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Starting Materials Selection and Life Cycle Management

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This article discusses the selection of Starting Materials (SMs) for the commercial manufacture of Active Pharmaceutical Ingredients (APIs) and challenges and potential solutions to the selection and agreement of SMs.

Selection of Starting Materials (SM) for commercial manufacture of an Active Pharmaceutical Ingredient (API) is an important matter for industry and regulators. This starting material, once approved, becomes the starting point for application of current Good Manufacturing Practice (cGMP), and manufacturing process and control commitments.

Regulatory expectations in ICH countries for selection of SMs are provided in Q11 "Development and Manufacture of Drug Substances." In Q11, a set of "principles" are provided for an applicant to consider as part of justification of proposed SMs. These principles provide a set of considerations that can support the proposal of an SM, but do not establish an algorithm for decision-making, so every applicant who considers a process will not immediately be led to the same SM proposal. This flexibility is appropriate as different approaches to manufacturing, supply and control can support different SMs and means that the SM proposal requires justification. The justification becomes a matter for review and approval. A regulator can question proposed SMs and may require the applicant to redefine their proposed SM, usually earlier in the synthesis. As this decision is clearly linked to the supply of the API, the refusal of a proposed SM can have significant impact on the applicant's supply intentions and thus, is worthy of careful attention and risk management.

This article considers the principles established in Q11 and examines the implementation challenges for industry and regulators. The article also provides insights into how an applicant might address such challenges.

It is important that regulators are assured that the applicant has an approach to SM supply and quality management that assures the quality of the API across the product lifecycle (i.e., from first approval and then through subsequent changes to supply).

Let's begin by considering regulatory expectations. It is a requirement of pharmaceutical manufacturing regulations globally that the marketing application (or change application) provides information on the API manufacture, either as part of the submission (3.2.S) or (in some countries) by reference to a separate master file. This API manufacturing process description starts with introduction of the proposed SMs. (EU regulators find a summary of the process used to make proposed SMs useful in evaluating the appropriateness of SM controls.) Global regulations require that API be made under cGMP for supply to patients and that cGMP is appropriately applied across the process described in the submission, i.e., SMs become the cGMP starting point. Global regulations also require manufacture be appropriately validated for commercial supply, and validation should encompass critical aspects of the described manufacturing process. Thus, the proposed SMs become the starting point for implementing approaches to validation.

The pharmaceutical manufacturer is responsible for ensuring quality by ensuring manufacture is conducted in accordance with cGMP and the product license. The regulatory role is to ensure the quality, safety and efficacy of product that reaches the patient. To appropriately address the accountability placed on the regulatory system, a

regulator needs to be able to assess API quality/safety and assess risks to quality/safety in API manufacture. Of course, industry also needs to control the same risks and needs to be "in control" of SM quality and supply. It is important to assure the regulator that such quality control is in place and can be maintained across time and change. Such assurance might be provided by sharing controls placed on the SM and its supply by the applicant, by being transparent why SM selection decisions are made and by providing information on how risks to quality are managed. Without such information, a regulator may not have sufficient confidence in the SM to approve it for commercial manufacture. Even with such information, the regulator may seek further assurances based on their assessment of the balance of risks to quality and quality controls. Providing information for assessment is a key component in achieving approval, and without transparency, trust in the proposal and the resultant quality would be harder to establish.

No "Absolute Rules" to Guide the Process of Selection, Justification and Acceptance of an SM

"Rules" are designed to be prescriptive. "Rules" could lead to regulators being obliged to accept a SM simply because it complies with "the rules" even if the proposed SM is one the regulator finds to be a concern. ICH determined that a lack of absolute rules is appropriate. Instead, Q11 provided certain principles for consideration that allow an applicant to make (and regulators to review) a proposal in a case-by-case manner, that is closely related to the case-by-case selection of manufacturing steps, suppliers and controls that optimally provides for manufacture of API.

