Strategies for Defending Regulatory Starting Materials Designation

Introduction

WuXi STA recently released an Xtalks webinar on 'Strategies for Regulatory Starting Materials Designation in Drug Development and Manufacturing'. The in-depth review featured a joint presentation, delivered by Dr. Valdas Jurkauskas, Vice President and head of CMC at Akebia Therapeutics and Dr. Ke Chen, Vice President of Process R&D at WuXi STA.

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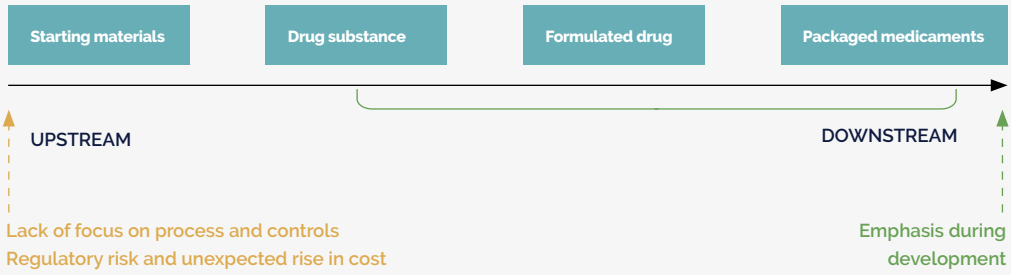
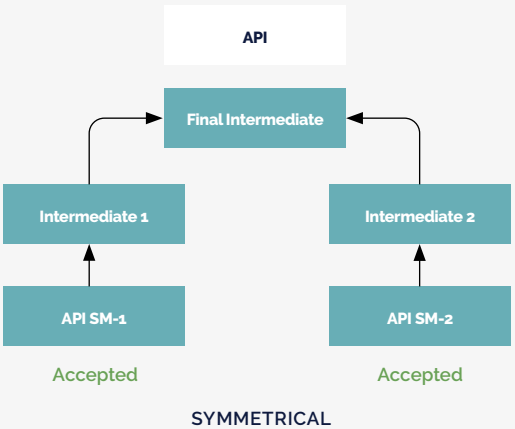
Background to RSM

Pharma companies often concentrate their attention on the downstream end of the pharmaceutical development supply chain – i.e. drug substance through to final product – for validation and regulatory alignment as their product nears commercialization. The upstream portion of the supply chain, starting materials and advanced intermediates, is consequently sometimes overlooked in mapping the full regulatory picture. However, failing to take due care and consideration of processes and controls regarding starting materials can lead to critical regulatory risk and unexpected rises in costs. For example, if a regulatory agency rejects a sponsor's starting materials designation then all downstream process development steps may need to be repeated in their entirety. The risks increase naturally the more regulatory bodies are involved, and so sponsors must plan alignment and approval based around defending RSM designation.



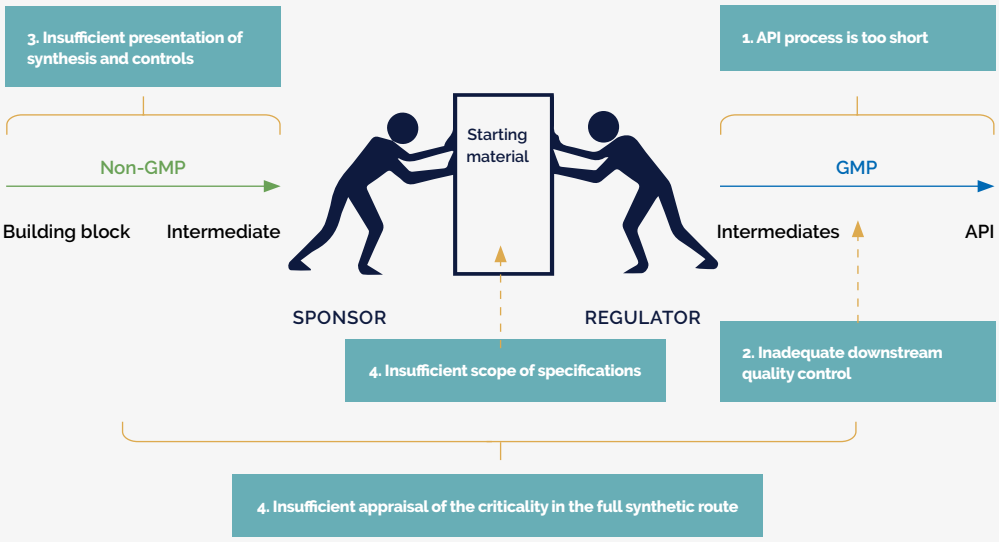
What is an RSM?

A Regulatory Starting Material could be a raw material, processed intermediate, or even the API itself. It could be a commodity, meaning it is available from multiple sources, and in large quantities, or more often for NCEs, it will be produced using a custom-designed manufacturing process. By definition, it should be used in the production of the API, and it should present a significant structural fragment of the API's chemical structure.



Reasons why agencies reject the proposed RSM designation

There are five main reasons as to why agencies reject the proposed starting material designation. Arguably the most common reason for rejection is that the API process is too short, with too few critical steps. Another reason for rejection that also relates to the GMP portion of the API process is an inadequate presentation of controls, which is usually related to a lack of process controls, or inadequate scope of specifications for formal process intermediates. The next two reasons are related to the RSMs themselves – these are an insufficient presentation of processes and controls and insufficient scope of specifications. And finally, after the agency has reviewed the entire application, they may feel that there was an insufficient appraisal of critically in the full synthetic route.



