White Paper

Identifying Appropriate-Quality Raw Materials in an Evolving Regulatory Environment

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Part I: Understanding Risks and Regulations Behind Raw Material Selection

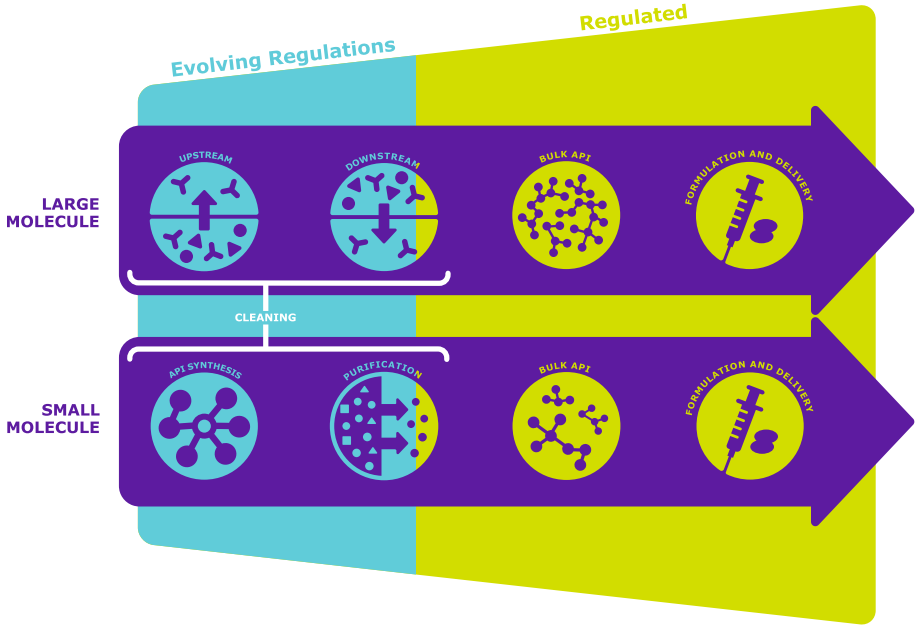
In recent years, pharmaceuticals have become more complex, progressing from primarily small molecule drugs to an increasing array of recombinant proteins, monoclonal antibodies and cell and gene therapies. This has led to necessary changes in regulations to accommodate new, more complex manufacturing processes that have more steps and are more sensitive to variability and contamination.

Contamination, in particular, is a concern for the raw materials used in early steps of manufacturing and may impact drug safety and efficacy. However, while quality attributes for materials used in later manufacturing steps – those steps close to the final drug product – are well-defined, regulations for raw materials are still evolving.

At the same time, the supply chains for materials needed for manufacturing have also increased in complexity. The materials themselves are more difficult to characterize, distribution systems are changing and expanding, and new suppliers are emerging.

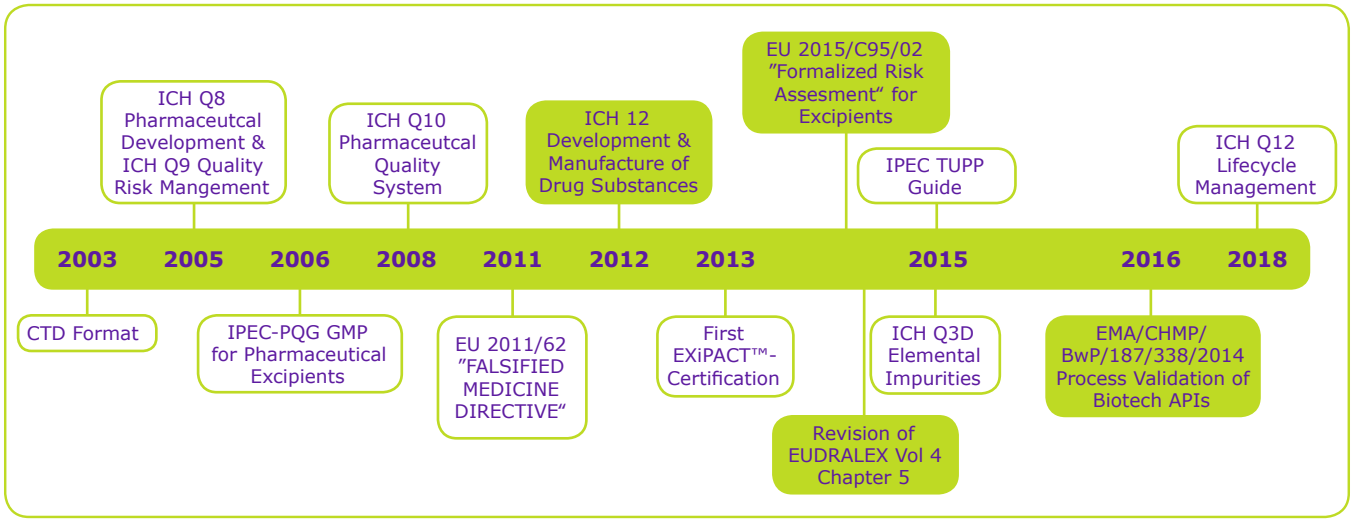
All these factors require manufacturers to ensure that the raw materials they use meet regulatory requirements and can be demonstrated to have appropriate, consistent and documented quality that mitigates risk and is traceable throughout the supply chain.