Q11 allows a material with significant pre-existing, non-pharmaceutical use (a commodity material) to be a proposed SM without further justification. Therefore, one potential "rule" could have been that "all SMs should be commercially-available" (if this concept could be simply defined). This rule, however, would prevent a SM without this prior usage being considered. The rule also would mean that if an applicant has to use only commodity materials as SMs, they could be "locked into" sub-optimal manufacturing routes (with adverse impacts on costs, waste, environmental impact, process safety, etc.) or need to use particular chemistries or technologies to elaborate the commodity SM to API that are not available to the applicant "in house."

The suggestion that "SMs should be commercially-available" is potentially useful as this precludes the need to manufacture any commodity material under cGMP to allow for its use in pharmaceutical manufacture. And, given the structural complexity of many APIs and the relative structural "simplicity" of most commodity chemicals, this rule could have the effect of keeping SMs simple and distinct in structural (and probably physico-chemical) terms from API. This has the effect of ensuring "significant chemistry" is done to produce the API and making it less likely that impurities from structurally dis-similar SMs will be present in API.

Thus, behind potential "rules" lie principles that underpin what is important in selecting SMs, e.g., that the SM quality has little likelihood of impurities impacting on API quality.

The suggestion that "SMs should be 'X' steps from API" is similar, as again significant chemistry will be conducted to convert SM to API and the isolations conducted will assist in the purge of SM-associated impurities during processing. The underlying principles that there should be little likelihood of carry-over of unmanaged impacts to API quality and ensuring the regulator will be provided with significant understanding of the manufacture of API and the risks that may be associated with its quality, allow proper assessment of associated controls.

So, deep concerns for quality management, transparency of manufacturing information and risk assessment of impurity risks and controls are reflected into the Q11 principles, and sought by regulators when assessing proposed SMs for manufacture of a commercial API. However, providing guiding principles makes interpretation and implementation more open to discussion than would "simple" (but inflexible) "rules."

Q11 makes clear that ALL the principles need to be considered to support SM selection, but that no one principle is an absolute expectation. The Q11 principles address building quality in to API through development and implementation of appropriate control strategies for significant materials.

The Q11 principles that support SM selection are:

- A SM will be a significant fragment of drug substance.
- Carryover of risks to drug substance quality is of lower potential impact the further the SM is from API (in terms of number of steps or structural similarity).
- The control strategy for API and process needs to be appropriate and to judge this, information on impurity potential presence and formation can be needed (even for some SMs).
- Manufacturing steps that significantly impact API impurity profile should normally be included in S.2.2 (i.e., after the SM).
- Each branch of a manufacturing process begins with one or more SMs.
- A SM should be of defined chemical properties and structure (and be isolated).

Q11 guides the applicant to provide a justification for why each proposed SM is appropriate in light of the general principles. The justification can include information on the ability of analytical methods to detect SM impurities; the fate and purge of those impurities and their derivatives in

subsequent steps and how the proposed SM specification contributes to the overall control strategy. (Changes to the SM specification are subject to change management).

This Q11 content is helpful, but as the guidance does not establish "simple rules" different companies may take different approaches to SM selection. Regulators can have questions and challenges on a company's SM proposal. Regulatory agencies can want to see longer regulatory syntheses than an applicant proposes. Regulators also note information on SM manufacture can be important to as part of risk evaluation.

So, every applicant can develop proposals based on Q11 principles and establish what they believe to be a justification for SM selection proposals. This needs to include information to allow regulators to reach conclusions on how risks have been managed and a well-rationalized control strategy for impurities.

The expectation for consistency of decisions has been a concern with the concepts built into ICH Q11. When applicants invest to different degrees in product and process understanding and controls, there is a very reasonable case for regulatory acceptance of differences from such applicants. Thus, the ideal outcome may not be consistency, but predictability about acceptability of justifications based on shared knowledge, risk management and controls applied.

