

Multiproduct Facility Design and Control for Biologics

Challenges and Considerations

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Multiproduct facilities are increasingly integral to corporate biologics network and supply chain strategies. Manufacturing capacity strategies ensuring appropriate facility design and procedural controls to manage the risks of producing multiple products are critical to the successful deployment of commercial and clinical supply plans.

A Chemistry, Manufacturing, and Controls (CMC) Strategy forum was held in Bethesda, MD, in August 2011 to highlight various challenges, risks, and control strategies associated with multiproduct facilities. Multiproduct strategies for the manufacture of a variety of product types at different life-cycle stages and potentially using different host cells were presented with case studies. Experts from both industry and global health authorities discussed facility design considerations as well as procedural controls such as cleaning



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validation and product testing. The importance of quality risk management (QRM) to multiproduct operations and controls was also discussed using practical examples of risk-based approaches to meet the challenges of multiproduct manufacturing.

SESSION 1: DESIGN CONSIDERATIONS **What are the principle challenges in building a flexible, scalable, multiproduct manufacturing network?**

The biotechnology environment is changing. Unprecedented yields are now the norm, but smaller batch sizes are needed to accommodate increasingly personalized medicines. New expression technologies such as

transgenics will require different dosage forms. Rising expectations for sponsors to build quality into their manufacturing processes rather than relying on end-product testing are resulting in a changing paradigm for validation activities and life-cycle risk management. Competitive pressure from biosimilars will require keeping cost of goods as low as possible without sacrificing quality.

Decisions must be based on comprehensive global and regional business and regulatory strategies as defined by each company — sponsors and contract manufacturing organizations (CMOs). That task can be complicated by many factors, including, for example, differing

PRODUCT FOCUS: ALL BIOLOGICS

PROCESS FOCUS: MANUFACTURING

WHO SHOULD READ: OPERATIONS, PRODUCT MANAGERS, QA/QC

KEYWORDS: RISK MANAGEMENT, SINGLE-USE SYSTEMS, COST MANAGEMENT

LEVEL: INTERMEDIATE

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regulatory interpretations in different jurisdictions. In addition, appropriate records have to be maintained. If there are multiple products and multiple jurisdictions involved, the recordkeeping can become extremely complex. Manufacturing challenges arise from the difficulty of working with newer and older generation products in multiple regions and with multiple product categories. Manufacturers must also keep up with guidances in multiple regions for multiple products, which is not a simple and straightforward undertaking.

Keys to successful decisions include using modular construction to maximize flexibility, ensuring an experienced mentor team is in place, and using best practices from lessons learned during past campaigns and from other companies' experiences. Using Six Sigma tools on system designs for most aspects of operations activities is also recommended.

Multiproduct facilities are being used, in spite of all complications, and companies have reported learning a great deal from their experiences to date with multiple-use facilities. They found that a high degree of upfront investment is required (not just funding, but also in time and resources) to fully establish a good strategy. It is important to have an empowered cross-functional project management team, so careful consideration must go into selecting personnel. Readily available assets from academic research institutions and in-house apprenticeships are valuable resources. Companies have

SESSION 1: MULTIPRODUCT FACILITY AND DESIGN CONSIDERATIONS

In the first session, presenters introduced the principle challenges in designing and operating a multiproduct facility for biologics. Regulatory agency and industry perspectives regarding the opportunities for and limitations to multiproduct facility flexibility were discussed. Specific considerations related to contract manufacturing organizations were also highlighted. The discussion focused on questions highlighted in the text.

Stefanie Pluschkell of Pfizer, Inc. was session chair. Presenters were Patricia Hughes (Office of Manufacturing and Product Quality, OMPQ, CDER, FDA), Pat O'Driscoll (Eli Lilly), and Michael Howaldt (Boehringer Ingelheim). The panel included the presenters plus Anthony Ridgway (Health Canada) and Kathryn Simon (Fujifilm Diosynth Biotechnologies).

recognized the different expectations from the European Union (EU) and the US Food and Drug Administration (FDA), and they stressed that, as always, it is best to keep the primary regulatory agency "in the loop."

