How ICH Is Changing Drug Development

Regulatory Starting Materials and the Importance of Starting with Big Ideas

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The desire for a dramatic increase in process understanding over the past eight years has left industry leaders and Global Health Agencies searching for a more relevant model for developing process and drug substance understanding. Most recently, the International Conference on Harmonization (ICH) has been drafting the ICH guideline Q11 on the development and manufacture of drug substances, which takes a considerable step forward, offering sponsors greater flexibility in the definition and selection of Regulatory Starting Materials (RSM).

Q11 aims to create an environment in which sponsors can develop a design space that will accommodate changes in suppliers and/or methods of synthesizing starting materials without compromising patient safety. These fundamental principles provide assurance that a given starting material meets requisite technical and quality elements to allow for successful commercialization.

Drug development has always been forced to balance the need to get safe, efficacious, and profitable new products approved and doing so in a way that is both timely and cost effective. The environment is also continuously changing with outsourcing. Two key aims of drug development—supply of material to keep the development program on track and establishment of an efficient and robust long-term manufacturing process—are interlinked but often in competition for resources and funding.

Timing can be critical. Executing process research and development can lead to costly delays in the drug programs and wasted assets given the high attrition rate during the development phase.

In contrast, an inefficient process during early development can in due course lead to increased cost because of lower yields, delayed delivery of materials, and insufficient awareness of potential long-term costs. Delaying the development of the long-term process can also potentially inhibit process control and the effective deployment of a Quality-by-Design (QbD) approach.

When it comes to decisions about investing resources in the development process, timing is just as important to ultimate success as it is to investing in the stock market. Invest when there is high risk at the top of the market and you are doomed. Pick the turning point at the bottom of the market and you are set for a big profit.

Ultimately, however, the choice and justification of RSM for new drug substances boils down to the issue of impurities. While a sponsor might choose a supplier based, in part, on business concerns (i.e., price, reliability of supply), regulators will always require assurances of consistent purity as they relate to product safety.

By using a science and risk-based framework, this article presents a few regulatory considerations that should be taken into account when selecting starting material and synthetic routes in light of ICH Q11 draft guideline principles. From a regulatory perspective, there are no universally right or wrong choices. Instead, the choice between a long versus short synthetic route comes down to developing the correct strategy to satisfy regulators' expectations.[1]

THE INTRODUCTION OF IMPURITIES

The term "starting material" has been adopted to indicate the point where regulatory change control and current good manufacturing practices (CGMPs) are introduced into the synthesis of a drug substance. Far less regulatory oversight is present in the manufacture of starting materials.

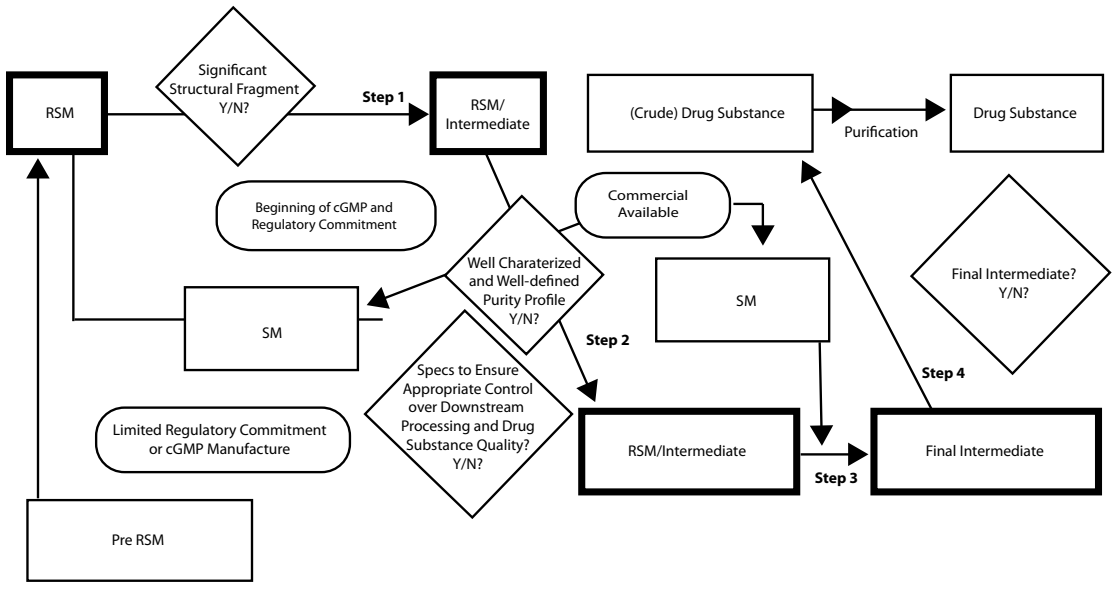

FIGURE 1: The example illustrates the importance of considering all general principles described when selecting an appropriate Regulatory Starting Material (RSM), rather than applying each general principle in isolation. A case can be made for a choice of points where regulatory change control and cGMPs are introduced, in accordance with the general principles.