To approach this predictability, there needs to be transparent exchange of information and a mutual appreciation of what needs to be delivered from the management of SM supply, and maintained across the product's lifecycle. Regulators welcome pre-submission on starting material proposals and associated control strategies.

The ISPE team collected key questions that regulators (assessors and inspectors) and industry had on this topic. Here we provide context to these questions and suggest some ways that concerns might be addressed. It is hoped that this will lead to increased mutual understanding and easier implementation of Q11 principles.

Regulators may not be Aware Why SM Selection Decisions are Made by Industry – Approaches Seem Very Variable Between Companies. Can This be Explained?

It would be helpful for an applicant to provide an understanding of why they have made SM proposals.

A company can have a variety of reasons in making the proposal for a SM, as several factors are important to a company in the finalization of the API manufacturing process. These factors include:

- Availability of commercial commodity materials, which can guide SM selected during development and also identify suppliers who might be able to provide a later process "intermediate," based on their capabilities and expertise.

- The applicant's internal manufacturing capabilities. Particular chemistries (e.g., low temperature reactions; high pressure reactions; particular functional transformations) may be most effective for efficient API manufacture but that the applicant cannot support in their facilities and are only available when working in partnership with suppliers who have specific expertise and facilities.

- Applicant's internal manufacturing capacity. This is a finite resource and may be managed such that vital final steps of all key medicines in the portfolio can be made. Capacity analysis considers manufacturing volumes of medicines (which can change with time) and process efficiency of manufacturing routes. Furthermore, some process steps can need dedicated plant or environmental treatment and all these factors have to be considered in determining the optimal route and process. "Convergent" rather than "linear" syntheses can be favored.

- Security of supply. Oftentimes, an API manufacturer will want > 1 source of a SM to manage efficient and secure supply and will establish relationships with key suppliers. There is no regulatory constraint on this approach, providing each source produces API of acceptable quality. Dependent upon capacity and capability, this also can involve a "make – buy" option wherein the applicant and other suppliers make a proposed SM. This explains why regulators can find that an applicant is making a proposed SM. This "make – buy" approach also can be utilized when applicant and supplier have collaborated to develop the process to manufacture the SM. Security of supply is not as easily assured if SM comes from a single source using "trade-secret" technology.

- Process understanding. The better an applicant understands the API manufacturing process, the clearer becomes the understanding of which process elements impact on API quality, and the understanding of what control strategy is needed to assure quality of the API. Thus, an applicant who knows little about the process may need to maintain similar materials and controls as used in development (e.g., same SMs and specifications based on supply quality received), whereas an applicant who has invested in increased product/process knowledge may know that significant API impurities result from later processing steps. Similarly, the applicant may understand that certain aspects of SM quality are more important than others in assuring API quality and thus the SM specification can include some attributes and not others and can establish limits wider than historical supply quality for some attributes, based on the applicant's knowledge of the purge (and fate) of SM impurities. This process knowledge also can enable the applicant to pro-

pose controls on unspecified impurities in the SM above the limit expected in the API.

- Number of steps conducted under cGMP. cGMP commences from the proposed SMs. The legislative requirement to manufacture under cGMP was introduced to assure quality of the final API. The more steps carried out under cGMP, potentially the higher assurance of quality.

- The manufacturer will select a manufacturing route to seek to optimize a variety of factors – manufacturing efficiency, environmental impact, and economics.

- Support process improvement. The manufacturing process at initial approval may not be optimized (for throughput, cost, environmental input, etc.) and the manufacturer may wish to improve the process. Some degree of regulatory flexibility may be sought by proposing short manufacturing processes. However, this needs to be balanced by considering what steps impact and what controls are necessary for API quality, which should then be included in the regulatory synthetic pathway. The risks to API quality are minimized when process understanding has been used to rationally select the SM.

Why are Commercially-Available/ Commodity Materials not Always Selected?

