Risk management and application approaches in responding to supply chain constraints during the Public Health Emergency (PHE)

FDA SBIA COVID19 Manufacturing, Supply Chain, and Inspection Webinar
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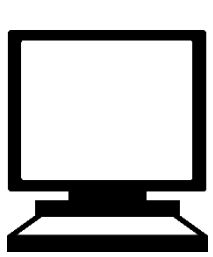
Pharmaceutical Quality

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



Pharmaceutical Quality

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

Drugs are no different.


Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their *next* dose of medicine.

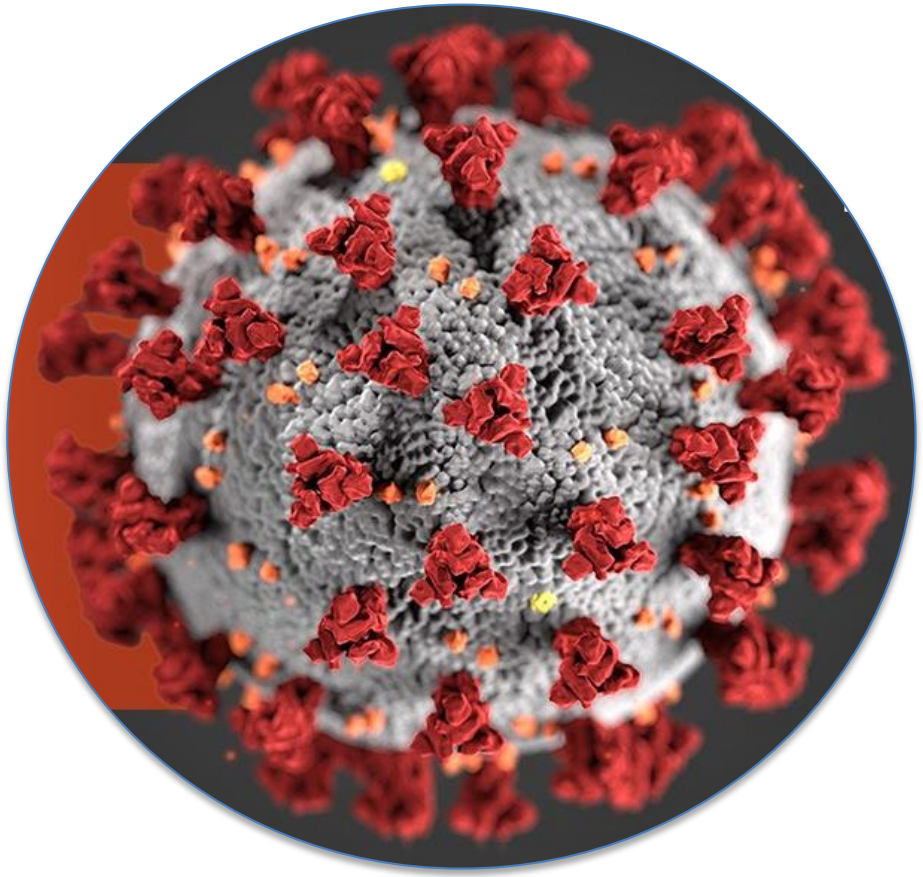
Outline

- Landscape
- CDER’s manufacturing and supply chain efforts
- Available application tools
- Concluding Remarks