What are the boundaries and limitations in multipurpose facility (MPF) flexibility (e.g., phase of development, product type)? The whole idea of an MPF is having multiple product types and processes in concurrent or serial production campaigns; upstream, downstream, and fill/finish. However, it is important to consider all elements of a process, product, and facility that could affect or be affected by other processes and products that will or could be present. That requires the expert input from multidisciplinary staff with process understanding to evaluate all aspects of manufacturing, including controls, risks, and risk-mitigation strategies.

In addition, new approaches, technologies, and innovations in the design, construction, and operations of an MPF, including retrofitting, building new single-use systems or disposables, and hardcopy or electronic recordkeeping are available

THE CMC STRATEGY FORUM SERIES

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum committee strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the forum meetings are published in this peer-reviewed journal with the hope that they will help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is cosponsored by the US Food and Drug Administration (FDA).

for implementation. However, operations must meet regulatory compliance requirements for good manufacturing practices (GMPs) to ensure product quality and consistency. Regulations on segregation of toxic or infectious materials (e.g., antibiotics, spore formers, live vaccines, highly toxic compounds) must be observed.

Risk assessment (RA) in alignment with ICH Q9 should be performed, and a suitable QRM plan should be generated to mitigate the risks associated with highly potent, toxic, or infectious products in a multiproduct facility. FDA expects manufacturers to evaluate scientific data and implement the appropriate level of controls necessary to prevent potential for cross contamination. The agency evaluates risk-management plans during GMP inspections.

Cross contamination is a major regulatory concern. It can be caused by mix-ups or operator errors, product or material retention, carryover from one campaign to another, mechanical or physical interactions, and airborne transmission of compounds or contaminants. Cross contamination during changeover is a major source of



CMOs need to find ways to streamline and **HARMONIZE** systems to be consistent but still flexible enough to adapt as necessary for each product and each client.

product recall, so risk mitigation must be thorough and effective. Risk mitigation may include the use of unidirectional workflow, segregated functions in closed systems, single-use systems, robust changeover procedures, validated cleaning and inactivation processes, thoroughly trained personnel and redundant controls (such as secondary containers).

Are companies designing facilities for multiple products upfront or retrofitting? What is the primary difference in approach? What are the advantages or disadvantages to retrospective or prospective approaches? During forum presentations, we saw examples of both a retrofit and a new construction for MPF. Both approaches require substantial investment in planning, preparation, and execution. No audience discussion of this question took place.

What multiproduct considerations and challenges are unique to CMOs? What should customers and service providers focus on and be prepared to provide when entering a CMO agreement? Special challenges for CMOs include having to handle many products with smaller campaigns and more campaigns; more clients, more quality systems, more process formats and platforms, more technologies; differing production scales, different cell lines, different molecules, more dosage forms, challenges with risk management and change control,

increased quality oversight, new paradigms (quality by design, QbD; process analytical technology, PAT; life-cycle approach), and more inspections.

Meeting various quality systems expectations of a diversity of customers, compliance requirements, and product-specific technical issues can push a CMO's capabilities to the limits. CMOs need to find ways to streamline and harmonize systems to be consistent but still flexible enough to adapt as necessary for each product and each client. They have to be efficient, coherent, compliant, and competitive to survive in today's and tomorrow's production environment.

Client-specific needs and desires coupled with corporate policies and procedures can constrict a CMO's flexibility of practices. It is important to distinguish between what is necessary and what would be nice to have. Sponsors and CMOs should address those issues jointly to achieve optimal solutions for high-priority elements. An implementation plan must be in place and followed for successful cooperation between a client and a CMO.

