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Pandemic's Impact for Supply Chain:

Regulatory Approaches to Manage Supply Chain Challenges for Single-Use Systems

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

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Drugs are no different.


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Pharmaceutical quality is
assuring *every* dose is safe and effective, free of contamination and defects.
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It is what gives patients confidence in their *next* dose of medicine.
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Outline

- Current single-use system (SUS) supply constraints
- Regulatory management of post-approval changes to SUS
  - Approaches for reportable and non-reportable changes
  - Role of Pharmaceutical Quality System (PQS) and Quality Risk Management (QRM)
  - Proactive approaches
- Case studies
- Conclusions

Single-Use System (SUS)

- SUS are ready-to-use, closed and disposable bioprocessing equipment consisting of integrated and pre-sterilized components.
  - Components are most often sterilized using gamma irradiation.
  - A definition:
    - "An engineered process and equipment solution, most commonly assembled from components made using polymeric materials, which together create a system or unit operation design for time campaign use" (PDA TR 66).
  - Examples of SUS:
    - A sterile filling train composed of a set of sterile disposable bags, tubing sets, connectors, and filling needles.
    - A single use bioreactor composed of disposable sterile tank liner bags, tubing sets and connectors.
    - A SUS bag with an inline bioburden reduction filter and various tubing sets and connector devices for holding column fractions.

PDA technical Report 66, "Application of Single-Use Systems in Pharmaceutical Manufacturing

Current Supply Challenges

- SUS have been widely used in biomanufacturing for the last 5-10 years.
- Market demand is increasing due to a significant increase in the production of sterile drug and biologic products.
- Biopharmaceutical industry is experiencing challenges for the continued availability of the SUS for biomanufacturing:
  - Supply chain under stress with delayed deliveries:
    - Lead times for orders has increased from months to years.

B. Cox, Pink Sheet 13 Jul 2921, "Pandemic Response Strains Global Biopharmaceutical Reactor Capacity"

Advantages of SUS

- Present advantages over traditional stainless-steel equipment or other multiuse equipment:
  - Provide for manufacturing flexibilities:
    - Simplified requirements for facility design, environmental controls and product changeover.
    - Streamlined manufacturing site transfers with the similar SUS process equipment.
    - Allow for improved microbial and cross contamination process control:
      - Operated as closed systems with integrated system components sterilized by gamma irradiation.

Supply Demands Continue to Increase

- Driven by a combination of factors, including:
  - Global market for biological products continues to expand.
  - Increasing adoption of advanced biomanufacturing technologies with high reliance on SUS:
    - Process intensification, continuous manufacturing, disposable sensors.
  - Current public health emergency (PHE)
    - Certain supplies of SUS prioritized with the implementation of the Defense Protection Act for COVID-19 therapies and vaccines.
    - SUS enable the availability of COVID-19 therapies with speed by providing manufacturing flexibilities during manufacturing site changes and product changeover.

SUS Supply Constraints

- Other factors:
  - Few or single-source suppliers:
    - Manufactures of SUS are concentrated in the US and Europe.
  - High degree of customization and lack of overall standardization:
    - Single-use components from different suppliers are always not interchangeable and replacement of components from different suppliers is not feasible.
  - Shipping/distribution disruptions during the PHE.

PDA COVID19 Task Force Webinar, "Mitigating Shortages of Critical Manufacturing Supplies During a Global Pandemic" June 7, 2021; PDA/PwC Poll April 2021

SUS Supply Constraints (cont.)

- More factors:
  - Most SUS are sterilized with gamma–irradiation using radioactive cobalt-60
    - Demand for gamma-irradiation is exceeding capacity and is increasing.
    - Limited construction of new gamma irradiation sites.
    - Lead time for SUS deliveries has increased due to a backup at the gamma sterilization sites.
      - Irradiation sites are highly regulated.
      - Few irradiation sites are available worldwide (mostly in Ontario, Canada).

BPSA "X-Ray Sterilization of Single-use Bioprocess Equipment; Part 1 – Industry Need, Requirement and Risk Evaluation" 2021 (https://bpsalliance.org/pdf-download-form-xray-part1/)

Role of FDA

- FDA has recently received reports of SUS supply chain constraints and potential drug supply disruptions.
- FDA has and will continue to provide feedback to sponsors/applicants and mitigate shortages of medically necessary drugs.
- The following slides will provide an overview of some of the regulatory approaches that may be considered to address SUS supply constraints.
  - Focus on biological products, but the same approaches are applicable to other sterile drug products.