Challenges of the COVID-19 Pandemic on Drug Manufacturing

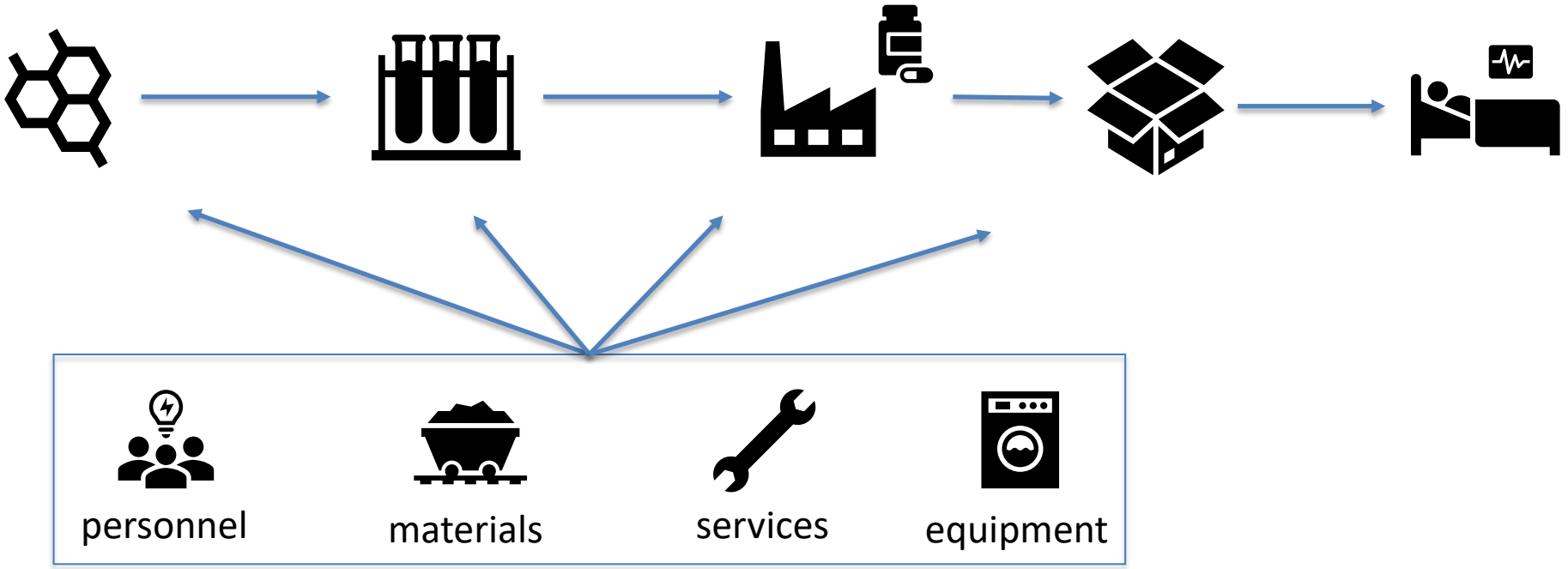
Long-existing quality issues are now magnified

- Information about current state of drug manufacturing and distribution
- Supply chain vulnerabilities
- Shortages due to manufacturing and distribution issues



Supply Constraints

The supply chain supporting the manufacture of FDA-regulated products has been impacted at multiple levels during the COVID19 public health emergency (PHE).



Supply Chain Challenges

- As a result, manufacturers of FDA-regulated products have found it necessary to make changes to meet current product demand or increase supply resilience, e.g.:
  - New material sources
  - New equipment
  - Additional manufacturers
  - Moving production to create capacity

Supply Chain: Risk Management Focus

- Coronavirus Aid, Relief, and Economic Security Act (CARES Act), enacted March 27, 2020:
  - includes a provision requiring manufacturers of certain drugs, or of any API or any associated medical device used for preparation or administration included in the drug to develop, maintain, and implement, as appropriate, a **redundancy risk management plan that identifies and evaluates risks to the supply of the drug**, as applicable, for each establishment in which the drug or API is manufactured

FDA/CDER COVID-19 Manufacturing and Supply Chain Initiatives

- Goals:
  - Provide clarity to industry on how to make facility and manufacturing changes needed to respond to disruptions in the global supply chain
  - Expedite assessment for drugs in shortage or drugs needed for COVID-19 response to ensure continuity of essential medications to patients

- Activities:
  - Provide direct feedback to inquiries on CMC changes and strategies related to COVID-19 response
    - Contact: CDER-OPQ-Inquires@fda.hhs.gov
  - Develop & Issue guidance and communication on CMC changes and strategies for COVID-19 response
  - Close collaboration with CDER Drug Shortage Staff

FDA/CDER COVID-19 Manufacturing and Supply Chain Initiatives

- From the start of the PHE - August 2021:
  - Fielded ~150 inquiries related to CMC change strategies
  - Facilitated approval of over 800 CMC supplements for products used in the treatment of patients with COVID19

