Regulatory Perspective on Raw Material Challenges

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Agenda

- Raw material challenges
- Opportunities
- Regulatory Environment
  - Regional guidelines
  - ICH guidelines
- ICH Q12
- Post-approval change management protocol (PACMP)
- Case study

Raw Material Challenges

- Challenging to examine the effect of all the raw material experimentally
- Variability in product quality caused by variability in the quality of raw materials
- Lack of robust raw material management Quality by Design system
- Lack of clarity in regulations to accommodate complex biologics manufacturing processes that have more steps and are more sensitive to variability and contamination compared to small molecules
- Lack of harmonization in global regulations
- Obtaining documentation from the suppliers i.e. availability of DMFs
- Supply shortages
- Cell and gene therapy production challenges

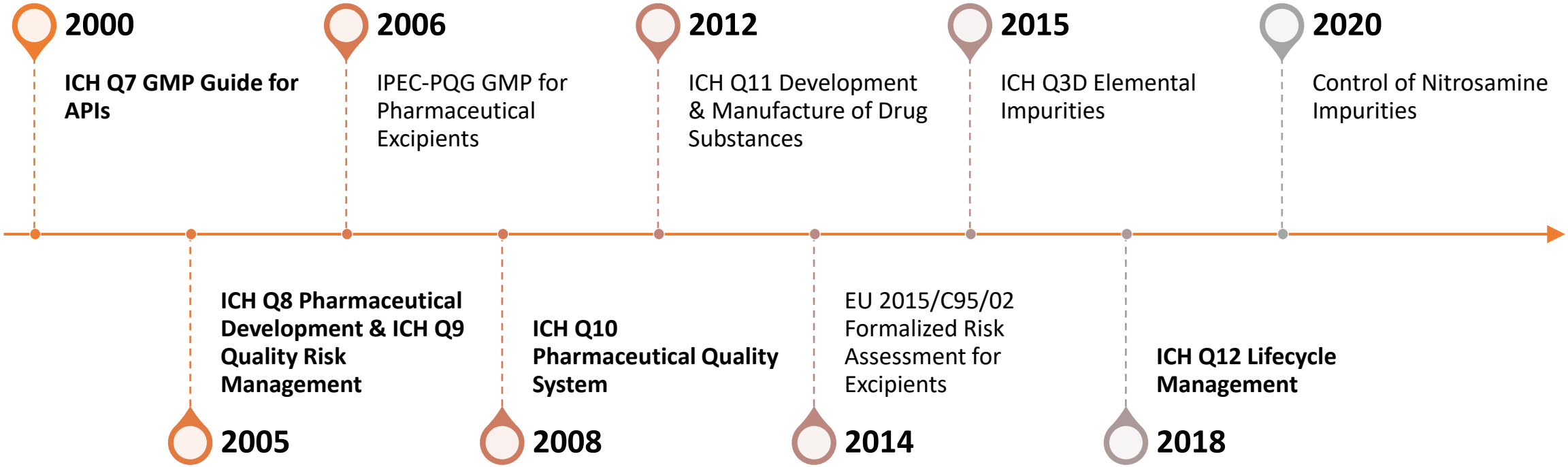
Opportunities

- Application of Quality by Design principles to raw materials as per ICH Q8
  - Differentiate critical V/S non-critical raw materials and attributes
  - Enhanced product and process understanding leading to identification of critical material attributes for raw materials

- Scale-down model for qualifying new lots and suppliers of complex critical materials
  - Developing testing strategies to ensure raw material quality and comparability
  - Evaluating whether specific tests are needed in order to ensure consistent material quality

- Setting up material/supplier risk assessments in the context of a supplier qualification exercise
  - Having a supplier qualification system in place which assesses supply and quality risks

Evolved Regulatory Guidelines



General principles from FDA/EU/Canada post-approval change guidelines

Major Changes:

- A raw material change that has a substantial potential to affect drug substance or drug product CQAs
- Change in raw material synthesis, source, specifications etc.

