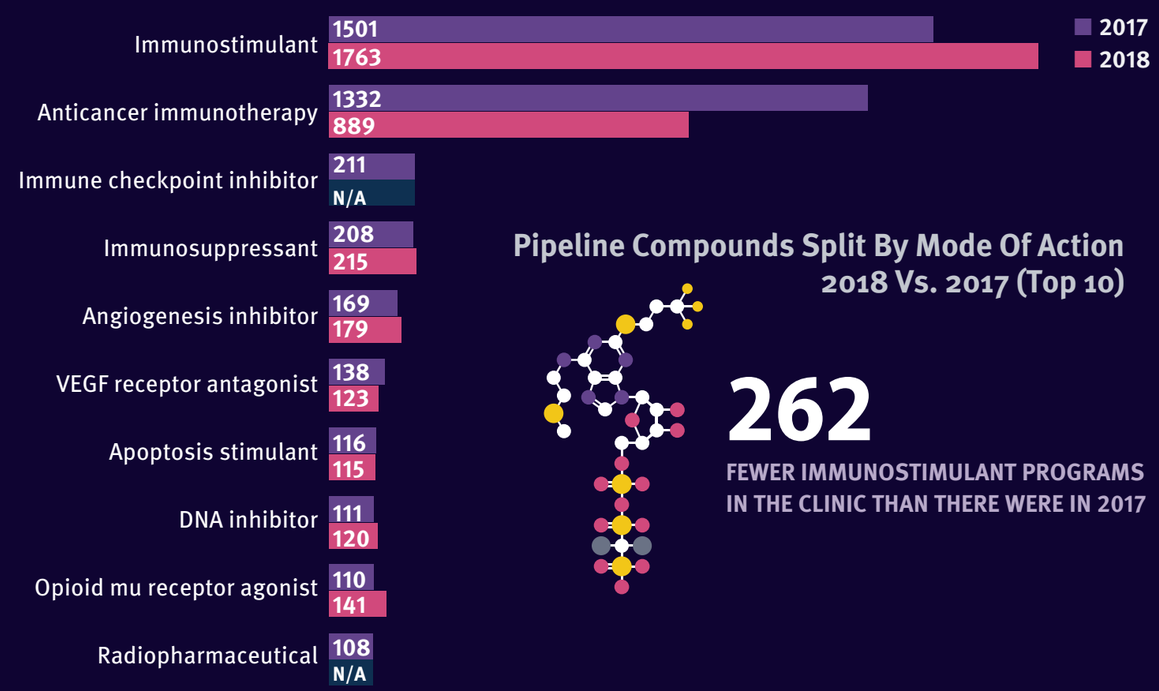
INCREASE IN THE NUMBER OF INJECTABLES FROM 2016 TO 2018



Route Of Administration Methods Across Pharma Pipeline In 2018

5150

TOTAL NUMBER OF ACTIVE COMPOUNDS IN THE 2018 PHARMA PIPELINE VS. 4540 IN 2017 (TOP 10 LISTED)

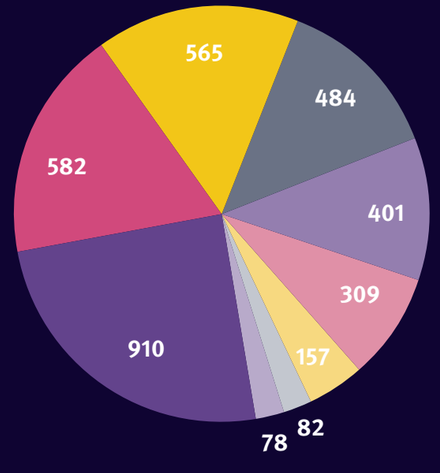


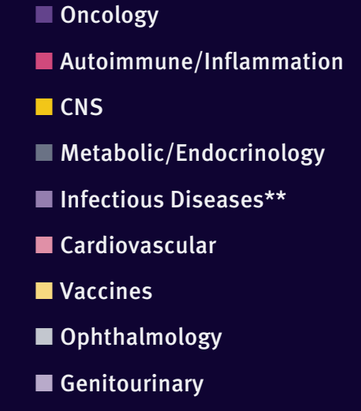
Pipeline Compounds Split By Mode Of Action 2018 Vs. 2017 (Top 10)

262

FEWER IMMUNOSTIMULANT PROGRAMS IN THE CLINIC THAN THERE WERE IN 2017

Industry-Sponsored Trial Count By Therapeutic Area - 2017*





* Trials may span multiple therapeutic areas
** Does not inlcude vaccine trials

SOURCES: Trialtrove; Pharmaprojects | Pharma Intelligence, 2018

In Vivo
Pharma intelligence | informa

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MEDTECH TIPS: Should A Combo Product-Maker's Quality System Be Device- Or Drug-Led? J&J, Eli Lilly Experts Weigh In

▶ By Shawn M. Schmitt

When Anita Michael walks into a facility to help facilitate a US FDA inspection of a combination drug-device product-maker, one of the first things she and agency investigators must determine is whether the firm's quality system is drug- or device-led.