CDER Active Engagement - Examples

- Guide applicant on strategy to execute complex changes to drug substance manufacturing, including new starting material sources, new drug substance manufacturing sites
- Provide feedback on extent of stability data needed to support a change
- Use grouped supplement pathway to qualify release and stability testing laboratory for dozens of products
- Provide feedback on strategy to qualify sterilizing filters, as well as appropriate filing category

Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers

- Guidance for Industry
- Provides insight into how FDA intends to approach inspections during the PHE
- Highlights how applicants can approach CMC changes for facilities and manufacturing processes
  - Risk based adjustment of reporting categories
  - Expedited assessments
  - Flexible submission strategies, including adjusting submission data requirements
- Provides reference to supporting CMC change guidance documents
- Link provided on the “resources” slides

Important Excerpts from MSC/I QA Guidance

- During PHE, FDA may consider available information and approaches to mitigate the risk to product quality associated with the change to **support a reporting category for certain supplements that is lower than what otherwise would be most suitable**

- Applicants should clearly provide the following information which is needed to consider a reduction in reporting category
  - rationale
  - supporting information
  - risk-mitigation approaches

- Highly aligned with ICHQ12 principles to streamline change implementation based on scientific knowledge and risk mitigation

Postapproval Change Implementation

- Several application tools exist for applicants to **proactively plan** and build change flexibility, as well as **react and implement** changes flexibly:
  - Risk-based change framework under 21 CFR 314.70 and 21 CFR 601.12
  - ICHQ12: Established Conditions
  - ICHQ12: Post-Approval Change Management Protocols, FDA: Comparability Protocols
  - FDA: grouped supplements

CMC Postapproval Changes

- An applicant must notify FDA about each change in **each condition established** in an approved application beyond the variations already provided for in an application" (i.e., an NDA or ANDA) – see 21 CFR 314.70
    - Similar language exists in 21 CFR 601.12 for BLAs

  – FDA regulations provide for a risk-based spectrum of change reporting options

- Further elaborated in changes guidance documents

ICH Q12 – Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

- Provides opportunity to further streamline change implementation through science and risk-based tools:
  - Using Established Conditions to identify which changes will require supplements and their reporting category vs those that can be solely managed by the pharmaceutical quality system (PQS)
  - Using Post-Approval Change Management Protocols to proactively plan and implement changes for one or many products
- Link provided on the “resources” slides

Established Conditions (ECs)

- ECs offer an opportunity to:
  - Modify the total number of changes that require a supplement
  - Reduce the risk level and reporting category associated with the change
- Enabled by utilizing product and process knowledge, enhanced development, and quality risk management principles (ICHQ8, ICHQ9, ICHQ11)
- Enabled by implementing an effective PQS (ICHQ10)

Established Conditions (ECs)

