

Raw materials in the manufacture of biotechnology products: Regulatory considerations

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The opinions and views expressed during this presentation are my own and represent my experience as an FDA reviewer.



FDA's Pharmaceutical cGMPs for the 21st Century Initiative emphasizes science-based and risk-based approaches in the manufacture of drugs.



These approaches are reflected in harmonization guidances ICH Q8 and Q9, and encourage the assessment of the manufacture of a biologic in a cohesive manner including all aspects of manufacture which have the potential to impact the finished drug product.

Management of raw materials is an important part of this initiative.



Overview

- What is a raw material?
- Classification of raw materials
- Regulations on raw materials
- Why should we care about raw materials?
- Risk-based approach to establish a program on raw materials
 - ⊕ Risk assessment
 - ⊕ Controls



What is a Raw Material?

According to ICH Q7, a raw material is a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Raw materials do not have a unifying denomination:

- ✦ In-process material
- ✦ Source material
- ✦ Component
- ✦ Constituent
- ✦ Ancillary reagent
- ✦ Starting material
- ✦ Excipient

Should a better definition of raw material be established?



What is a Raw Material?

My work-in-progress definition

Any element or component used in the manufacture of a biotechnology product that comes in contact with the API or the API starting material. A raw material may be reactive or non-reactive with the API.



Classification of Raw Materials

According to its origin:

- ✦ Biologically-derived RM
- ✦ Chemically-derived RM
- ✦ Physical RM

According to their use in the manufacture step:

- ✦ Cell culture RM
- ✦ Purification RM
- ✦ Packaging RM

There is not a comprehensive classification of raw materials



Water is a raw material !

Regulation of Raw Materials

There are not specific regulations for raw materials.....

21 CFR 610.15 constituents shall meet generally accepted standards of purity and quality.

21 CFR 211.80

Control of components and drug product containers and closures

Components are required to be controlled by a Quality Control Unit to ensure appropriate management, testing and monitoring of components....Components should be tested for identity and for conformity for purity, strength and quality.

21 CFR 211.110

In-process materials shall be tested for ID, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit..



Guidance in Raw Materials

ICH Q7 in the context of the API manufacture:

No ([raw](#)) material should be released or used before the satisfactory completion of evaluation by the quality unit(s)...

The quality unit should establish a system to release or reject raw materials, intermediates, packaging and labelling materials.

Specifications should be established and documented for raw materials,.....Acceptance criteria should be established and documented for in-process controls.

The ([API](#)) impurity profile should be compared.....in order to detect changes to the API resulting from modifications in raw materials,



***Why should we care
about raw materials?***



- Quality/Safety/Efficacy
- Lot-to-Lot consistency
- Specification failure
- Comparability
- PK/PD
- Adventitious agents
- Chemical contaminants
- Adventitious agents
- Immunogenicity



Animal-derived raw materials

- Although viral contamination has not been implicated in the transmission of infectious agents to a patient, cases of contamination arising during manufacture have been reported.
- Contamination during manufacture has implicated mostly BSA (Cache Valley virus, epizootic haemorrhagic disease virus (EHDV), bovine viral diarrhoea virus (BVDV)).
- Contamination by minute virus of mice (MVM) has also been reported but the source has not been clearly identified.
- Porcine trypsin, antibody affinity columns and biological excipients should also be carefully evaluated



Case Studies



Case Study: *PEG Supplier change*

Observation

Significant changes in Pharmacokinetics.

Investigation

Investigation pointed to lots manufactured with polyethylene glycol from new vendor.

Physicochemical testing did not reveal any Differences compared to the drug product lots manufactured with old PEG.

PEG analysis revealed changes in the mix of PEG isomers.



Case Study: *Protein A leachates*

Observation

Protein A limits exceeded during manufacture of a protein.

Investigation

Investigation correlated protein limit failure to use of a new lot of Protein A.

The sponsor did not have procedures in place for testing new lots of Protein A.

The sponsor assumed the vendor would not distribute protein A resin with high levels of leachate.



Case Study: *Protein A leachates*

Conclusion

The sponsor implemented a new raw materials test for Protein A leaching.



