Regulatory Considerations for Raw Material Qualification and Related Controls for Biotechnology Drugs

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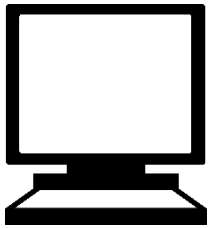
Pharmaceutical Quality

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.

Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.

Outline of presentation

- Background on raw materials as a critical component of good manufacturing practices
- Types of raw materials
- Considerations for quality control of raw materials (compendial and non-compendial)
- Changes to raw materials used in a licensed product

Background

- **Raw Material:** A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs*.
- *Biological Raw Material* - Raw material from a biological source (e.g., animal, human or plant), which is intended to be used as a processing aid in the manufacture of a biological product. It may be absent from the final product or may remain as an impurity in the final product at the end of the manufacturing process (e.g., biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin, etc.).**

*Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (2001)
**Guidance for Industry, Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products (2017)

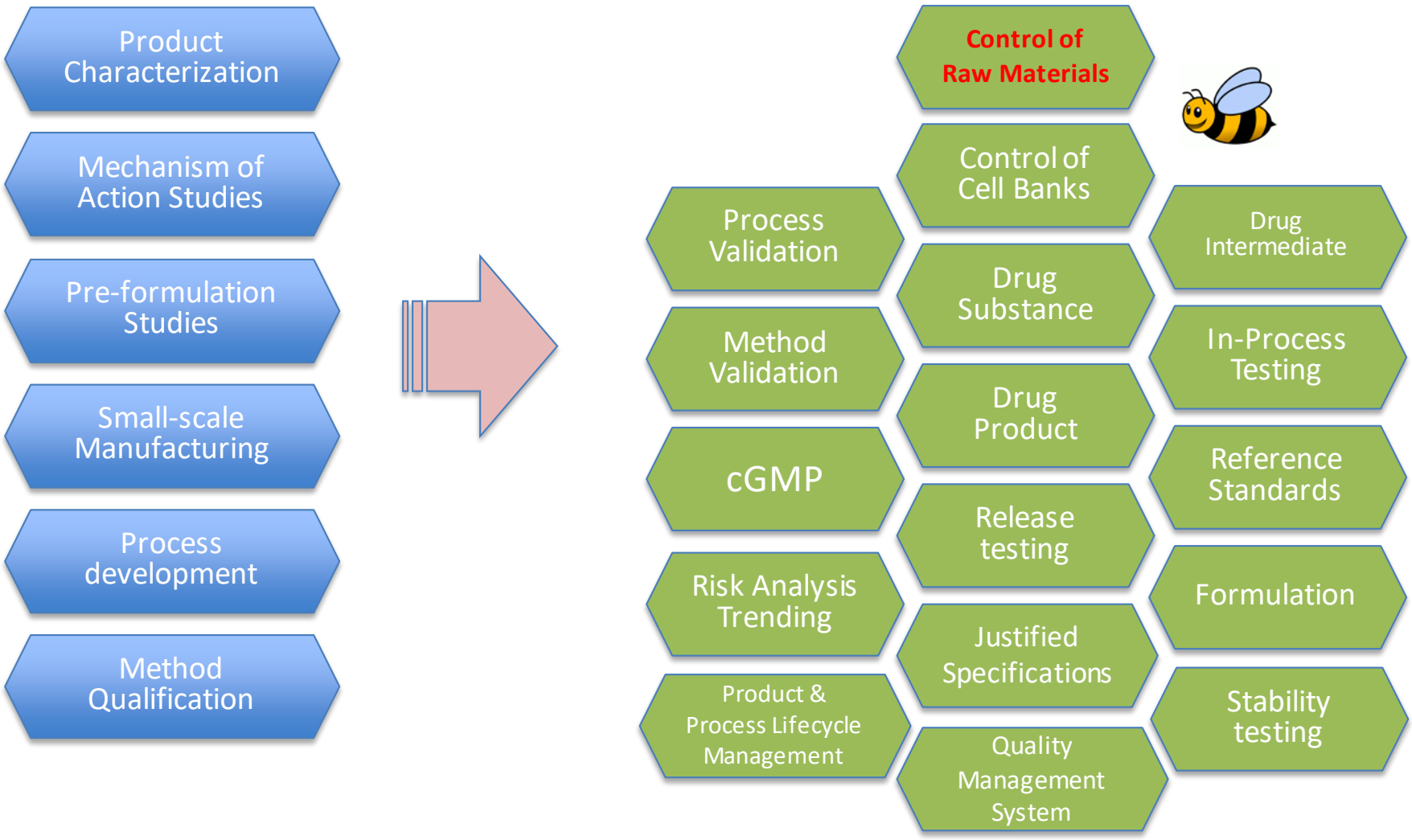
The goal throughout a drug's developmental lifecycle

- To prevent unreasonable and significant risk of illness or injury to human subjects [21 CFR 312.42(b)(1)(i)]
- Provide sufficient information to assess risk to human subjects [21 CFR 312.42(b)(1)(iv)]

Common types of raw materials

- Starting materials for the biotechnology manufacture
  - Cell lines, media, serum, growth factors, selection agents, antibodies, antibiotics, antifoam, bags and tubing
- Material used during purification and downstream manufacture
  - Resins, buffers, matrix components, protease/DNAse, antibodies, column components, single-use and reusable components, mixing vessels, separation devices, collection devices
- Critical raw material for analytical testing and assays used for release and stability testing
  - Buffers, antibodies, solvents, chemical reagents, plates/tubes/containers, column components, reference materials, positive/negative controls

Control strategies for biotech products



Specifications

Specification, as per § 314.3 and 600.10(kk), means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product.