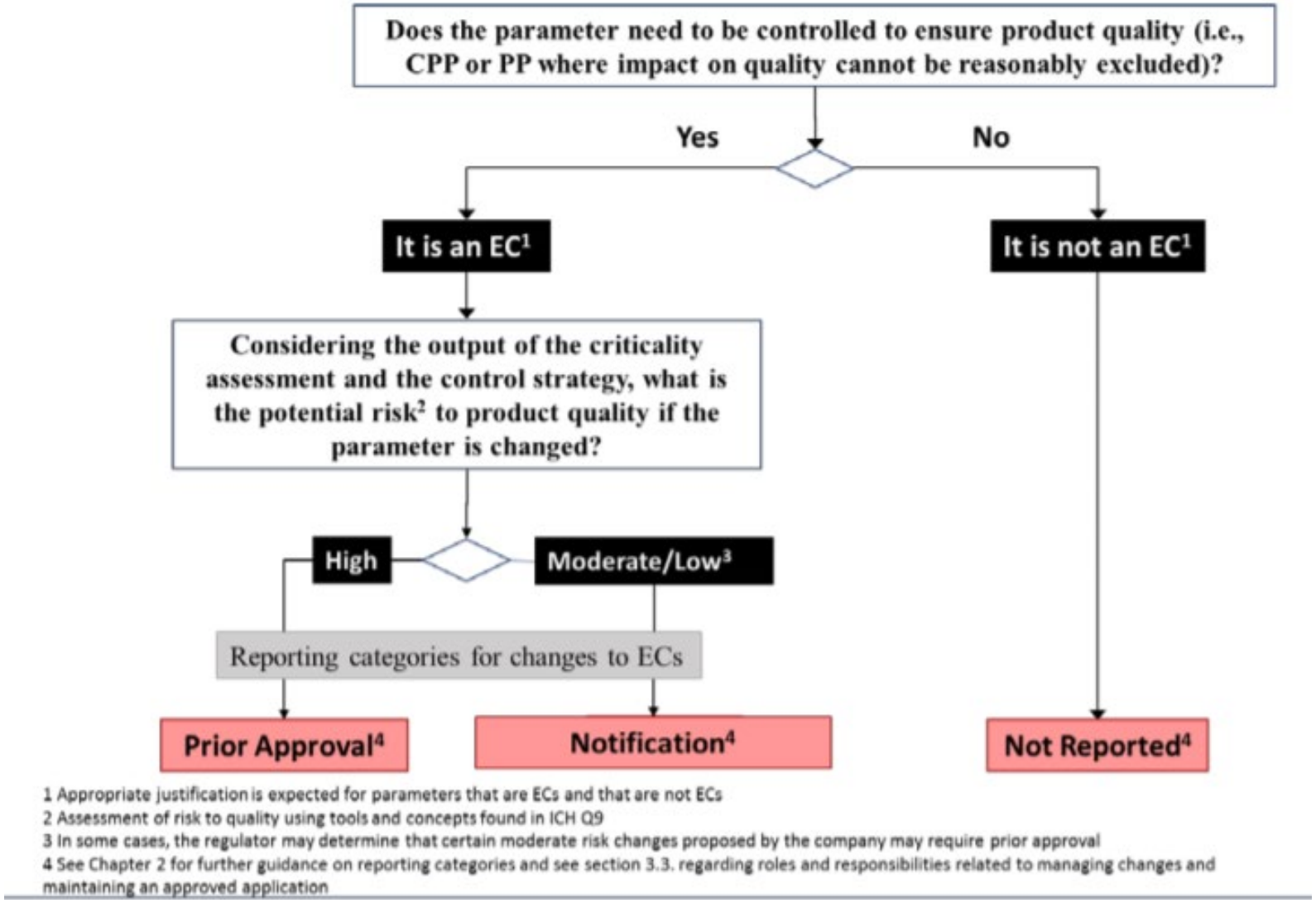
- ICHQ12 states that ECs are legally binding information [within an application] considered necessary to assure product quality
- As a consequence, any change to ECs necessitates a submission (PAS, CBE, AR) to FDA
- The extent (number and how narrowly defined) of ECs will vary based on a number of factors, including:
  - product and process understanding
  - characterization
  - the firm's development approach, and
  - potential risk to product quality

Established Conditions (ECs)

- After identifying ECs, applicants may propose a reporting category for post-approval changes to the EC with justification
  - Follow existing regulations and recommendations in guidance (e.g., SUPAC guidances; Changes to an Approved NDA or ANDA guidance) or
  - Propose alternate reporting category (e.g., CBE-30 instead of a PAS)

- Reporting category (RC) is influenced by the potential risk to quality
  - Risk assessment activities should follow approaches described in ICH Q9
  - Consider the overall control strategy and any possible concurrent changes

Identifying ECs and RCs



1 Appropriate justification is expected for parameters that are ECs and that are not ECs
2 Assessment of risk to quality using tools and concepts found in ICH Q9
3 In some cases, the regulator may determine that certain moderate risk changes proposed by the company may require prior approval
4 See Chapter 2 for further guidance on reporting categories and see section 3.3. regarding roles and responsibilities related to managing changes and maintaining an approved application