Managing Post-approval Changes

- Changes to an application must be managed in accordance with:
  - Applicable regulatory requirements described in 21 CFR 314.70 and 601.12.
    - Post-approval changes are categorized into three reporting categories (prior approval supplement [PAS], changes being effected [CBE30/CBE] or annual reports [AR]) based on the potential to have an adverse effect on product quality (major, moderate, or minimal).
- Guidance recommendations on how to comply with requirements are provided in several FDA Guidance documents.

https://www.ecfr.gov/current/title-2 https://www.fda.gov/drugs/guidance-compliance-regulatory-information 1;

FDA Guidance on Post-approval Changes

- Relevant guidance for biological products:
  - Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, 1997 (https://www.fda.gov/media/75318/download)
  - CMC Postapproval Manufacturing Changes for Specified Biological Products to be Documented in Annual Reports, 2021 (https://www.fda.gov/media/106935/download)
  - Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products, 2021 (https://www.fda.gov/media/109615/download)
  - Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls information (R1) draft 2016
  - Q12 Technical and Regulatory Considerations for Pharmaceutical Products Lifecycle Management, 2021 (https://www.fda.gov/media/148476/download)
  - Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2016) (https://www.fda.gov/media/71518/download)
  - Q9 Quality Risk Management (2006) (https://www.fda.gov/media/71543/download)
  - Q10 Pharmaceutical Quality System (2009) (https://www.fda.gov/media/71553/download)

Examples of Post Approval Changes

- Potential changes to mitigate SUS supply constraints:
  - Change of suppliers (with or without a change in product contact material).
    - Different suppliers of filters, bag or connector systems.
      - Qualifying alternate suppliers of SUS.
  - Change similar components of different material or design.
    - Different process configuration; connectors, tubing, sampling bags, etc.
    - Change from bags to stainless steel tanks; reduce usage of SUS
  - Reduce the number of SUS components used in the manufacturing process.
    - Removal of redundant sterilizing filters.
  - Extend the use of components by increasing throughput.
    - Reduction of filter changeouts; reduce usage.
  - Qualify the re-use of components.
    - Reuse of vent filters.
  - Standardize SUS use across processes and manufacturing sites for part interchangeability.

Post-approval Changes: Reportable and Non-reportable

- To manage post approval changes, applicants should:
  - Review existing FDA regulations and guidance
  - Perform a thorough risk assessment before addressing SUS supply chain constraints in accordance with ICH Q9.
  - Determine the appropriate post-approval submission category to communicate post-approval changes to the FDA.
  - Manage changes to SUS not described in an application within the firm's pharmaceutical quality management system (PQS) (ICH Q10).
    - Non-reportable changes are the lowest risk changes to product quality and may be verified during routine or other inspections.

PQS and QRM

- Pharmaceutical Quality System (PQS) is a management system to direct and control a pharmaceutical company with regard to quality (ICH Q10)
  - All CMC changes to an approved product should be managed through a company's PQS.
- Quality Risk Management (QRM) is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle (ICH Q9).
  - Integrated within the PQS and supports compliance with regulatory requirements.

Risk Assessment

- Applicants should perform a risk assessment to identify and address risk factors associated with a change in a SUS.
- Some risk factors to consider:
  - Intended use of the SUS in the manufacturing process and impact on product quality (risk level and associated impact on product quality).
    - E.g., Examples of high-risk changes are those involving a final product sterile filtration or viral filtration.
  - Presence of other risk reducing mitigating factors.
    - E.g., Use of redundant filtration steps with closed processing.
  - Process knowledge acquired over a product lifecycle
    - Extent of available supporting data.
  - Ability of in-process analytical and release methods to detect differences in product quality attributes.

Guidance Examples of PAS Reportable Changes (High Risk)

- Drug substance:
  - Change from a stainless steel to disposable (e.g., bag) bioreactor or vice versa.
  - New or revised recovery procedures
  - New or revised purification process
  - Change in the method(s) for virus or adventitious agent removal or inactivation.
- Drug product:
  - Addition, deletion, or substitution of unit operation(s) or change in their sequence.
  - Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion, or substitution of steps in an aseptic processing operation.
  - Change in a membrane material or dimensions of the final sterilization filter.