It may not be needed to propose a commercially-available commodity SM to assure API quality, and to do so may not allow for optimization of cost and manufacturing robustness. In addition, this approach could be "non-scientific" if the generation of API critical quality attributes could be assured by focus on later steps and by provision of controls for later materials, one of which could be proposed as the SM, supported by appropriate justification.

"Commercial availability" may change across time – the chemicals industry may target non-commodity intermediates in pharmaceutical manufacturing as commercial opportunities. This could bring very cost-effective and efficient new materials to the market. It would be strange if later manufacturers of the API should be able to adopt such later intermediates without question of the overall control and quality management approach, and it would be strange if an innovator company could not also switch to such materials as they became available (the innovator being best-positioned to understand the control needs for the later intermediate).

It would be helpful for an applicant to provide explanation of why they have not proposed a commercially-available commodity material as the proposed SM.

A company can have several reasons in choosing not to propose a commercially available commodity SM:

- The expectation that a commodity material be the SM can lead to certain processes/ chemistries being needed within manufacturing that 1. may not be optimal for API manufacture; 2. may not be available to the applicant in their facilities; and 3. may lead to one route being selected over another simply on the basis of the current catalogue of commodity chemicals.

- Building a relationship with a supplier of a commodity material to provide a later material in the manufacturing route can improve overall effectiveness and economy of manufacture.

- Proposal of a commercially available commodity material as SM does not remove the need for the proposed SM to have a suitable specification and appropriate control methodology to assure API quality.

- One does not always know how a commercially available commodity material is made. Thus, understanding the needs of control methodologies in terms of impurity monitoring capabilities can be difficult. Conversely, if one has developed chemistry to a later intermediate (or co-developed this with a supplier), one understands the "later steps" in the SM manufacture and thus can more readily develop control methodology/specifications.

- A commodity material can have multiple suppliers and different quality from different supply sources. Each source can have different potential impurities. This makes quality assurance less easy and can make manufacturing less robust. Reliance on commodity sources can appear to increase supply chain security and quality but can have the opposite effect.

- Even if a later intermediate comes available over time, it does not mean that the "late" commercial material will necessarily be suitable for use as SM as it needs to both meet specification and assure against, e.g., cross-contamination risks from manufacture/supply. Thus, a SM being made for an applicant from a partnership with a limited number of suppliers can be a more stable and secure position than "commercial availability."

Of course, it can be necessary to utilize commodity materials as SMs in API manufacture. This can happen when a late fragment in a convergent synthesis comes from a commodity material. There is nothing wrong with such a proposal as long as the risks to API quality are considered and appropriate specifications/control methods put in place to assure API quality.

The underlying principle is that the applicant needs to control risks to quality and the regulators need to be able to

assess the controls put in place. When this is considered, use of only commercially-available commodity materials as SMs need be no more appropriate than the proposal of a later material as the SM. There may be no correlation between commercial-availability and the risk to API quality.

Why is a Certain Number of Steps not Always Proposed?

This "number of steps" approach is seen as a means of guarding against carry-over of impurities and managing against contamination risks. It might be reasonable to have increased levels of concern any time a SM proposal is made which does not mean that a certain number of steps (or isolations) to API results. However, it should continue to be possible for an applicant to make a justification of a SM with a low number of steps to API provided risks to quality are adequately addressed. After all, in a convergent synthesis, few steps may be used to convert commodity materials to API and in some syntheses, a late commodity material can enter a process very close to API. Both cases can be acceptable and in both cases the focus is on the adequacy of controls and assurance of API quality and not on absolute step-counting.

It would be helpful for an applicant to provide more understanding of why they have proposed SM closer to the API as the proposed SM.