Regulations of Raw Materials Used During Production Process



Regulatory environment for raw materials

Over the past several years, regulations for drug manufacturing have been updated to adapt to the emergence of new and more complex pharmaceuticals. Some of the recent regulations address aspects of raw material sourcing that are relevant to this discussion.



ICH Q11 Development and Manufacture of Drug Substances

ICH Q11 addresses risk assessment recommendations for raw materials used in drug manufacturing and has been adopted as a guideline by the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (MHLW/PMDA). It describes the need for manufacturers to do a thorough risk assessment of the entire drug product manufacturing process and applies concepts that are becoming ubiquitous – risk management, quality by design and critical control parameters.

The guidance states that drug manufacturers must have a deep understanding of their entire development and manufacturing process and the parameters that critically impact drug quality. It also makes it the drug manufacturers' responsibility to understand and define raw material attributes to control variability and risk of contamination by impurities. Although the ICH Q11 specifically states the need to include raw and starting materials in this assessment, highlighting biological processes, it does not set specific quality standards for them.

EudraLex vol 4, part 1, chapter 5

EudraLex vol 4, part 1, chapter 5 is a revision of the EU rules governing GMP for medicinal products, related to production. It adds strict guidance for steps that manufacturers should take to qualify suppliers of starting materials. For example, it states that "the selection, qualification, approval and maintenance of suppliers of starting materials … should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use."[1]

Quality requirements should be discussed and agreed upon with the suppliers, and appropriate quality aspects documented in a quality agreement or specification. Supporting documentation for each supplier and approved material should be maintained.

EMA/CHMP/BWP/187338/2014

EMA/CHMP/BWP/187338/2014 is an EMA guideline on process validation for the manufacture of biotechnology-derived active substances and the data to be provided in the regulatory submission. With regard to raw materials, it provides guidance on risk assessment, supported by documentation, to control the impact of raw materials on the quality of the final drug substance. The guidance recommends that "in the light of the variability (e.g., intrinsic to the material, related to change in supplier) of certain raw materials and based on their potential influence on the quality of the product, the impact of these materials should be addressed" as early as possible in the development process.[2]

EU 2015/C95/02

EU 2015/C95/02 is a European guideline that addresses the quality attributes of excipients, and was recently adopted by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a guidance document for the PIC/S Participating Authorities.[3] It provides guidance on the formalized risk assessment for appropriate good manufacturing practice for excipients of medicinal products for human use. Manufacturers must define the appropriate GMP for their process and then ensure that the excipient meets those standards. This

guideline is also relevant to the discussion of raw materials because manufacturers may want to apply some of these principles to how they manage the quality of all raw materials. For example, required characteristics of excipients vary due to many factors including dosage form, route of administration, dosage quantity and frequency, possible interactions with the API and formulation technology – but only the drug manufacturer knows all these details. Therefore, only the drug manufacturer is in the position to determine the correct quality for each excipient used.