What are some of the expectations with respect to the future direction of MPF designs? Future MPF designs will include flexible facilities that enable smaller and more frequent campaigns. FDA representatives said that they see a trend in which manufacturers intend to use disposables to allow flexibility. The agency may allow a downgrade in HVAC requirements in case of a single-use, closed system. However, those lower requirements cannot impact product-quality standards. The FDA is still grappling with all of the components of risk, including modular manufacture and mobile manufacture where facility requirements might be minimized, but the agency is not yet sure what all the new risks will be.

Disposable systems are faster and more flexible to implement than permanent fixtures, but single-source suppliers are very risky. Depending on one source for any critical component could jeopardize supply if that manufacturer has problems. This is

SESSION 2: APPLICATION OF RISK-BASED PRINCIPLES TO MULTIPRODUCT FACILITIES

In session two, presenters described risk-based approaches to multiproduct facilities, specifically, approaches in cleaning validation and case studies from industry. The session included explanations of how using different quality risk management (QRM) tools to address diverse multiproduct facility problem statements may influence risk-assessment outputs and associated control plans. Discussion topics included leveraging QRM to determine appropriate cross-contamination controls for multiproduct facilities. Discussion focused on questions highlighted in the text.

Julia Edwards (Genentech) chaired this session. Presenters were Karen Williams (ImClone), Jenna Carlson (Genentech), and Kristin Murray and Stephen Reich (both with Pfizer). The panel comprised the presenters with Patrick Swann (CDER, FDA).

both a major business risk and potentially a risk to patient safety. If faults in disposables cause a high cost in failures, part of the business risk can be factored into the choice of systems. Industry will likely drive this choice, which is not likely to be all-or-none. It is more likely that hybrid systems involving combinations of materials and systems will evolve.

The question was asked, "Can there be a future with interchangeable disposables?" Possibly. However, the source plastic is not necessarily intended for pharmaceutical use where quality and consistency standards are the very highest. Plastic compound quality can vary greatly from vendor to vendor. Vendor companies will require incentives to produce the quality of disposables required for pharmaceuticals, and that could make them prohibitively expensive in some cases.

The FDA expressed concerns about robustness of manufacturing processes worldwide (e.g., leachables and leaks), which could cause contamination of facilities and/or products. As always, the agency expectation is high-quality products manufactured consistently to your regulatory commitments with a

high degree of assurance that each batch will be safe and effective.

SESSION 2: APPLICATION OF RISK-BASED PRINCIPLES

Does the execution of complex QRM approaches enhance or limit network flexibility?

Two case studies were presented that showed the attendees both process and facility details and the risk-assessment and risk-management strategies the companies used. Both did extensive ‘paper exercises’ with tremendous mining of information using quality tools, followed by targeted data collection — bench, worst-case, challenge studies, then routine, full-scale — to verify the assumed outcomes of the risk assessment.

A panel member stated, “The risk in using QRM is what you do with the data. The risk is how we might use or interpret the data.” Over-assessing is unlikely and will be more unlikely as companies become accustomed to using the risk-assessment tools and have the right team of experts looking at the data that have been collected. The risk assessment should always be facilitated by a leader trained in the tool. It is also important to remember that a risk assessment is a living document. It will and should be revisited, with changing results, throughout the lifetime of a product.

What are the limitations of applying QRM principles in the design of an MPF producing products for a global supply chain? How could such challenges be overcome?

There are no limitations to appropriate application of QRM tools. They are designed to help identify components and gauge the magnitudes of risk elements. However, tools don’t make the final decisions — they help you justify the decisions you make. Whatever tools you use, they need to be used by people trained to use them, working with all relevant subject-matter experts. Otherwise, the exercise will be flawed.

Although companies observed consistency among global regulators in accepting the risk-assessment exercise as useful, they did not see global consistency among regulators in accepting the outcome of the risk

SESSION 3: PROCESS- AND PRODUCT-SPECIFIC CONSIDERATIONS

Session three began with an update on the PDA Task Force for Single-Use systems. Industry experience was then presented, including the special considerations necessary to operate and control manufacture of concurrent processes for biotechnology products. The regulatory perspective for biotechnology and classic biologics from an inspectional viewpoint was also discussed. The central questions included those highlighted in the text.