Q12 annex: Powder Blending

	Parameter	Acceptable ranges and reporting categories (White boxes are ECs, and orange ones are not ECs.)		
		Parameter Based Approach	Enhanced Approach	Performance Based Approach
Input Materials	API PSD	20-50um Tighten (NL) Widen (PA)	5-200 um Tighten (NL) Widen (NM)	5-200 um (NM) Tighten (NL) Widen (NM)
	API Moisture	<1.0% (NM)	NR	NR
	Excipient #1-3 Specification	Pharmacopoeial	Pharmacopoeial	Pharmacopoeial
Equipment and Parameters	Operating Principle	Diffusion mixing (PA)	Diffusion mixing (PA)	Diffusion mixing (PA)
	Equipment type	V-Blender (NM)	V-Blender (NL)	NR
	Scale	200kg Increase >10x (NM)	200kg Increase >10x (NL)	200-600kg Increase >10x (NL)
	Blend Speed	20rpm (NM)	Design space consisting of Speed: 10-20rpm Time: 15-25 minutes (NM)	15rpm (NR)
	Blend Time	20 minutes (NM)		20 minutes (NR)
Output performance measure	Homogeneity Method principle	HPLC (NM)	Not Tested	NIR online analyser (PA)
	Homogeneity acceptance criteria	<5% RSD IPC (NM)	Not Tested	<5% RSD IPC (NM)

Established Conditions: Impact

- Reduce submission of unnecessary supplements
  - Risk-based principles allow focus on most important changes during assessment and inspection
  - More flexibility for industry to implement changes
  - Greater ability to react more quickly to supply chain challenges

- Enables more effective and proactive postapproval product lifecycle management strategies

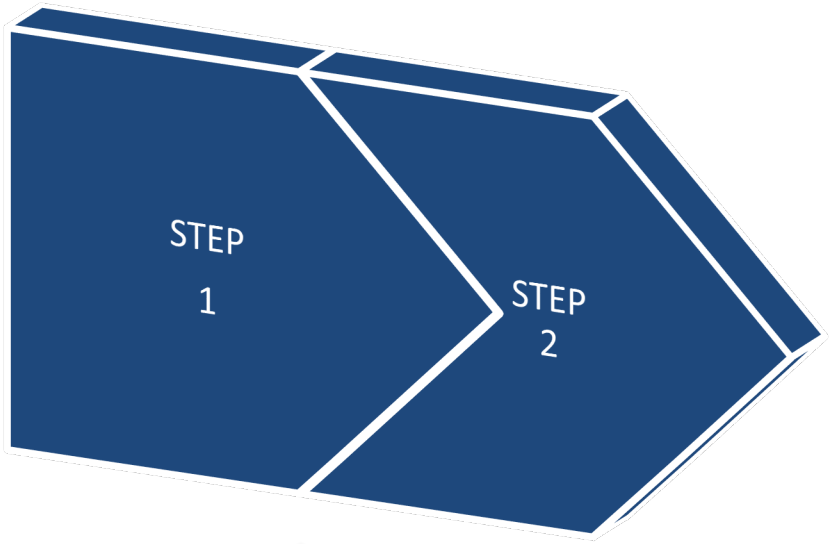
Post-Approval Change Management Protocol (PACMP)

- A PACMP is a regulatory tool that provides predictability, transparency, and alignment in terms of the requirements and studies needed to implement a change
- Provides opportunity for lower reporting category when implementing changes
- Provides opportunity for proactive planning and risk mitigation
- **In FDA system, known as Comparability Protocols (CP)**
  - Link to draft guidance provided on the “resources” slide