Excipient suppliers cannot warrant their products as "suitable for" a particular application but they do have the responsibility to follow established guidelines (e.g., IPEC-PQG GMP, EXCiPACT™) and to provide data and documentation to support the drug manufacturers' risk assessments. The risk assessment should be performed and documented in a formal way and the documentation prepared and available for review during regulatory authority inspections.

It is recommended that the drug manufacturer engage with the excipient supplier to work together to support continuous improvement and process optimization. Similarly, this model of formalized risk assessment for excipients can also be applied to the selection of other critical raw materials as many of the same risks apply.

European Biopharmaceutical Enterprises (EBE) Concept Paper: Management and Control of Raw Materials Used in the Manufacture of Biological Medicinal Products, 29 November 2017, Version 1

This concept paper, developed by a biopharmaceutical industry consortium, "discusses background information related to raw materials regulatory requirements and industry challenges, and then highlights key principles to consider in setting up a risk-based raw material management approach and control strategy ... then provides an example of how to translate those key principles into a detailed RM risk assessment methodology, and how to apply this methodology to specific raw materials."[4] This document is effectively the first industry "how-to" translation of the various regulations relevant to qualification of raw materials.

Ensuring Sufficient Quality for Raw Materials

- Raw materials' attributes: Understand & define raw materials' attributes to control variability & contamination
- Supplier information: Appropriately document qualification & maintenance of suppliers
- Impact on quality of final drug: Address risk assessments to control raw materials' impact on final drug's quality
- Excipient model: Use regulatory approach for excipient quality as a model

Raw material and supplier selection, qualification and approval roadmap

- Drug manufacturers have the responsibility to understand and define raw material attributes to control variability and risk of contamination by impurities. Specific quality standards are not defined.
- Selection, qualification, approval and maintenance of suppliers of starting materials should be documented as part of the pharmaceutical quality system with a level of supervision proportionate to the risk of the material.
- Risk assessments to control the impact of raw materials on the quality of the final drug substance should be addressed as early in the development process as possible.
- The regulatory approach to quality attributes of excipients may be a helpful model for establishing similar strategies for selection of raw materials.

Risk assessment and quality by design are important topics for regulatory agencies, and manufacturers must stay current on recommendations for appropriate selection of raw materials and selection of suppliers. Control of manufacturing process parameters and raw material quality is necessary to mitigate risks. This risk assessment process demands a deep understanding by the drug manufacturer of raw material attributes and supply chains. However, although general regulatory guidance is given for "non-regulated" or "evolving regulation" raw materials, no detailed quality attributes are currently described, and manufacturers must develop their own strategies for risk management when it comes to establishing quality attributes for their raw materials.

Part II: Important Supply Chain Considerations

The manufacture of biopharmaceuticals includes more steps than that of small molecule drugs and can involve dozens of chemical raw materials, as well as filters, single-use processing equipment and chromatography materials, all of which must be part of the risk assessment and mitigation strategy. Each material that is used can pose a contamination risk in terms of metal or elemental impurities, residual solvents, extractables, leachables and insoluble matter that can be carried into downstream steps.

Transparency and consistency needed in supply chain

To mitigate the contamination risks posed by the many raw materials that are used, manufacturers need to have a supply chain that is transparent and consistent.

Transparency refers to the available access to all the required information about the supply chain and quality of each raw material. An important factor here is the raw material suppliers' willingness and ability to provide this information, and the convenience with which it is provided.

Consistency refers to the need to be sure that the suppliers' quality systems are designed to continue to meet the quality requirements each and every time the raw material is purchased, and to provide change notifications in case of change of any relevant parameters.

In the absence of clear regulatory definitions for raw materials – such as process chemicals used in upstream, early downstream, early synthesis steps or clean-in-place – there is a need to define appropriate quality requirements that mitigate risk but are not excessive or over-engineered for their intended use.

Strategies for selection of suppliers and raw materials

Selecting the right grade of raw materials

In the industry there can be a preference for a conservative approach, which leads to the selection of GMP or compendial grade raw materials for processing use. However, although these products have high levels of product quality and control, they can add unnecessary complexity and cost to manufacturing processes and may limit a manufacturer's choice of suppliers, thus introducing supply risk.

Compendial grade materials are not designed for processing applications and many suppliers are not equipped to develop analytical methods to support these needs. Additional confusion is introduced by compendial-tested products that may not have complete GMP supply chain traceability nor specification parameters important to bioprocessing such as endotoxin, cytotoxicity or cell performance assessment.