The session was chaired by Bo Chi (CDER, FDA). Presenters were Robert Repetto (Pfizer), Carla Rumazza (BMS), Jun Park (CDER, FDA), and Nancy Waites (CBER, FDA). The speakers were joined on the panel by Martin Nemeč (Health Canada).

assessments (e.g., the degree of acceptance of risk). Regulators encouraged proactive discussions among all global regulators to better understand the sources of their concerns for product quality risks and to factor those concerns into risk assessment discussions. For example, CBER expressed concerns about nondedicated direct contact equipment (which could be covered in risk assessments). It was agreed that, as always, the best approach is to engage regulators in discussions early and often.

Although QRM is important, what cross contamination controls are critical to successful MPF strategies in the absence of a formal risk assessment? Before ICH Q9 and the more widespread use of QRM tools, there was more uncertainty and consequently many more restrictions on operations. Industry did a lot of testing and had less regulatory flexibility. Although there is no change in baseline best practices, there is now a greater awareness of risks as a result of using QRM.

The question was asked, “Do you always have to use a formal risk assessment tool, or is a technical narrative sufficient for regulators?” ICH Q9 states that in general, you do not have to use a formal risk assessment tool. However, MPFs are

highly complex, highly risky ventures, and they should be approached with the most formal strategic mechanisms available to ensure regulatory — and thus business — success.

How might the use of the “wrong” QRM tool influence the risk assessment outputs and resulting control plan? When the right group of experts is involved, the highest risk items seem to be quite consistent whether you use a formal tool or not. The group saw examples of four different MPF-relevant scenarios that were assessed with very different QRM tools (some not the most frequently used in biotechnology) as examples of the diversity of approaches that can be tried.

The question came up, “Are there any orthogonal ‘calibrations’ of the QRM tools to verify the outcomes of the risk assessments performed?” Some groups stated they do perform reassessment of the risks using different tools, or on different days, to see how closely the results match. You may get different risk profiles, but it’s still beneficial to use QRM tools to get a handle on the source and nature of the risks. Rankings may change a bit over time with increased experience with the process, product, and facility.

What are appropriate cleaning validation limits and approaches? What studies and analyses can be performed to reduce the amount of testing required during cleaning validation? Are there any circumstances, for example in vaccine manufacture, in which it is acceptable to use the same direct product contact equipment (e.g., filling needles, pumps, formulation vessels) for multiple products? Appropriate cleaning validation limits and approaches include applying US and European pharmacopea (USP, EP) limits, minimum and maximum dose limits, or acceptable daily exposure (ADE) toxicology limits. The 2010 ISPE *Baseline Guide* can be used for setting the maximum allowable carryover (MAC) based on ADE. Some companies use ≤10 ppm product residue as the cleaning validation limit for shared equipment. The FDA has

stated that whatever approaches are used they should be conservative and based on the specific products under consideration. The agency would expect to see justification and rationale for the chosen approach and limits.

CBER concerns regarding direct contact equipment are for the control of aseptic filling operations. It is tough to justify nondedicated direct contact equipment because the risks to patients are quite high in the case of a system contamination. You might be able to justify use of the same direct contact equipment if you were to generate enough data, but do you really want to?

SESSION 3: PROCESS- AND PRODUCT-SPECIFIC CONSIDERATIONS

Under what circumstances is concurrent manufacture feasible?

What are some of the product-specific challenges and limitations? Regulators answered, "It depends." If you have adequate design and controls to mitigate any type of cross contamination, mix-up, or other issues previously discussed with data to support it, then perhaps concurrent manufacture would be feasible. Actual concurrent manufacturing operations would require closed operations, pressure tests, filter integrity tests, and adequate procedure controls, including suitable cleaning procedures and personnel and material flow.