Moderate Changes:

- A change in a supplier of raw materials used to aid in filtration (e.g., celite, diatomaceous earth, activated carbon) and storage (e.g. components of container closure systems)
- Change in sterilization of storage components

Minor Changes:

- A change in a supplier of raw materials that have a minimal potential to affect product quality, provided that the materials' specific use, physicochemical properties, impurity content, and acceptance criteria remain unchanged

Example – Multiproduct Minor Filter Change

- Supplier notification of the change – well established supplier of commonly used sterile filter used withing industry globally
- Change from fluorinated to a non-fluorinated surfactant used to manufacture PVDF filter used for sterile filtration of final DP
- Supplier assessment - Raw material characterization, leachable extractable, biocompatibility, membrane performance qualification, bacterial retention and aging studies
- The change assessed as minor but reported because of the critical nature of the filtration step
  - Same CAS number - No chemical difference between the two surfactants
  - Filter integrity validated
  - The surfactant does not interact with the drug molecule
  - No impact to DP manufacturing process validation

Is there a standard for consistent reporting of such changes? Agency expectation for reporting minor changes when detail is provided in dossier Vs. not mentioned in dossier?

ICH Guidelines – Key Highlights on Raw Materials

- ICH Q7 (GMP Guide for APIs) – Manufacturers must establish written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of raw materials

- ICH Q8 (Pharmaceutcal Development) - The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient
  - Defines elements of QTPP
  - Critical Quality Attributes
  - Risk assessment - identifying which material attributes and process parameters potentially influence product CQAs
  - Design space - The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes
  - Control strategy - Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality

ICH Guidelines – Key Highlights on Raw Materials

- ICH Q9 (Quality Risk Management) – Provides general principles for Quality Risk Management as part of raw material management. Manufacturers should perform comprehensive evaluation of suppliers and contract manufacturers

- ICH Q11 (Development and Manufacturing of DS) – Provides general principles for selection, justification and qualification of starting materials or sources for synthetic and Biological drug substances

- ICH Q12 (Lifecycle management) – A well-characterized, risk-based categorization of regulatory communication requirements is important to the efficient use of industry and regulatory resources. Describes general principles for established conditions, categorization of post-approval CMC changes PACMP, and PLCM

ICH Q12 Elements

Established Conditions (ECs)

- Once ECs are identified, an updated assessment of the potential risk to product quality associated with changing the EC, considering the overall control strategy informs the reporting category for the EC.

PACMP – Postapproval Change Management Protocol

- A PACMP is a regulatory tool that provides predictability and transparency in terms of the requirements and studies needed to implement a change as the approved protocol provides an agreement between the MAH and the regulatory authority.

PLCM - Product Lifecycle Management Document

- The PLCM document outlines the specific plan for product lifecycle management that includes the ECs, reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. The PLCM document should be updated throughout the product lifecycle as needed.

PACMP – Post approval change management protocol

Application of PACMP

- Step 1 – Submit written protocol defining proposed change, rationale, risk management activities, proposed studies, criteria, proposed reporting category and other supportive information. Obtain approval
- Step 2 - The tests and studies outlined in the protocol are performed and change submission is filed

Elements of PACMP

- Description of change
- Initial risk assessment/impact
- Impact to control strategy
- Any qualification studies to be performed
- Supportive data/previous experience
- Proposed submission category
- Impacted sections of dossier

PACMP – Post approval change management protocol

Types of PACMP

- One or more change(s) associated with a single product
- Broader protocols –
  - One or more changes to be implemented across **multiple products** (e.g., change in raw material used by multiple products): the same risk mitigation strategy should be applicable across all impacted products;
  - 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): the same risk mitigation strategy should be applicable across all impacted products and/or sites