A company can have several reasons in not choosing to propose an earlier material as the SM. These factors include:

- The optimal manufacturing process is a convergent one, and thus, commodity SMs are closer to the API.
- A commodity material enters the process closer to the API.
- In a process to an API, no significant API impurities come from earlier steps/materials. Significant impurities result from early steps in some syntheses and later steps in others – convergent syntheses can often support more impurity purge in a shorter number of steps than linear syntheses due to greater difference between SM and API properties.

How can Specifications/Control Strategy Manage Risk to Quality (Even for a SM not Separated From API by Many Steps)?

An applicant can invest in understanding what impurities should be controlled on the specification of a proposed SM. This understanding can be based on knowledge of how the proposed SM is made, which potential impurities (organic materials, solvents, elemental residues) could be associated with its manufacture (even by a number of potential routes of synthesis), which impurities need to be specified, which need to be capable of monitoring by the analytical methods, and what levels of impurities can be accepted in the SM to assure API quality. This approach may not be taken by all applicants, but a proposal from one applicant does not need to match that from another, it only needs to be appropriate based on the knowledge the applicant has shared and the controls that the applicant has put in place to manage risks to API quality.

This is best done when the latter stages of SM manufacture are known to the applicant. The SM specification is most meaningful when links from the impurities specified on the SM specification to the API specification are clearly understood – i.e., which impurities purge, which progress to API, perhaps in modified form, and what levels should be controlled.

An applicant who presents such understanding of their control strategy that supports the specification of the proposed SM will have gone some way to convincing the regulator of the appropriateness of the SM proposed. The regulator may still have questions on how this understanding and quality is maintained against change and how this proposed supply manages cross-contamination concerns the regulator may have. The API manufacturer can work with the SM supplier to address such concerns, e.g. by ensuring that changes in SM manufacture are communicated from the SM supplier to the API manufacturer.

How can Specifications/Control Strategy/ Quality System Manage Changes to SM Supply?

The acceptance of a proposed SM and its associated control strategy needs to maintain quality across the product lifecycle. This is a significant concern, as if a process description and control strategy begins with the SMs, then all changes prior to this point will not be under regulatory purview.

Furthermore, some changes could be significant, but invisible to the test methodologies applied, so materials that should fail could be passed due to the inability of control methods to manage the change made. Thus, reliance on the control strategy may not allow the regulator to meet their responsibility to ensure quality of the medicine.

This risk could exist irrespective of the length of a route and irrespective of whether the proposed SM is commercial or not (indeed, a commodity SM might be most at risk from such invisible changes). What needs to be considered by applicant and regulators alike are questions such as: 1. how can the manufacturer of API be aware of changes and manage their impact? 2. does the analytical methodology have the power to manage this change? and 3. is SM specification still relevant?

An API manufacturer can establish an agreement with the supplier to communicate changes to SM manufacture so that the API manufacturer can assess any risk to API quality. The API manufacturer can evaluate the change in SM manufacture for any new potential impurities that may be present and evaluate whether the analytical methodologies

remain valid to assure SM quality. If the analytical methods are unsuitable, then new methodologies should be developed, so that the change can be properly evaluated. If the analytical methods are able to detect new potential impurities and the post-change SM continues to meet specification, the change is likely to have no impact on API quality. If there are new detected impurities in the post-change SM, it may be that the material should not be used until it is understood if the new impurities lead to any significant change in API quality. Where there are changes to the SM specification or the analytical methods this should be communicated to the regulators.

Regulations require that the company quality authority is independent of the manufacturing responsibility and that there is a professional and independent quality authority within a company to oversee the proper working of such documented change management processes.

How Can Manufacturing Route Risk Assessment Support SM Selection Decision?

An applicant thinking rationally about what SMs to propose, knowing regulators might be hoping for at least "X" steps, and a solid rationale for anything less, should bring their understanding of the process to bear on the SM justification and present the knowledge about what impacts API quality to the regulator.

An applicant can understand which API manufacturing steps lead to significant API impurities. The applicant can share this knowledge with the regulator as part of the SM justification. The applicant also can understand what the (potential) SM impurity profile is and how the SM impurities are handled by the API manufacturing process – Do they purge? Where? How much? Are they converted to other materials downstream?