A Health Canada representative suggested that concurrent manufacturing may require procedural limits on the number of concurrent activities that can take place in a given facility. Product-specific limitations would be based on the nature of the materials (e.g., BL2, BL3, highly toxic, highly immunogenic).

FDA representatives indicated that keys to success with an MPF include early dialogue with the agency (such as Type C meetings) with well-informed strategies designed to get meaningful input from FDA. Keep regulators in the loop as things evolve. The worst possible approach is to provide everything in one prior-approval supplement as a fait accompli.

The question of concurrent manufacturing may have implications beyond concurrent manufacturing operations. It might also be reflective of flexible manufacturing processes. Perhaps this concept could enable a single product to be produced at different scales depending on the production needs over time

Presentation of PDA Technical Report for Single-Use Systems: A PDA task force conducted a survey of members regarding use of single-use systems. Certain questions and answers came up consistently among most users, and the technical report attempted to outline and address those issues. The technical report team found that the most important factor in success is dialogue between users and suppliers on what is needed for implementation, including technical, regulatory, and quality issues as opposed to focusing only on what is technically possible.

From its survey, the PDA developed a technical document establishing a framework by which organizations can establish a manufacturing strategy for implementing single-use technologies with special consideration for their individual needs, goals, and competencies. A successful manufacturing strategy must balance business and industry drivers to ensure that the primary customer-based goals of patient safety, product availability, and product and process understanding are met when implementing new technologies. The report presents a flexible approach for achieving those goals by outlining science- and risk-based considerations for technologies and system integration, business drivers, qualification, and implementation.

With regard to traceability for single-use systems, how can you assure that any adverse event can be linked to a single-use system if needed? As part of the GMP requirements for documentation of all materials and components, any batch should be traceable. However, needing to go back to a supplier may be problematic. An audience member illustrated that point by describing an

experience with base film used in his company's single-use system. In that case, it was difficult to even define what a batch was, because the material is a continuous film cut in sections. The BioProcess Systems Alliance, a consortium of single-use systems users, is looking at those sorts of issues.

Someone asked whether variability in disposables in single-use systems is more a business risk than a product-quality risk. It is, of course a business risk. It is a major issue in the future success or failure of the biopharmaceutical industry to widely adopt disposables. Because only a small percent of the plastic produced by suppliers is purchased by the biopharmaceutical industry, it is unlikely that the industry will have much influence on the quality of the base compounds used in plastic resins. GMPs apply back through the supply chain, so it may be necessary for the industry to push back to have the plastics industry control variations in its incoming materials.

Going beyond facility controls to the product itself, what elements of detection and control for cross-contamination (e.g., identity testing, adventitious agents detection) are important? This question initiated focused discussion on identity testing as an important detection control for cross-contamination. The potential for a CMO MPF that could produce both an innovator product and a biosimilar of that product was discussed as an example. The panel also discussed other potential scenarios, including implications of identity testing if two competitor innovator products were being produced by the same CMO or two versions of an innovator product (e.g., first- and second-generation products).

In the case of identity testing, a company does need to be able to distinguish one product from all of the other products likely to be present in the facility to meet 21 CFR 610.14 requirements. The question was asked, "When would regulatory agencies expect to see actual ID testing as opposed to barcode and certificate of compliance documentation? An FDA

representative responded that identity testing is required for raw-material testing, but experiences varied depending on stage of manufacture (drug substance or drug product), different inspectors, and different groups within the agency (e.g., CDER or CBER). A Health Canada representative indicated that they do not require ID testing upon receipt of active pharmaceutical ingredients (APIs).

A representative from Boehringer Ingelheim GmbH indicated that the company tests identity upon receipt as a talk sample. Distinguishing one product from all others is easy enough to do if a CMO is working for a sole sponsor. However, in cases in which multiple products are produced by a CMO, that task can be more difficult given confidentiality requirements.