Submission

- PAS, Type II or original registration

PACMP – Case Study

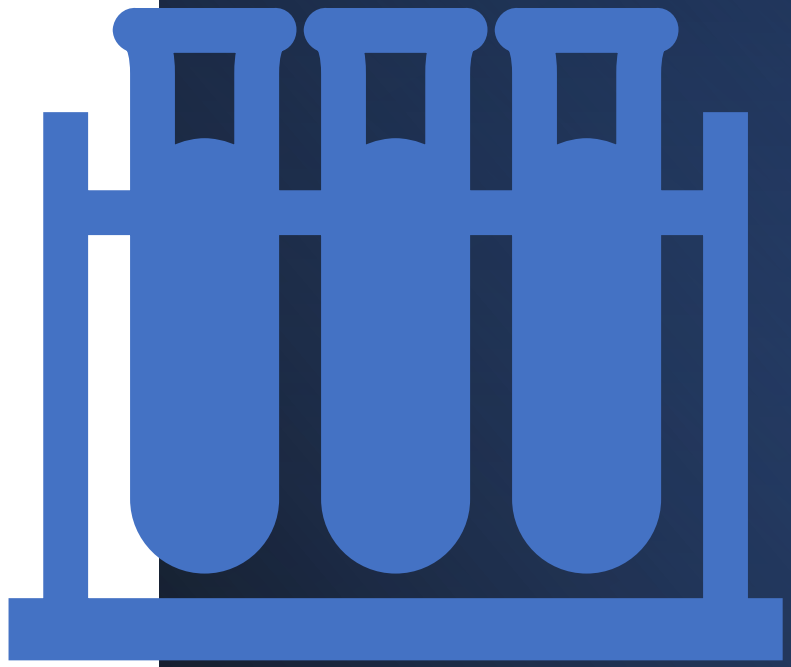
API Raw Material Supplier Change

Change Background

- ✓ Post-Approval Change Management Protocol (PACMP) to qualify an additional supplier of a raw material used in drug substance manufacturing
- ✓ Proposed reporting categories:
  - ✓ US - CBE-30
  - ✓ EU – Type IB (B.I.e.5.c)

Feasibility Evaluation – Proposed Supplier

- ✓ Supplier qualification (cGMP status)
- ✓ Validation of the manufacturing process
- ✓ Evaluation of impurities
- ✓ Analytical package evaluation
- ✓ A side-by-side analytical evaluation of current Vs. proposed raw material
- ✓ Three (3) scale-down FBDS runs data using proposed raw material
- ✓ A scale-down dissolution study



Quality Risk Assessment of the Proposed Change

- ✓ Quality risk assessment was performed using a quantitative risk rating system to identify, analyze, evaluate and mitigate the potential risks to process performance and final FBDS and DP CQAs
- ✓ Risk element evaluated included:
  - ✓ Residual solvents assessment
  - ✓ TSE/BSE
  - ✓ Impurities - Risk of increased high molecular weight species of final FBDS from use of new raw material
  - ✓ Reagent and solvent carryover into FBDS
  - ✓ Elemental Impurities
  - ✓ N-nitrosamines
  - ✓ Microbial levels (Bioburden, BET)
  - ✓ Differences in dissolution profile
  - ✓ Difference in container closure
  - ✓ Stability of FBDS shelf-life
  - ✓ DP process and final DP quality

Control Strategy

- ✓ One of the two starting materials used in manufacturing differs at current Vs. proposed supplier
  - ✓ Supplier specifications for these starting materials ensure adequate control over downstream processing, to assure consistent quality of the raw material for use
  - ✓ Manufacturing process at new supplier fully validated

- ✓ Proposed raw material lots were tested in accordance with the current incoming specification
  - ✓ Three proposed raw material lots CoAs were compared against three current raw material lots CoAs to confirm quality and equivalency

- ✓ No anticipated changes in the FBDS control strategy, including the in-process limits and FBDS specifications as a result of implementation of this change based on:
  - ✓ Quality risk assessment
  - ✓ Physicochemical comparability of raw material from both suppliers
  - ✓ Results of the small-scale FBDS run

Comparability Strategy for FBDS

- ✓ Two commercial-scale post-change FBDS lots were tested for release and stability testing and additional characterization studies for comparison with pre-change FBDS lots
- ✓ Post-change data comparison with pre-change data
  - ✓ Comparability acceptance criteria based on 95% confidence interval using release/stability results from recent pre-change FBDS lots
  - ✓ An evaluation of historical results was only performed for the FBDS attributes that were considered be potentially impacted by the proposed change
  - ✓ Additional characterization studies tested and compared with pre-change FBDS

Stability Plan for FBDS

- ✓ The two (2) commercial scale post-change FBDS lots were placed in the stability monitoring program under long-term, intermediate, and accelerated storage conditions per ICH
- ✓ The results-reporting submission included minimum 3 months FBDS stability data from the long-term, intermediate and accelerated storage conditions, along with an assessment of comparability that included a comparison of the results from the two post-change lots to historical trends
- ✓ Forced degradation study of FBDS
- ✓ Based on FBDS extensive evaluation, drug product stability evaluation was considered redundant.

Thank You