"We would want to know, what is your main system? Do you have a CGMP [Current Good Manufacturing Practice] quality system focused on pharmaceutical manufacturing, or are we looking at a device Quality System Regulation system? That would be our first question," said Michael, a principal consultant for PAREXEL who has assisted FDA during inspections as a pharmaceutical expert for 16 years.

"For instance, if your company is mainly a pharmaceutical company and you're making combination drugs, then you would leverage that quality system under the CGMP, and then you would streamline and add the regulations that are required by the QSR," Michael explained.

"The opposite would be if you're primarily manufacturing devices and you have a combination product such as a drug-eluting stent product," she added. "In that case, you would want to make sure that the company understands all of the regulations that meet the [QSR] requirements, and then the streamlined approach would be the [CGMP] regulations that are set forth for pharmaceuticals."

A 2017 final guidance from FDA, "Current Good Manufacturing Practice Requirements for Combination Products," backs up Michael's assertions. *(Also see "FDA Issues Final Guideline On Combination Product GMPs" - Medtech Insight, 11 Jan, 2017.)*

The document states that manufacturers can "implement a streamlined approach for combination products that include both a drug and a device by demonstrating compliance with either the drug CGMPs ... or the device Quality System Regulation," and by "also demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements."

If a quality system is drug-led, in addition to complying with drug regs 21 CFR, Part 210 and Part 211, it must also comply with:

- Management responsibility (21 CFR, Part 820.20);
- Design controls (Part 820.30);
- Purchasing controls (Part 820.50);
- Corrective and preventive action (Part 820.100);
- Installation (Part 820.170); and
- Servicing (Part 820.200).

Conversely, if a quality system is device-led, in addition to complying with device reg 21 CFR, Part 820, it must also comply with:

- Testing and approval or rejection of components, drug product containers, and closures (21 CFR, Part 211.84);
- Calculation of yield (Part 211.103);
- Tamper-evident packaging requirements for over-the-counter (OTC) human drug products (Part 211.132);
- Expiration dating (Part 211.137);
- Testing and release for distribution (Part 211.165)
- Stability testing (Part 211.166);
- Special testing requirements (Part 211.167); and
- Reserve samples (Part 211.170).

The guidance also notes that firms can choose to "demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product." A quality system under that scenario would fully follow both sets of regulations for drugs and devices.

"So, figure out what your company is doing. If it's manufacturing pharmaceuticals and now it wants to go to combination drugs, then the firm should use the streamlined approach and add the device regulations," Michael said. "And if the firm is strictly manufacturing devices that are [moderate-risk] class II, then it should probably do the streamlined approach and add the GMPs for pharmaceuticals."

But no matter which path is chosen, "the people who are in place in management, in quality and executive roles, need to be proficient in understanding how combination products work, the regulations that surround them and how inspections are conducted," she said.

Susan Neadle, **Johnson & Johnson**'s senior director for Global Value Chain Quality Design, doesn't believe "that one way is better than the other."

Rather, "it should be based on what your primary mode of action is and what your base quality system is at your facility," Neadle said.

A "primary mode of action" is the constituent part of the combination product that offers what is deemed to be the most important therapeutic action.

"The challenge, though, is that people should be aware that regardless of whether they're using a drug-led or a device-led approach, regardless of what your base quality system is, be very careful to make sure you're aware of the things that are uniquely interpreted for the device constituent or the pharm constituent or the biologic constituent that is not the primary mode of action."

That means firms should make sure employees speak the language of both devices and drugs. (See Compliance Corner story, "J&J Quality Expert Urges Makers Of Combo Products To Be 'Bilingual' In Device- And Drug-Speak," below.)

"Let's say you have a drug-led quality system that's been implemented in your business, then you need to recognize that some of the words you use – like 'master project plan' or 'target profile' – have equivalents in the device world," Neadle said.

How Eli Lilly Does It

Eli Lilly & Co. Quality Director David Shore agreed with Neadle, noting that there "isn't a right answer" when deciding whether a quality system for manufacturing combo products should be drug- or device-led.