What additional controls are needed for QRM in the case of a multi-product operation? Both FDA and Health Canada provided comprehensive overviews of what controls are expected in an MPF. Those presentations were tied to each country's laws and guidances. For an industry perspective, Carla Rumazza (BMS) presented a comprehensive case study of the company's MPF strategy. Regulators and industry were consistent in including elements of physical segregation and procedural controls in their overall MPF control strategies.

The company's risk assessment revealed that they would need to ensure primary segregation (physical and facility controls) and secondary segregation (engineering, process, temporal, and procedural controls). She further described the steps necessary to implement concurrent manufacturing, which included the following elements highlighting the complexity of implementing concurrent MPF operation:

- Facility personnel flow SOPs were harmonized to ensure and safeguard concurrent manufacturing.
- SOPs were created or revised regarding column and resin tracking and material flow.
- Detailed control documents and check lists were needed before

SESSION 4: REGULATORY STRATEGIES FOR MULTIPRODUCT FACILITIES

This session included presentations and discussions on the expectations for multiproduct facilities from global regulatory authorities. Possible strategies intended to facilitate the dossier review and inspection of multiproduct facilities were also discussed.

Session four was cochaired by Jun Park (CDER, FDA) and Nancy Waites (CBER, FDA). Presenters were Kathleen Sniff (Amgen), Julia Edwards (Genentech), and Martin Nemeč (Health Canada). The presenters were joined on the panel by Bo Chi (CDER, FDA).

implementation of concurrent manufacturing.

- Degradation studies were required.
- Coupon studies and TOC method validation were necessary.
- Clean systems were calibrated.
- Personnel were trained in the new SOPs.

Both regulators and industry were in agreement that QRM must consider the risk to patient safety. A robust QRM program must identify all potential risks to product, process, and facility. And it must be demonstrated that procedural and detection controls adequately reduce those risks to acceptable levels.

Questions included in the risk assessment included how compliance with procedures used for concurrent manufacturing operations are verified. For example, compliance with procedural controls such as changing gloves is extremely difficult to monitor. It is imperative that a quality system adequately track and trend deviations, training, and corrective and preventive action (CAPA) when necessary.

How can a holistic approach to cross-contamination controls be developed keeping in mind facility, equipment, and product? Can QRM be effectively applied in such an approach? Data-driven approaches are the most successful. QRM can be applied, but isn't "one and done." It is an iterative strategy that must be

reviewed and updated over time. For example, new sources of risk may be discovered given changing circumstances of findings of quality investigations. QRM, when done properly, is holistic and iterative. However, implementation of a truly holistic QRM program is complex given the variety and extent of multiproduct operations and variety of tools and approaches offered by ICH Q9.

The presenters reached general agreement that the value of QRM is significant for a business, although not always considered a regulatory requirement by health authorities. QRM, when executed in a comprehensive and systematic manner, provides a degree of transparency to a sponsor's decision-making process that presents well during health authority audits and regulatory submissions. Currently, FDA/CBER does not require a formal and documented risk assessment. FDA/CDER does require risk assessments for high-risk, highly potent products in MPFs and strongly recommends it for all MPFs. A well-executed risk assessment can raise the agency's confidence by clearly providing rationale and justification for design and control decisions made in setting up MPFs.

Julia Edwards of Genentech reported on its Super eCP, representing the "ultimate holistic approach." The company established risk-based controls and requirements for introduction of a commercial product at a facility licensed only for single-product operations, introduction of a clinical product at a facility licensed for production of commercial products, and introduction of a product derived from a host cell not currently licensed for production at the facility. Genentech excluded highly toxic or highly potent products and "layered" the regulatory filing strategy based on the degrees of risk.

SESSION 4: REGULATORY STRATEGIES
What are the highest priority items regulators look for regarding an MPF during inspection? FDA has particular concerns around shared equipment, open processes, and animal-derived

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raw materials. Regulators will look for evidence of how a sponsor is effectively and continually mitigating those risks. Health Canada added segregation of materials to that list and noted that special emphasis is due treatment and management of closed systems. An industry participant reported that an inspector had taken the company's risk assessment and used it as a road map as he walked through the facility to verify all elements were in fact being handled properly as per the risk assessment.