Qualification of suppliers should be thorough for raw materials used early in the manufacturing process but can follow processes that are more flexible than those used for excipients or APIs. Non-GMP or non-compendial grade raw materials may be considered if their manufacture at least utilizes GMP concepts and elements, and occurs at an ISO 9001 certified site. Manufacturing processes should be well defined, well documented and consistently reproducible but they do not have to be fully validated. Process control concepts can be applied to ensure product consistency, and change control parameters close to GMP standards can be used.

Similarly, analytical methods for raw materials should be proven and documented but do not require validation. Working with specialized life science suppliers that offer such relevant quality standards and that understand the requirements of different technologies and applications can be one strategy for the successful selection of the most appropriate grade of raw materials to mitigate risk, minimize cost and ensure security of supply.

Suppliers in emerging markets

Cost and availability considerations make it necessary to consider suppliers from all over the globe, including those from emerging markets. It is important to have a strategy in place for working with these suppliers as they increasingly represent a high percentage of the global availability of many essential product groups such as carbohydrates, amino acids and salts. Some manufacturers choose to completely avoid the risks posed by emerging market suppliers by not working with them at all while others work almost exclusively with them to reduce costs.

For those that do work with these suppliers, a few strategies have been found to be successful to mitigate risk:

- Establish a local presence to build networks and provide access to manufacturing sites and supply chains.
- Put capabilities in place to further process and re-purify some raw materials.
- Work with a large specialized supplier that has already established a regional presence.

Purchasing from the original manufacturer

While purchasing from the original manufacturer is not a regulatory requirement, biopharmaceutical manufacturers are encouraged to source their starting materials from the original manufacturer whenever possible to have full traceability of the supply chain.

However, this is not always practical, for example, in the case of large industrial manufacturers. Pharmaceutical manufacturing is not their primary focus and they may not be willing or able to invest in the necessary resources to support the quality needs of a pharmaceutical customer. Their distributor network might also not be set up to handle the documentation requirements of pharmaceutical manufacturers.

Instead, one successful approach to achieve maximum traceability is to work with specialized suppliers that actively qualify and audit such manufacturers and that offer additional quality support in terms of reprocessing, repackaging, quality control and documentation.

Documentation

Obtaining accurate raw material documentation in a timely manner is one of the biggest challenges to performing complex risk assessments. Delays in

getting supporting documentation from suppliers can cause uncertainty across the supply and manufacturing chain.

In order to reduce surprises, manufacturers should get commitments from their suppliers regarding the documentation that they need. Make it clear from the start of the relationship what will be needed and start discussions about quality agreements as early as possible in the qualification process. Questionnaires can be easy to complete but communication is key to ensuring there are no misunderstandings and that there is appropriate quality behind the answers.

Working with a supplier that already has detailed documentation packages prepared and readily available for raw materials of the appropriate quality can save time and resources.

Making the Supply Chain Decisions

- Ensure transparent and consistent supply chain
- Select appropriate grade of raw materials
- Mitigate risk when working with suppliers in emerging markets
- Buy from original manufacturer when possible
- Inform suppliers early about documentation requirements

Conclusion

As pharmaceutical manufacturing processes and raw material supply chains become more complex, drug manufacturers are challenged to mitigate the inherent risks of sourcing raw materials that are used in manufacturing in a continually evolving regulatory environment. The key to success is to work with specialized life science suppliers that both understand the unique quality requirements of raw materials used in pharmaceutical manufacturing and that also proactively support each biopharmaceutical manufacturer's need to identify well-defined, well-documented and consistently reproducible materials.

The Emprove® Program provides an example of one approach to this challenge. The Emprove® Program provides raw materials that are stringently qualified to industry-leading standards and are supported by comprehensive online documentation packages that meet pharmaceutical manufacturers' information needs when qualifying raw materials, completing a risk assessment or optimizing a manufacturing process.

Manufacturers must navigate the regulatory environment while at the same time ensure that raw materials used at early stages of the manufacturing process will not compromise later stages through impurities, contamination or variation. By working with an expert partner, manufacturers can develop a clear strategy for success.

References

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