Good manufacturing practices (GMPs) are required from the starting material forward in the manufacture of an active pharmaceutical ingredient (API).[2] To ensure consistent quality, regulators traditionally would prefer that GMPs start as early as possible and that suppliers and/or processes remain unchanged to prevent the introduction of novel or unanticipated impurities that existing analytic methods are not set up to detect.

Thus regulators often strive to limit risk by encouraging several strategies. First, they recommend lengthening synthetic routes to APIs by numerous steps to require GMPs further back in the synthetic sequence and reducing impurities through additional isolation/purification steps.

They recommend limiting the production of an RSM to one or more approved routes, making it possible to predict likely impurities and ensuring that analytical methodology is in place to detect them. And finally, they recommend limiting a manufacturer to a single or limited number of suppliers of an RSM to take advantage of due diligence performed by the manufacturer on selected suppliers and to prevent the introduction of novel impurities existing methodology can't detect or remove.

The overarching goal of sponsors then should be to present regulators with sufficiently discriminating analytical methodology, appropriately set starting material acceptance criteria, and effective purification processes. Moving forward, the application of the general principles described in ICH Q11 can help drive a successful negotiation strategy for obtaining regulatory approval of selected RSMs.

JUSTIFICATION WITHOUT UNDERSTANDING

FDA GUIDANCE

Much has changed since 1987, when the Food and Drug Administration (FDA) issued its initial Drug Substance Guidance for Industry. FDA's Guidance for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances[3] outlines the following criteria for defining an RSM: It is incorporated into the new drug substance as an important structural element; it is commercially available; it is a compound whose name, chemical structure, chemical and physical characteristics and properties, and impurity profile are well defined in the chemical literature; it is obtained by commonly known procedures. However, the guidance does not define "commercially available" or "well defined."

The new paradigm for the 1990's included "negotiated" starting materials, yet no official guidance or policy was ever established. In more recent times (2004), while the FDA Draft Guideline—Guidance for Industry: Drug Substance: Chemistry, Manufacturing, and Controls Information[4]—did not introduce the concept of RSM, it centered on a two-tiered checkbox documentation approach and was viewed by many as overly prescriptive.

It was eventually withdrawn. Although the guideline had worthy intentions for developing stringent selection principles, inflexible rules regarding starting materials represented an impediment for sponsors desiring to discuss alternative strategies for more designed impurity control.

EMEA GUIDANCE

Much akin to FDA's original guidance, the CHMP Guidance on the Chemistry of New Active Substances suggests that an RSM is incorporated as a significant structural fragment into the structure of a drug substance and also marks the beginning of the detailed description of the drug substance synthesis.[5] It proposes that RSM should also be fully characterized to ascertain suitability for intended use and complete specifications and should include an impurities profile.

In addition, the guidance states that starting materials should be justified. And once more this is subject to broad interpretation.

ICH Q GUIDANCES

ICH Q7A includes the following points regarding a starting material:

- It is a raw material, intermediate, or an API that is used in the production of an API.
- It is incorporated as a significant structural fragment into the structure of the API.
- It can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.
- It has defined chemical properties and structure.
- The guideline maintains that the company should designate and document the rationale for the point at which production of the API begins.

While this guideline is intended to provide guidance regarding GMPs for the manufacturing of APIs under an appropriate system for managing quality, it is not intended to define registration/filing requirements and does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements. More recently, ICH Q8, ICH Q9, and ICH Q10 introduced the concept of QbD, a more science-based approach, to create a more flexible mindset to regulatory control as well as a more systematic approach to quality risk management and quality systems for pharmaceutical products.[6,7,8]

FURTHER CHANGE IN THE AIR

As the scientific approach continues to evolve, some sponsors are willing to spend time and effort studying and improving their processes. Subsequently, ICH has sought industry collaboration in creating a guideline that is soundly grounded in scientific principles to complement the aforementioned ICH Q guidelines that support QbD.

New technologies and mindsets, led in large part by ICH's documents, are combining to help the pharmaceutical industry catch up to other industries. The draft ICH Q11[9] includes information enabling sponsors to clarify and apply the principles and concepts described in ICH Q8, Q9, and Q10 as they pertain to the development and manufacture of drug substance as well as further clarifying the type of information to provide in CTD sections 3.2.S.2.2–3.2.S.2.6.

Just as important to highlight, the draft guideline states that a company can choose to follow different approaches in developing a drug substance, identified as "traditional" and "enhanced." The traditional approach (quality by chance) to RSM identification and development, for example, generally involves only two steps[10]: providing minimal starting material information about the level and fate of impurities and defining and maintaining tight specifications for starting material and drug substances to compensate for limited synthetic knowledge.