The applicant who understands the potential SM impurity profile is well placed to establish appropriate methods for SM control and best placed to develop the manufacturing process for the API to build in processing operations that can remove impurities as the manufacturing process proceeds. With this knowledge, an applicant may be able to propose a SM with no potential impurities that carry-over to API, or propose a SM which has carryover, but where the downstream control and qualification needs are managed.

Does Proposed SM Need to be Before the Point of Introduction of Chirality?

Chirality is a critical quality attribute of many active substances. Regulators have considered that the step that establishes the API's chiral quality should be on the regulated process description and that the SM should be before introduction of chirality.

With time, it has been recognized that this is not essential, as the control strategy applied to a chiral SM, and downstream intermediates and API, can assure the API's chiral quality. This allows for use of "chiral pool" SMs (sugars and amino acids, etc.), and for products of resolutions (enzymatic or chemical) to be accepted as SMs when supported by suitable controls. This flexibility supports innovation, as industry can then adopt different approaches to produce the chiral SM, providing the SM specification continues to assure quality of the SM and API – e.g. a SM resulting from chiral resolution (with a 50% loss of the unwanted enantiomer) can be optimized to a route where the chirality is established in other ways (e.g. asymmetric hydrogenation), leading to more efficient API manufacture.

Does Proposed SM Need to be Before the First Use of Mutagenic Reagents?

A regulator needs to know the applicant is in control of such risks to API quality. Mutagenic impurities can be seen as potentially critical quality attributes and thus, regulators can expect that steps that use/generate mutagenic materials should be on the regulated process. Good process design can however look to use/generate mutagenic materials early in manufacturing (precisely to lessen the likelihood of carry-over to API).

Again, it may not be essential for steps using/generating mutagenic materials to be on the described manufacturing process provided the control strategy adequately manages risk.

The quality of a proposed SM (e.g., an aromatic amine) can be controlled with respect to mutagenic potential impurities (e.g., precursor aromatic nitro compound) by analytical method and as need be by specification. Again, the applicant can with knowledge of the manufacturing process of the proposed SM, build necessary controls into the SM specification. In this case, the mutagenic impurity can be controlled at the SM either at the required API limit or at a limit that purges to the necessary API limit. (Note that a mutagenic impurity introduced early may be purged during subsequent processing and may not have the potential to impact API quality.)

How can GMP Risks Associated With the use of a SM That Enters a Manufacturing Process at a Late Stage be Managed?

Short routes from SMs to API may increase cGMP risks to API quality by carry-over of "unknown" impurities (or contaminants from manufacture of the proposed SM).

Such risks can be managed by agreeing with the supplier to, e.g., establish appropriate cleaning/cross-contamination management procedures during manufacture. An API can be manufactured by the applicant from a SM produced by a supply partner under such an agreement (that can also include

change communication), and together with an appropriate control strategy, this can be a suitable manufacturing strategy. Having a supply agreement with a SM manufacturer does not, however, provide the basis for a SM proposal.

There is no presumption that subsequent API suppliers entering the market (say for supply of a generic product) should have the same agreed SM as the original product. Approval should be on the basis of how that supplier manages risks to API quality from their proposed manufacturing supply chain.

Summary

There are a number of factors to be considered in API SM selection and justification. This selection decision can be approached in a case-by-case manner using scientific understanding and the quality system to manage risks. This flexibility is well-supported by the Q11 principles. These provide useful guidance and can lead to effective SM selection, provided the spirit of these principles is appropriately applied.

Hopefully, the consideration here of key questions that arise from API SM proposals enable improved communication that supports smoother discussion of API SM proposals. Quality management of pharmaceuticals is of paramount importance to all stakeholders, including patients, and managing SM quality plays a foundational role in assuring quality of medicines.

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