Jun Park, CDER spoke about the FDA's view. Because of the complex structures of biotech products, extensive characterization is required. He talked about identity testing, which must be able to distinguish one product from another similar product or the two will be prohibited from being manufactured concurrently or a new identity assay will have to be developed for one or both. Identity assays must be requalified and revalidated for each product they are used to identify.

Nancy Waites, CBER, discussed control of raw materials, cross-contamination between products, workers alternating between processes and types of products, and cleaning difficulties. She stressed that a facility must be designed for the highest containment that will be required there. Nancy also spoke about product changeover, defined as a "logical series of steps performed to assure that the multiuse processing suites and equipment have been properly cleaned

before processing a different product." The procedure must be detailed in a standard operating procedure (SOP).

Martin Nemeč (Health Canada) detailed what constitutes a "contaminant": particulate matter, adventitious biological agents, foreign chemical substances and carryover (cross-contamination), sources of contamination, and means of segregating or protecting products from contamination. In Canada, "Premarket submission review of biologics quality. . . comprises three concurrent processes: review of paper/electronic dossier, the new drug submission (NDS); on-site evaluation, and laboratory assessment of product consistency." He then went into detail about facility information required for the NDS, which is extensive.

Does submission of a robust MPF strategy as part of the BLA help companies during inspection? Which elements should be in a dossier, and which should be left for inspection?

Health authority inspectors generally appreciate a robust MPF section in a BLA. By providing thorough descriptions of all elements with justification and rationale for acceptance criteria, including a discussion of how they are controlled, and presenting the details on the facility construction, you can help inspectors focus on key issues during inspections.

The observation was made that FDA district inspectors may have different expectations for MPFs for biotech products. CDER is working diligently with districts in improving understanding of biotech products and processes and associated expectations.

As a sponsor, it's a good idea to do whatever you can to help improve communications with district inspectors on background information that supports QRM. Amgen shared positive feedback from providing information on its risk assessment and QRM to district inspectors to actively navigate the inspection of MPFs with sufficient rationale and justification.

There was general consensus among attendees that little is understood regarding global requirements for MPFs. It was agreed

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that the US FDA, Health Canada, and the EU were easier to predict than other jurisdictions. Other regions were declared "very challenging," but those challenges must be resolved if global supply chains are ever to be improved and expanded. It was pointed out that global regulatory concerns are becoming more important as sponsors experience diminishing returns on legacy products and some products are nearing the end of their life cycle.

Someone asked, "Now that FDA is member of the Pharmaceutical Inspection Cooperation Scheme or PIC/S, has it seen any significant impact on prior guidance for reviews or inspections?" So far, audience members have seen no noticeable differences on the biotech side. However, there is an inspection harmonization effort underway with FDA and EMA.

Amgen's and Genentech's case studies at this forum demonstrated that your approach must be practical and pragmatic, but that doesn't mean you can't be creative in finding efficiencies and successful nested strategies.

FDA agreed that change protocols (CPs) make their lives easier by streamlining their review efforts and helping their workload. CPs improve inspection processes when harmonized operational elements are in evidence at all sites. A well-designed, well-executed eCP (enhanced change protocol) helps improve a sponsor's ability to maintain control and consistency of global operations. FDA has frequently seen gaps and disconnects in multisite inspections, especially in international sites.

A robust MPF strategy offers many

advantages, including QRM, assessment of options, and presentations to regulators. Regulators expressed appreciation for submissions leveraging sound scientific strategies such as those presented at the forum by industry representatives, which give them more confidence in common best practices. Regulators will try to remember that just because something is different or new doesn't mean it's wrong; but they will likely have many questions for you to explain and justify why it can be right. 🌐

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