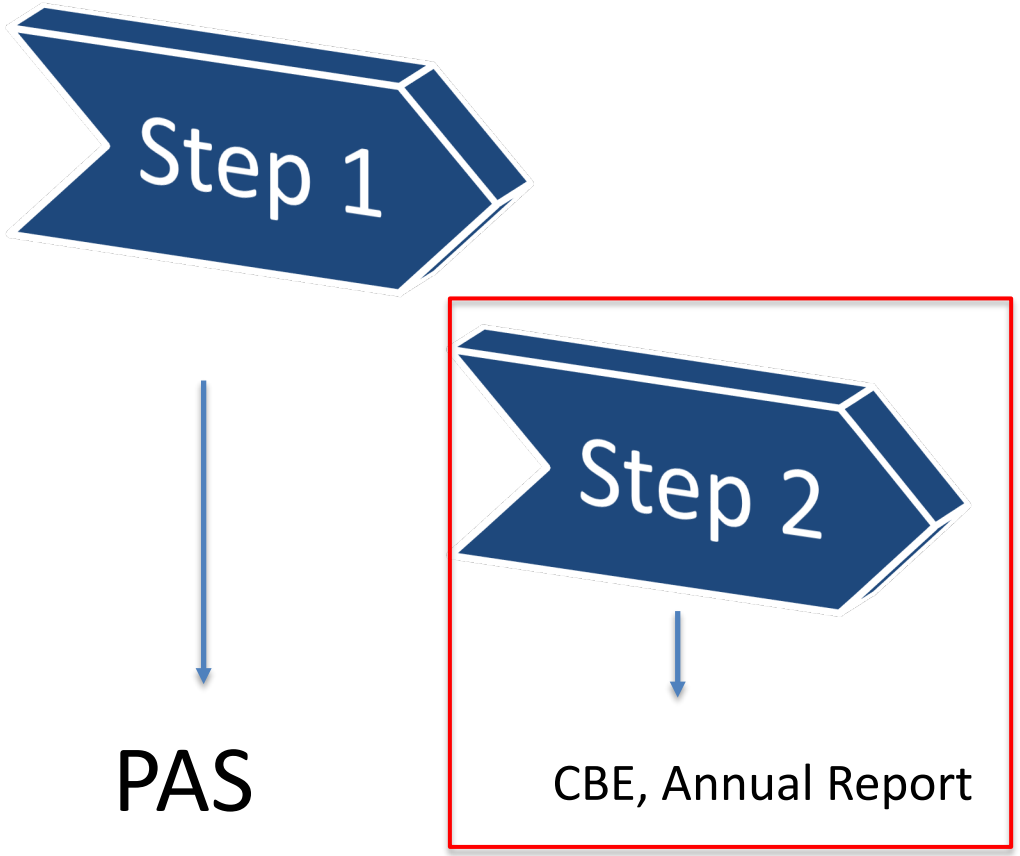
PACMP Approaches

- One or more change(s) to a single product
- One or more changes to be implemented across multiple products
  - E.g., change in stopper across multiple products that use the same container closure system
- One or more changes to be implemented across multiple products and at multiple sites
  - E.g., change in analytical method across multiple sites, change in manufacturing site(s) across multiple products

Impact



PAS



PAS

Recent Examples of CPs

- Switch from single use mixing bags to stainless steel tanks in case bag supply become critically constrained
  - Broader prospective strategy

- Relocate multiple filling lines to a new proposed manufacturing facility
  - Planning for a specific, known change

- Implementation of an alternate bioburden reduction filter, container closure system, and freeze/thaw equipment for the drug substance manufacturing process due to supply constraints
  - Planning for concurrent changes

ICH Q12 Tools - Summary

- Both tools provide a platform for:
  - risk management
  - preparation and flexibility for change implementation

- Enables faster reaction to stimuli for change, e.g.
  - Supply chain constraints
  - Capacity limitations

FDA: Grouped Product Quality Supplements

- Supplements submitted concurrently that provide for the same CMC changes to multiple approved products can be grouped together
  - One review process for multiple supplements
- Allows for efficient submission, action, and implementation across multiple products at one time
- Called “trans-BLA” for Biologic License Applications
- Link to FDA policy and procedure provided on the “resources” slide

Recent Examples of Grouped Supplements

- Changing the release and stability testing laboratory for multiple drug products to increase capacity

- Changing to a new glass vial for multiple products (that currently share the same glass vial) in response to supply constraints of existing vial

Cross Cutting Supply Constraints: Glass Vials and Stoppers

- Multiple inquiries from component suppliers and sponsors regarding FDA's expectations for CMC changes related to glass vials and stoppers (e.g. manufacturing process, composition, and design)