"There are multiple answers, and that's the reason the FDA has given us such flexibility [through its guidance]. But a quality system does need to most closely align with the business," Shore said. "You need to think about what your primary business is, and I would focus your quality system there. Because what you don't want is your business fighting your quality system. You want to try to maintain as much alignment as possible."

Although it is primarily a pharmaceutical company, Eli Lilly manufactures drug-delivery devices for some of its medicines, including the *Forteo* pre-filled syringe system for osteoporosis.

Shore said different Eli Lilly facilities have different quality systems focuses. Some completely follow both QSR and CGMP requirements, while others are drug- or device-led.

In those facilities that make the device components of products like Forteo, "we've structured ourselves around a 100% device quality system," said Shore, who works in the company's Indianapolis device manufacturing facility. "I work in a device quality system, so we are responsible for design control and design oversight, and then manufacturing of the medical device components.

"But we also have fill-finish organizations that are strictly pharma, so they focus their quality system on 100% pharma," he noted. "We also have production sites that integrate [device and drug], and they've gone with the streamlined approach."

Shore said it's "key to define expectations and internal quality agreements to make sure it's clear to yourself, and to the regulator, who really owns those specific elements of the streamlined approach."

In his facility, "we own design control throughout the entire process," Shore said. "The only thing the production site really needs to own is design transfer acceptance activities. That's kind of the design control element they must implement.

"We have to clearly communicate in quality agreements that the expectation would be if a design change is required, that [production] would communicate that back to the design owner in my organization," he added.

Comments from Shore, Neadle and Michael came at FDAnews' 12th Annual FDA Inspections Summit in Bethesda, Md.

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FDA Invites Comment On Continuous Manufacturing

By David Wallace

Draft guidance on quality considerations for continuous manufacturing has been published by the US Food and Drug Administration (FDA). With a 90-day period for interested parties to submit comments and suggestions, the document covers small-molecule oral solid-dosage forms regulated by the center for drug evaluation and research (CDER).

Describing "key quality considerations", the guidance gives recommendations for how abbreviated new drug application (ANDA) and new drug application (NDA) sponsors for continuous-manufacturing products should address these considerations. These include 'key concepts' of continuous manufacturing, control strategy and process validation.

Quality Considerations for Continuous Manufacturing Guidance for Industry

"This guidance focuses on scientific and regulatory considerations that are specific or unique to continuous manufacturing," the FDA indicates, including process dynamics, batch definition, control strategy, quality systems, scale-up, stability and bridging batch manufacturing to continuous manufacturing. "Recommendations broadly applicable to both continuous and batch processes are generally not covered."

Quality, Consistency, And Cost Savings

Commissioner Scott Gottlieb and CDER director Janet Woodcock said continuous manufacturing was "one of today's most important tools for modernizing the pharmaceutical industry", transforming the "traditional, stepwise manufacturing processes into a single system that's based on modern process monitoring and controls". The latest guidance would "help advance the adoption of these manufacturing innovations", they suggested.

Continuous manufacturing "helps to ensure consistently-made products, allows manufacturers to more easily scale their manufacturing operations to meet demand, and can help reduce drug shortages by minimizing operational stops and starts", they said, as well as requiring smaller footprints to operate and leading to cost-reducing efficiencies.

Acknowledging that the area was "still new and developing", the pair indicated that realizing the "full potential" of continuous manufacturing would "require us to invest time and resources in developing scientific standards and policy and supporting implementation". "This is why we've charged the FDA's emerging technology team to help early adopters of continuous manufacturing," they noted.

Guidance Aids Adoption

"This draft guidance will clarify the FDA's current thinking regarding innovative continuous manufacturing approaches and can help resolve potential issues some companies have as they consider implementation, such as concerns that use of new continuous manufacturing technology might impact the time FDA takes to assess applications for new products and switching from a batch to continuous manufacturing process for existing products," Gottlieb and Woodcock stated. "The draft guidance also supports a global effort with other regulatory authorities to encourage implementation of continuous manufacturing."

Having recently issued a lengthy rebuttal to criticisms of the FDA's oversight of generic drug quality issues *(Also see "FDA Insists Its Quality Controls Are Up To The Task" - Generics Bulletin, 26 Feb, 2019.)*, Gottlieb and Woodcock said that continuous manufacturing was "a key step towards promoting drug quality and improving the efficiency of pharmaceutical manufacturing".

"The FDA is committed to helping more companies advance these continuous manufacturing platforms owing to the public health benefits of these more modern approaches," they emphasized. "We support the early adopters that are embracing this innovative technology and we look forward to working with other interested companies."

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