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, 1997; Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products, 2021

Guidance Examples of CBE-30 Reportable Changes (Moderate Risk)

- Drug substance:
  - Change in the filter or resin supplier with no change in the resin material, operating or performance parameters.
  - Addition or reduction in number of pieces of equipment (e.g., filtration devices, etc.) to achieve a change in purification scale not associated with a process change.
- Drug Product:
  - Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology, process operating parameters or aseptic processing.
  - Change to a final sterilization filter supplier with no change in material, dimensions, or sterilization method.
  - Changes to sterilization cycles for sterile product contact equipment.

Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, 1997; Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products, 2021

Guidance Examples of Annual Reportable Changes (Minor Risk)

- Addition or replacement of equipment of the same size and material of construction used in harvesting and pooling with no change in the process parameters specified in the approved BLA.
- For sterile drug products, change to ranges of filtration process parameters that are within previously validated parameters.

Proactive Approaches to Manage Supply Constraints

- Use of comparability protocols per 314.70(e) or 601.12(e):
  - May allow for a less burdensome reporting category.
- Requests for expedited reviews
  - Certain conditions must be met.
- Implementation of ICH Q12
  - Identification of established conditions (EC) and use of a Postapproval Change Management Protocol (PACMP).
  - Allows for efficient and less burdomsome management of changes throughout a product lifecycle.
- Low risk non-reportable changes managed through PQS and QRM.
  - Changes to SUS not described in the eCTD.

Comparability Protocols (CP)

- A CP is a written plan for assessing the effect of a proposed CMC change(s) on product quality.
  - Submitted as part of the original application or a PAS
  - A CP when approved may justify a less burdensome reporting category.
  - Proactive approach to change management:
    - Provides early feedback from FDA.
    - Provide greater predictability for implementing CMC changes.
    - Allows for an earlier distribution of products with the CMC changes.
    - May allow for a more efficient management of supply chain.

Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, draft (R1), 2016.

Scope of a CP

- May cover one or more proposed changes.
- Should contain supporting information (any analysis and risk assessment activities), a plan for implementing the change(s) and the proposed reduced reporting category.
  - Used for a one-time change(s) or used repeatedly for a specified over the lifecycle of a product.
  - May cover identical change(s) that affects multiple applications (group supplements or trans-BLA submission).

Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, draft (R1), 2016.

Limitations of the CP Approach

- An approved CPs may not be able to support a lower reporting category for the change and ensure product quality and patient safety:
  - Insufficient understanding of impact on product or process
  - CGMP compliance status of the facility not acceptable
  - Where data from nonclinical safety, pharmacokinetic/pharmacodynamic, and safety and efficacy studies are needed to evaluate the effect of changes on product quality.

Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, draft (R1), 2016.

Requests for Expedited Review

- Applicants can request an expedited review of supplements.
- MAPP 5310.3 (R2) "Requests for Expedited Review" describes CDER's Office of Pharmaceutical Quality (OPQ) policies for granting or denying a request to conduct an expedited review for a new PAS.
- Expedited reviews will be conducted:
  - When a public health need arises with or without a request from an applicant.
  - Requests will be considered on a case-by-case basis
  - Review completion date will depend on the availability of OPQ's resources and the rational for the expedited review.

Considerations for Expedited Review

- Supplements may be granted an expedited review in the following situations:
  - Drug shortages - to resolve a shortage.
  - Special review programs - such as the President's emergency plan for AIDS relief.
  - Public health emergencies (PHE).
  - Certain government purchasing programs.
  - Statutory mandates or other legal requirements – to comply with Federal or State mandates or other legal actions.
  - Extraordinary hardship on the applicant
    - Review for public health reasons or if a delay would impose and extraordinary hardship on the applicant (catastrophic or unforeseen events).

Role of ICH Q12

- ICH Q12 is a tool that can enable post-approval changes in a more predictable, efficient and prospective manner over the lifecycle of a product.
  - Clarifies which elements in an application assure product quality:
    - Defines established conditions (EC) are legally binding elements required to assure to assure product quality.
    - A change in an EC necessitates a submission to the FDA.
  - Describes the Post-approval Change Management Protocol (PACMP):
    - A proactive regulatory tool similar to the CP
      - Allows for the planning and implementation of future changes to EC.
    - Approved in advance of the protocol execution and allows for a lower reporting category and or shortened review period.
      - Submitted as part of the original submission or a PAS
    - Two step process is described in ICH Q12.