- Concerns that vaccine production and increased manufacturing of therapeutics could strain supply chains for glass vials and stoppers

- Proactive engagement between FDA and suppliers regarding supply status

FDA COVID-19 Guidance: Container Closure System and Component Changes - Glass Vials and Stoppers

- Goal:
  - Facilitate the rapid implementation of CCS changes for critical drugs and biologic products

- Actions:
  - Clarify existing CMC expectations across multiple product types
  - Clarify existing regulatory tools for streamlined change implementation (e.g., Comparability Protocol)
  - Apply other streamlined change implementation approaches introduced through related COVID-19 guidance documents

- Link to guidance provided on the “resources” slide

Content: Common Changes to Glass Vials and Stoppers

- Three change topics
  1. Properties of Glass Vials and Stoppers
  2. Source or Site of Manufacture for Glass Vials and Stoppers
  3. Manufacturing or Processing of Glass Vials and Stoppers

- For each, provide baseline guidance as well as current practice for specific situations that could support a reduction in reporting category

- Tabular format chosen for clarity, and comparability between drugs and biologics

Content: Common Changes to Glass Vials and Stoppers

Table A: Changes to the Properties of Glass Vials and Stoppers: New Drug Applications/Abbreviated New Drug Applications*

Proposed Change	Recommended Information to Support the Change	Recommended Reporting Category	Reference to Current Guidance[1]	Specific Considerations for Reporting Category
Change from glass to a new material (e.g., plastic)	Confirmatory batch data, including release and stability data (accelerated and real time▪), and data to support sterility assurance Extractables and leachables risk assessment and supporting data	PAS	Section IX.B.4. of *Changes to an Approved NDA or ANDA* (April 2004)	
Change to different composition or type of glass[2]	Confirmatory batch data, including release and stability data (accelerated and real time), and data to support sterility assurance	PAS	Sections IX.B.4. and IX.C.1.a. of *Changes to an Approved NDA or ANDA*	FDA may consider a lower reporting category based on the circumstances of the specific change[2]

continued

Cross Cutting Supply Constraints: Filters

- Multiple inquiries from manufacturers regarding FDA's expectations for CMC changes related to filters, e.g.
  - Filter suppliers
  - Control strategy
  - Validating cycles for reuse

- Currently working with applicants on strategies for change implementation and supplement requirements

Concluding Remarks

- Supply chain vulnerability presents a risk to consistent supply of high-quality drugs
  - Exists at multiple levels
  - Impact felt across product types

- Risk management activities extend to change management
  - Implement proactive risk mitigation measures
  - Efficiently implement changes
  - Enabled by strong product and process knowledge and mature Pharmaceutical Quality Systems

Concluding Remarks

- Early engagement with FDA is vital for success
  - For CDER-regulated products, applicants should contact CDER-OPQ-Inquiries@fda.hhs.gov
  - For CBER-regulated products, applicants should contact the office responsible for the product's regulation
  - If the product could enter, or is currently in, drug shortage
    - DRUGSHORTAGES@FDA.HHS.GOV for products regulated by CDER
    - cbershortage@fda.hhs.gov for products regulated by CBER.

- Shared responsibility between FDA and Industry to maintain supply of high-quality drugs for patients

Resources

1. Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers: https://www.fda.gov/media/141312/download

2. Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Guidance for Industry: https://www.fda.gov/media/148476/download

3. ICH Q12: Implementation Considerations for FDA-Regulated Products: https://www.fda.gov/media/148947/download

4. Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information Guidance for Industry: https://www.fda.gov/media/97148/download

5. Manual of Policies and Procedures 5015.6, Review of Grouped Product Quality Supplements: https://www.fda.gov/media/72531/download

Resources

6. COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers: https://www.fda.gov/media/146428/download

7. CDER's Work to Meet User Fee Goals During the Pandemic: https://www.fda.gov/industry/fda-user-fee-programs/cders-work-meet-user-fee-goals-during-pandemic

8. Resiliency Roadmap for FDA Inspectional Oversight: https://www.fda.gov/media/148197/download

9. CDER NextGen Portal – manufacturing capacity (**For products in development for COVID-19**):