- ***Acceptance Criteria*** means numerical limits, ranges, or other criteria for the tests described. § 210.3 (a)(20) extends this definition to include rejection criteria and unacceptable quality level.
- ***Test method***

Linking your historical clinical success to your future safety and efficacy

ICH Q7a

- An *API starting material* …can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.
- No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use.

Qualification of Raw Materials

- **Source**
- **Identity**
- **Purity**
- **Physicochemical or biological activity**
- **Safety**
- **Stability**

Compendial and non-compendial raw materials

- Compendial methods related to raw materials are verified and not validated under actual conditions of use.*
- Limits outside compendial acceptance criteria are allowed with supporting justification (e.g. use of a surfactant at a composition that is more stable for specific API).
- Non-compendial raw materials with supporting methods and acceptance criteria are allowed and reviewed under the justified context of use (e.g. a novel excipient or recombinant source of natural product)

*USP General Chapter <1226>Verification of Compendial Procedures

Steps in the qualification program

- **Identify** and **select** material based on **suitability** during manufacture and testing
- Compendial and non-compendial raw materials with **in-house testing** and qualification, depending on the **context of use**
- **Characterization** of raw material during process and product development
- **Quality assurance** consistent with above

Source and Identity

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this (including microbial/endotoxin testing)
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Source and Safety

- Traceability and qualification of human or animal-derived raw materials
  - Herd qualification and country of origin certification (*e.g.* Fetal Bovine Serum and TSE/BSE-free certification)
  - Human donor source and infectious disease status
  - Adventitious agent testing (*e.g.* viral contaminants)
  - Source host cell proteins (*e.g.* yeast or plant derived raw materials)

During early product and process development

- Risk assessment can help identify the material attributes and process parameters with the **potential for impacting drug substance CQAs**.
- The ability of the drug substance manufacturing process to **remove** that impurity or its derivatives should be considered in the assessment
- Risk related to impurities can usually be **controlled** by specifications for raw material/intermediates and/or robust purification capability in downstream steps.
- Identify CQAs for which there are inherent limitations in detectability in the drug substance (e.g., host cell impurities). In these cases, such CQAs should be **controlled at an appropriate point upstream** in the process

ICH Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) (2013)

Safety considerations specific to raw materials

- Sterility, Bioburden
- Endotoxin
- Mycoplasma
- Leachables from containers, transport and delivery devices
- Source species-specific host cell proteins from animal or plant-derived raw materials
- Source species-specific adventitious agents from animal or plant-derived raw materials
- Context of use, stability and interaction of residual material with API, formulation or container closure components
- Sensitivity of target patient population

Raw material qualification information in regulatory submissions

- Description of Manufacturing Process and Process Controls (3.2.S.2.2);
- Control of Materials (3.2.S.2.3);
- Controls of Critical Steps and Intermediates (3.2.S.2.4);
- Control of Drug Substance (3.2.S.4);
- Container Closure System (3.2.S.6).

Case study 1
Animal derived raw materials

- Raw materials obtained from slaughterhouses
- Sponsor had supply chain and inventory issues
- Differences in identity and activity of biological activity in animal-derived raw material resulted in the need for an inspection of the facility
- Increased control on the potential impurities in the raw material and control on the supply chain.
- Sponsor clarified their process for qualifying sources of the raw material and reporting of changes to this qualification with the Agency.

Case study 2

- Leachables from raw materials (plastic tubing, and containers holding DS or DP)
- Aggregates formed on stability due to leaching from a bag holding DP during manufacturing
- Discussed with sponsor that raw material can be also material with product contact
- Sponsor provided leachable studies to determine worst case scenario for risk assessment with defined hold times as control strategy.

Changes to raw material after licensure

Examples of types of filing

- Prior approval supplement (PAS)
  - A change in a supplier of raw materials that have a substantial potential to affect product quality, including *inactivation, detoxification, immunization in the production of hyperimmune plasma, or conjugation* (e.g., PEG, acridinium ester, biotin, beads); and
  - A change in a supplier of raw materials that have a substantial potential to affect product quality, including an ability *to maintain specified pH or ionic strength in the manufacture of plasma-derived fractionated products* (e.g., phosphate, tris, ethanol)

Changes to raw material after licensure

- Change in a Supplier of Raw Materials
- CBE-30
  - A change in a supplier of raw materials used *to aid in filtration* (e.g., celite, diatomaceous earth, activated carbon); 2. A change in a *supplier of trypsin or serum* used in the manufacture of viral vaccine products.
- Annual Reportable
  - A change in a supplier of raw materials, reagents, and solvents that have a *minimal potential to affect product quality*, provided that the materials' specific use, physicochemical properties, impurity content, and acceptance criteria remain unchanged.

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