Case Study: *Water change*

Observation

Low cell viability during cell culture and fermentation

Investigation

Investigation pointed to a change in quality of the cell media purchased from vendor.

Media analysis revealed zinc levels 6-fold lower than expected.

Zinc is a critical component for cell growth. Although requirement of Zn for cell growth was known, there was no monitoring of the Zn already present in the media.



Case Study: *Water change*

...Investigation

Vendor confirmed a change in their water purification system used in the manufacture of cell culture media.

Conclusion

Vendor was using “more pure” water that lead to insufficient zinc to maintain appropriate cell growth conditions

Manufacturer can supplement additional Zn in the media. Zn level is critical for viability, so it should be monitored in the incoming media.



Case Study: *DP final container as RM*

1. Change in source of natural latex used to make rubber stoppers

Lead to particulate contamination of final product.

2. Change in contract manufacturer for vials from untreated to AmSO_4 -treated

Lead to failure of pH specification.

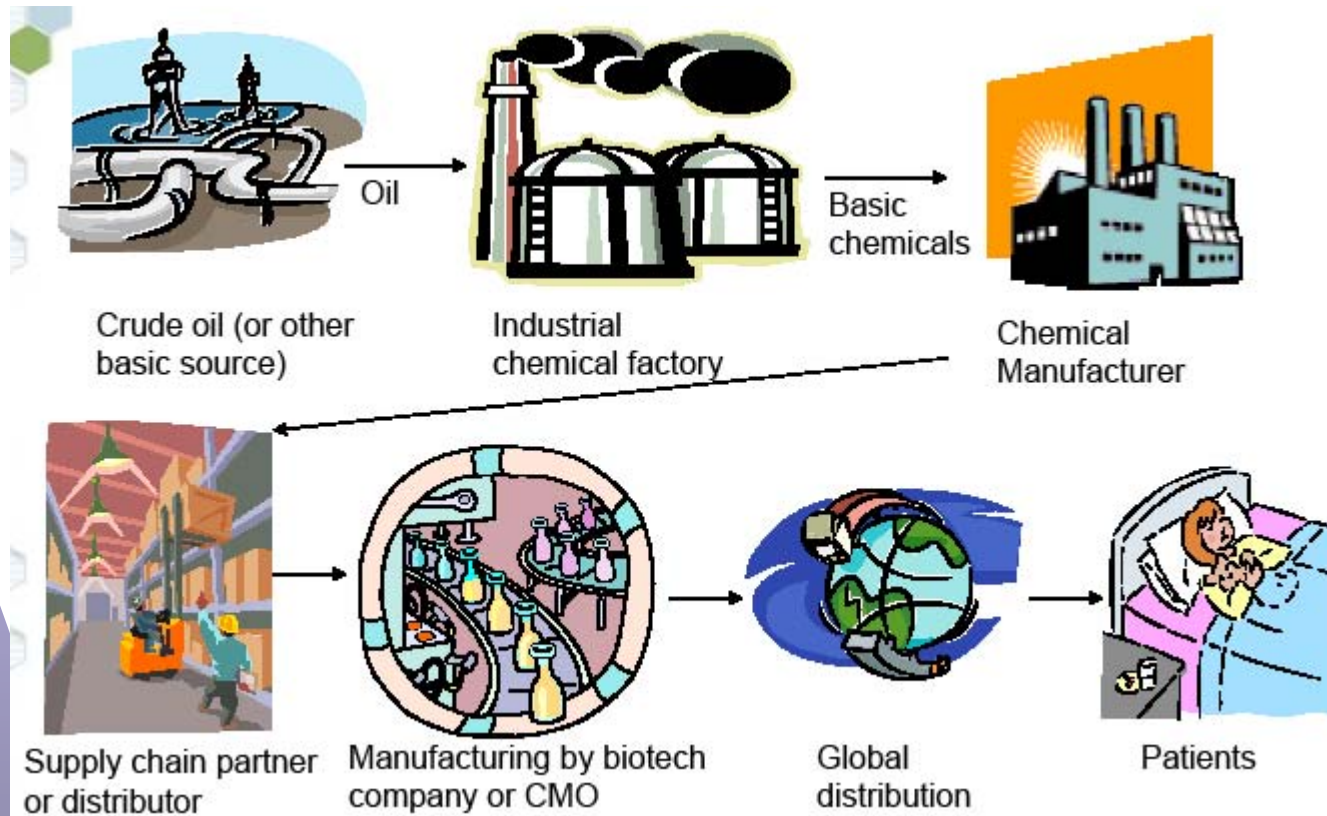


The Ideal Raw Material

- Safe
- Consistent quality throughout its life-cycle
- Well-characterized (known MQAs, MFAs)
- Known product interaction
- Compliant to regulatory requirements
- Continuous supply of consistent quality
- Supply chain transparency
- Manufacturer/Vendor open communication
- Manufacturer/Vendor auditing systems
- Approved back-up supplier



Supply chain of a raw material



The life cycle of a drug product may be critically impacted by the life cycle of the raw material



Risk-based approach to establishing a raw materials program

ICH Q9-Quality Risk Management

- Risk-assessment
- Risk Control
- Risk Communication
- Risk Review



Risk Assessment of Raw Materials

The primary goal of a risk assessment exercise should be to minimize the risk that a raw material may have on the quality, safety and effectiveness of the drug product.

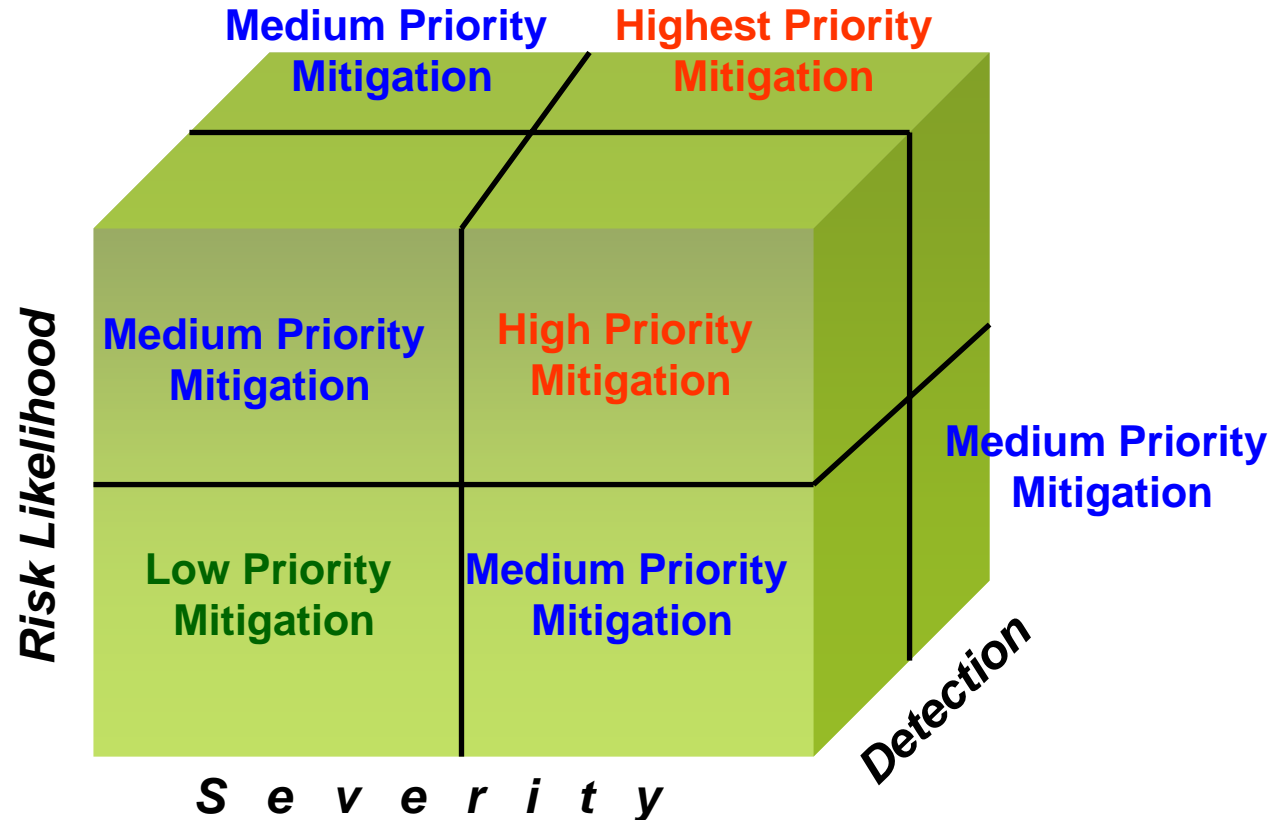
A risk assessment should:

- ✦ Have a comprehensive scope (all inclusive)
- ✦ Have appropriate prioritization
- ✦ Use a comprehensive and appropriate analysis tool (e.g., FMEA, criticality risk scoring)
- ✦ Integrate all appropriate personnel levels (e.g., purchasing, process development, QC, QA, manufacturing, upper management)
- ✦ Be capable to re-assess itself



Risk Tolerance Diagram

- Impact/Severity
- Risk Likelihood
- Detection



Adapted from 2007 PDA

Common Risk Factors

- Biological or Chemical raw material?
- How well-characterized?
- How much charge-in is necessary?
- Sole sourced raw material? Or back-up source available?
- Understanding of the supply chain
- Vendor failure preparedness
- The quality agreement-audited quality systems, change notification
- In-house testing-Is only ID testing sufficient?
- Is supplier CoA sufficient?
- Storage conditions
- Use, re-use



Controls of Raw Materials

- Biological-derived raw materials
- Chemical raw materials
- Testing-material quality attribute (MQA)
- Sampling-ANSI
- Stability-storage
- Qualification
- RM used for multiple drug products



Controls of Raw Materials

- A good understanding of the protein and its interaction with the raw materials as early in development as possible helps to identify the impact of a change in a raw material
- A good understanding of the important parameters of the manufacturing process helps ensure that raw materials will meet specifications.
- Do not assume that any parameter in the process is unimportant
- Identify and validate all important process parameters
- Consider using raw materials at the high and low ends of the specification range during development (pre-clinical and clinical impact, flexibility)



Controls of Raw Materials

Biologically-derived raw materials

Minimize the risk of contamination by tracking and testing

- ⊕ USDA regulations for bovine serum under 9 CFR.113 is being re-evaluated? European (CVMP CPMP Japanese) have modified the number of tests required.
- ⊕ TSE guidances focus on minimizing risk (European CPMP) (Certificate of suitability EDQM)
- ⊕ TSE/BSE method of inactivation/clearance (e.g., preparative chaotropic ultracentrifugation, nanofiltration)



Controls of Raw Materials

Bio/Chem-derived raw materials

Minimize the risk by knowing MQAs and criticality to impact DP quality/safety/efficacy

- ⊕ Vendor testing (e.g., ID, purity)
- ⊕ Manufacturer testing
- ⊕ Lot-to-Lot consistency
- ⊕ Vendor manufacturing process



Controls of Raw Materials

What about excipients?

Are all excipients USP-tested? How much qualification/testing is required?

How well-characterized is the excipient and its interaction with the API?

How much is known of the residual solvent that may be present in a finished excipient?



USP <467> has new testing procedure guidelines for residual solvent.



Controls of Raw Materials

Globalization

How do manufacturers meet compliance with multiple Pharmacopeias?

How do manufacturers reconcile vendor differences from multiple countries?

- ⊕ Chain supply
- ⊕ Quality agreements
- ⊕ Audits
- ⊕ RM change communications



Conclusions

- An initial step in establishing a Raw Materials Management Program requires an appropriate definition of raw material.
- Current classifications of raw materials (e.g., biologically-derived) may not be comprehensive enough to consider all raw materials introduced during the manufacture of a biotechnology product.
- A robust raw materials management program that utilizes comprehensive risk assessment and mitigation strategies would expect to minimize root cause investigations attributed to raw materials and/or raw materials changes.
- A risk-based raw materials management program allows manufacturers to be preventive rather than curative when considering the impact that a raw material may have on the Q/S/E of a biotechnology drug product.



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