In contrast, the enhanced (design space) approach involves selecting starting materials based on scientific understanding of the drug substance synthesis and available control mechanisms; understanding the source, formation, and fate and purge of impurities; and understanding how changes to the synthesis of the starting material may influence impurity profiles. As highlighted in ICH Q8, a greater understanding of the drug substance and its manufacturing process can create the basis for more flexible regulatory approaches.[6] The degree of operational flexibility can then generally be predicated on the level of relevant scientific knowledge provided in the application for marketing authorization.

DIFFERENT APPROACHES, DIFFERENT GOALS

The traditional approach to choosing a RSM suffers to some extent from two main shortcomings. First, sponsors often do not fully understand their manufacturing processes, rendering any justifications they offer meaningless. Second, this approach presupposes that if you change nothing, everything remains the same.

In reality, neither raw materials nor processing conditions remain fixed. Many small changes are introduced by operators or the relocation of equipment.

Even if a new supplier's raw material is within specification, its particular impurity profile may vary. This problem is exacerbated by quality assurance staff afraid to generate, much less submit, new data about manufacturing, lest they send regulators the message that they don't understand their processes well.

Furthermore, in contrast to the science and risk-based approach, it was only 20 years ago that regulatory affairs professions were taught that generating data about your processes that you cannot explain hurts more than helps. And even where understood, submitting too much information was even further discouraged.

It is also essential to emphasize here that these approaches are not mutually exclusive. Committing to one or the other, and at what time, is ultimately a risk-based decision regarding regulatory requirements (e.g., a shorter synthetic route with more analytical controls or a longer synthetic route with a reduced level of analytical controls that meet the desired quality standards).

A BIG IDEA AND PRINCIPLES

Anchored in draft ICH Q11, the following general principles should be considered together (not in isolation) when selecting starting materials[9]:

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance.
- To conduct the assessment, enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process; how changes in the process could affect the formation, fate, and purge of impurities; and why the proposed control strategy is suitable for the drug substance manufacturing process.
- Manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in Section 3.2.S.2.2 of the application.

- Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug substance.
- A starting material should be a substance of defined chemical properties and structure. Nonisolated intermediates are usually not considered appropriate starting materials.
- A starting material is incorporated as a significant structural fragment into the structure of the drug substance. "Significant structural fragment" in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials. Commonly available chemicals used to create salts, esters, or other simple derivatives should be considered reagents.

Throughout development, once new information is gained, changes to the RSM can then continue to be justified through these general principles.

INVESTING EARLY

In return for greater operational flexibility, sponsors will need to demonstrate a willingness to develop a robust control strategy focused on analytical capability, starting material acceptance criteria, and process purification capability. Regulators are likely to question any change that was not thoroughly considered at the time the control strategy was developed.

By establishing critical controls early, you can distinguish those factors that truly are critical from those that are not. The sponsor must be prepared to provide data supporting the following control aspects:

Analytical Control—the initial characterization of the starting material and a discussion of how selected analytic methods would detect and control impurities at all stages, including those that arise from changes in supplier or process.

Process Control—make known enough of the process and control strategy throughout the synthesis, identify the final intermediate and discuss in detail the fate of impurities and how the proposed design space is set up to detect and control impurities arising from synthesis changes.[10]

The ability to demonstrate the existence of such controls will go a long way toward heading off regulators' requests to limit the number of suppliers of starting materials or the need to require a longer synthesis.

WHERE DO WE GO FROM HERE?

Focusing on good science—not necessarily exhaustive science—is imperative. Every company has its own unique in-house capabilities, resources, and project portfolios, so no single template can drive these decisions for every sponsor or every project.

However, the principles discussed herein and these histories gained demonstrate that the road map for developing a robust, efficient, and cost-effective process is established during the earliest phase of development. Prompt discussion of RSMs with regulators allows time for full development of analytical and process data to support any new proposals or strategy changes.

The justification of regulatory starting materials and choice of synthetic route for a drug substance is a balance between appropriate regulatory control and sustainable economic manufacture. A variety of factors can impact the practicality and economic feasibility of applying regulatory change control or CGMPs. Draft ICH Q11 serves to suggest that selection of an RSM is best managed case-by-case by means of the general principles and discussed holistically, rather than in isolation.

ICH Q11, like the other ICH Q guidelines, demands focusing on safety throughout clinical, production, and testing. Sponsors must be proactive in addressing safety concerns throughout the development process and clearly document their rationale in the filing.

This requires an alignment of business practices with big ideas, in light of ICH Q11. The successful marketing application will link these elements in a development summary that forcefully supports the sponsor's case. Start with big ideas and let science drive the decision.

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DISCUSSION POINT

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What have been key challenges and a common set of expectations for the selection of a regulatory starting material?

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