Postapproval Change Management Protocol (PACMP)

- Step 1: A PACMP is submitted as a written protocol in the eCDT Module 3.2.R.
- The protocol should consist of:
  - A description of proposed change(s) and rationale(s)
  - A risk assessment and based on identified risks to product quality, a list of specific tests and studies to be performed to evaluate the impact of the proposed change(s).
  - Any changes to the approved control strategy.
  - Confirmation that certain process qualification step will be completed before implementation.
  - Any additional supportive information from previous experience with the same or similar products.
  - The proposed reporting category for the change(s) for step 2

Postapproval Change Management Protocol (PACMP) (Cont.)

- Step 2: Involves PACMP execution:
  - Results from the executed protocol studies are submitted for review to the regulators (e.g., FDA).
  - Based on the reporting category the approval for change implementation may or may not be required.
  - If the acceptance criteria and or other conditions are not met the change cannot be implemented.
    - In this situation, existing regulation and guidance and the associated reporting category must be followed.

FDA Feedback on SUS Supply Constraints

- FDA has and will continue to provide feedback to sponsors/applicants:
  - Feedback is intended to prevent shortages/disruptions of medically necessary drugs.
  - Applicants should be ready to provide all relevant information to obtain relevant FDA feedback:
    - A list of affected product(s) and processes(s);
    - A description of the proposed changes to mitigate effects of the component shortage on product quality and supply;
    - Involvement of other products and /or manufacturing facilities (including CMOs) and
    - Any information related to potential or actual drug shortage concerns.

FDA Feedback

- Feedback should be obtained prior to submitting a change in a lower reporting category supplement than is required by regulation or recommended through guidance.
- Applicants should contact the FDA in the event of supply chain interruptions:
  - Use of atypical or flexible submission strategies may be warranted.

FDA Contact Information

- For impending or existing shortages contact:
  - for products regulated by CDER: DRUGSHORTAGES@FDA.HHS.GOV);
  - for products regulated by CBER: cbershortage@fda.hhs.gov
- For additional questions for
  - CDER products: CDER-OPQ-Inquiries@fda.hhs.gov;
  - CBER products: applicants should contact the appropriate CBER review office.

Case study 1: Change in Drug Product Sterilizing Filter Suppliers

- An applicant proposed to use alternate suppliers of sterilizing grade filters and proposed to submit a PAS.
- The PAS would include the following information and data:
  - A description of the alternate filter, including differences ad similarities with the approved filter.
  - Small scale data from characterization studies designed to support process or product quality.
    - Including product specific microbial retention studies and supporting media fills.
  - An update of the eCTD to include the use of alternate filters.
- The applicant committed to submit at scale production data from one run in an AR once the change was implemented.
- FDA agreed with the submission approach and the supporting scale-down data in the PAS.

Case study 2:
Use of an Alternate Viral Filtration Filter

- An applicant proposed to submit a PAS to support the use an alternate viral clearance filter.
- FDA provided the following feedback:
  - Agreement with a PAS submission to support the use of an alternate viral clearance filter.
  - Commented that performance of virus clearance studies could be applicable to multiple products depending on the similarity of the virus filtration parameters for different products.
  - Recommended that execution of virus filter validation studies be conducted under worst-case conditions for each product or each generic /modular study.
  - Recommended that virus clearance levels be recalculated and provided in the PAS.
- The applicant committed to provide at-scale data in an AR once the change was implemented.

Case Study 3: Use of Alternate Filters

- An applicant proposed to communicate the use an alternate bioburden reduction filters (e.g., drug substance intermediate and final drug substance filters) in an annual report (AR).
- Approved supplier of filters was listed in the eCDT.
- FDA agreed with the filing categorization and recommended the following:
  - Filters from different suppliers be shown to be interchangeable based on scale-down studies (performance, compatibility studies).
  - Established bioburden limits prior to any bioburden filtration step remain unchanged.
  - The eCDT be updated to include the use of alternate filters.

Conclusions

- Several regulatory approaches are available to manage post-approval changes needed to address current and future SUS supply chain constraints:
- For reportable changes -
  - Use of existing FDA regulations and guidance to determine submission reporting categories.
  - Use of comparability protocols to efficiently manage necessary changes
    - May allow for downgrading reporting categories.
  - Use of expedited review requests under certain conditions.
    - To resolve an impeding drug shortage.
  - Implementation of ICH Q12 and proactive use of PACMP to manage change over the lifecycle of a product.
    - Less burdensome approach.
  - Use PQS and QRM in managing changes.

Conclusions (cont.)

- For non reportable changes:
  - Lowest risk changes to product quality not described in an application are generally not reportable
    - Should be managed within a firm's PQS and QRM
    - May be verified during a routine inspection.


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