> When push back happens, the sponsor should not be taken by surprise, but rather be prepared for such an event.
>
> Dr Valdas Jurkauskas

Get ahead with a Type C meeting

During the development of a new drug candidate the sponsor typically holds three discussions with the FDA before NDA filing – one during the discovery phase (to discuss IND-enabling requirements), one at the end of phase II (to seek FDA's agreement on starting material designation, and the scope of critical quality attributes etc.), and one final pre-NDA meeting (to review minutes from previous meetings, discuss the submission plan and post-approval commitments). However, we suggest requesting an additional 'Type C' meeting ahead of the pre-NDA meeting to ensure alignment between the FDA and sponsor, which minimizes the risk of having to delay drug application submission should issues arise in the pre-NDA meeting.

Interactions with FDA

When to consider RSM risk mitigation

In general, if the proposed RSM is less than three chemical steps away from the final drug substance, one should consider risk mitigation for strategic planning. Bearing in mind that three steps refer to chemical transformations. From the reviewer's perspective, only C-C or C-X bond formations count when it comes to RSM design. Additionally, RSM risk mitigation is crucial for programs that either target global filing – the more regulatory agencies involved the mores scope for push back – or if they have aggressive clinical timelines (i.e. for first-in-class indications with accelerated timelines).

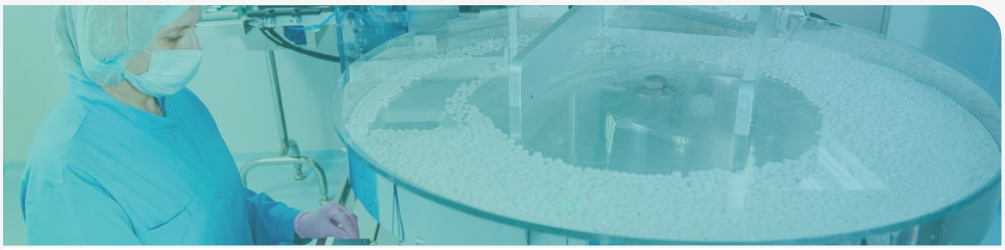
Approaches to RSM risk mitigation

There are three common approaches to RSM risk mitigation. The first approach involves manufacturing the RSM for the registration under GMP control, so there is no impact on NDA stability legitimacy. In the second approach, the CMC team will need to initiate accelerated work on the new back-up RSM options, should an agency push back on your RSM selection. With this approach, it is critical that to know that capacity won't be an issue because there will be a lot of activities to cover within a very short amount of time, so it is better suited to sponsors working with a CDMO with very large capacity. A third approach, the CMC team still submits the NDA package using current RSM, but alongside this, a QbD and validation campaign is carried out in the background. This activity can be done either before or parallel with NDA submission. It delivers a much more balanced timeline, but requires extra financial investment upfront, so it is often preferred for those must-win programs as long as you can get clearance on the budget. Both FDA and EMA typically require 6 to 12 months for the initial review. So as long as you complete RSM activity before the first run response your plan should work out perfectly.

Case study 1

Preparing for FDA and EMA objections

- Client files an NDA application that was prepared by their previous CDMO partner] to maintain the drug's development timeline
- In the background, a comprehensive risk assessment is conducted and considerable risk with the current CMC package was found, especially on the RSM designation
- The client initiated a collaboration with WuXi STA to carry out additional studies – including additional impurity identification, method development, and PGI assessment –to support the justification of RSM
- The studies helped effectively address the questions from FDA reviewers and eventually lead to approval from FDA using the current RSM designation
- Based on the FDA's first round of questions, the client recognized the potential risk of RSM push back from EMA and subsequently worked with WuXi STA to initiate activities on a new RSM
- EMA rejected the initial RSM but accepted the new one for NDA approval



Case study 2

Identification of trigger points for mitigation

- A biotech client with a first-in-class drug candidate targeting US filing worked closely with WuXi STA, who designed and mapped out the overall CMC strategy
- A back-up RSM was also identified, along with two trigger points for the mitigation plan, in parallel
- The first trigger point was the end of Phase II meeting with FDA, during which the client received some feedback on the CMC data set – including RSM designation – and the second trigger point was a readout from a pivotal clinical trial
- A decision tree was designed to appropriately respond to potentially negative feedback from the FDA during the trigger points, whereby WuXi STA would initiate additional work on the back-up RSM before NDA submission
- The program is still ongoing, but the first trigger point has been passed successfully, and we are confident that the CMC activity will remain off the critical path for the NDA filing.

Case study 3

Capacity to run hundreds of tests key to maintaining timelines

- A client developing a drug candidate with multiple indications unexpectedly received negative feedback from the EMA on their RSM designation - the client and WuXi STA started a collaboration to address this challenge
- Rapid initiation of the back-up plan for new RSM, followed by extensive R&D and a successful validation campaign lead to the eventual acceptance of the CMC data set.
- Parallel commercial production using the new RSM also minimized the impact on commercial launch
- Vast testing capacity was needed to address the unexpected push back on RSM designation quickly, maintaining the overall timeline for NDA filing and launch

Conclusion

RSM is often overlooked when mapping out the full regulatory picture, hence this could lead to critical regulatory risk, unexpected delays and rising costs should problems arise. Agencies can reject RSM designations for several reasons relating to the GMP portion of API synthesis, the RSMs themselves, or the following review of the entire NDA application. Having an additional 'Type C' meeting with the agency can help prevent unexpected push backs before the pre-NDA filing meeting. RSM risk mitigation should be strongly considered if the proposed RSM is less than three chemical steps away from the final drug substance, and in all accelerated pathways.