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Part 3: Designation and Justification of API Starting Materials: Proposed Framework for Alignment from an Industry Perspective

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ABSTRACT: Designation and justification of an Active Pharmaceutical Ingredient Starting Material (API SM) is an important aspect of the drug development and commercialization process and defines the point at which the GMP manufacturing process starts (ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients). In 2014, the API SM Working Group of the International Consortium for Innovation & Quality in Pharmaceutical Development (IQ Consortium or IQ), composed of representatives from the Active Pharmaceutical Ingredient and Analytical Leadership Groups, published two manuscripts on API SMs that provided (1) a review and industry perspective of the regulatory guidances that support designation and justification of API SMs, and (2) a summary of current practices across member companies of the IQ Consortium on designation and justification of API SMs based upon a survey completed by the IQ member companies. The information and data presented in these manuscripts provided a thorough overview of current practices but more importantly revealed the absence of a universal approach within the pharmaceutical industry to justifying API SMs. Using the information from manuscript 1 and 2, this manuscript, which represents part 3 of the topic series, will provide a guiding framework that is based upon the principles described in ICH Q11 and which includes relevant experiences of the IQ member companies, for the justification of a proposed API SM to the regulatory agencies.

1. INTRODUCTION

The material in this manuscript was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium or IQ). The IQ Consortium is a not-for-profit organization comprised of pharmaceutical and biotechnology companies with a mission of advancing science-based and scientifically driven standards and regulations for pharmaceutical and biotechnology products, worldwide. Today, IQ represents 37 pharmaceutical and biotechnology companies. Please visit www.iqconsortium.org for more information.

The IQ Consortium is composed of 10 Leadership Groups that allow experts in major areas of pharmaceutical science to discuss and develop strategies to address key challenges within the industry. Within each Leadership Group are a series of Working Groups, project-based expert groups, which are formed to address specific, critical, and timely issues in drug development. Within this framework, the API Leadership Group, in 2011 formed an API Starting Material (API[1] SM) Working Group to adddress three key questions related to understanding how IQ member companies make important decisions around the designation and justification of API SM that include:

1. How has the regulatory perspective on API SM designation developed over time?[2]
2. What are peer companies doing now and how many steps from the API SM to the drug substance (DS) have been typically required to control carry-over of impurities, with special consideration for mutagenic impurities (MIs)?[3]
3. What should the industry do, if anything, to improve the current process?

Questions 1 and 2 were addressed in manuscripts 1 and 2 of this series. *The primary goal of this manuscript is to provide an answer to question 3.*

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While there is guidance (ICH Q11[4] and ICH Q7[5]) and literature available that describes examples for the API SM selection and justification process, there are opportunities to provide greater clarity, as noted in several publications and guidances.[2−7] Several questions that have been repeatedly asked are listed below, for example:

- How should the standards from ICH Q11 be interpreted and consistently applied?
- What constitutes an API SM, and what represents a "significant structural element" of the DS?
- What level of API SM manufacturing process detail should be included in the API SM justification package?
- What extent of data for impurities (including byproducts, MIs, catalysts, and residual solvents) present in the API SM synthesis should be described in API SM justification packages?
- How much data is needed to facilitate the regulatory agency's impact evaluation of the selected API SM on DS quality?
- What is the relationship between API SM structural or synthetic complexity,[8] number of GMP steps from the API SM to the final DS, and the related acceptable risk?
- What is the most effective way to address the concerns that changes in the steps of the API SM manufacture (1) may impact DS quality and (2) are outside the direct oversight of regulatory agencies?
- What is the definition of criticality as it pertains to a step in the synthetic sequence?

The above questions can highlight the need to provide a common framework for justification of the API SM and greater clarification on key aspects of that framework to further improve the current process. The scope of this manuscript is not to answer all the questions outlined above but to propose a common framework of data that can support the API SM justification. This manuscript will outline the high level content of this common framework and the value that each element can bring to the API SM justification.

Prior to submission of marketing applications, sponsors have the opportunity to share process knowledge and data demonstrating robust process control, with the aim of gaining regulatory authority assent to proposed API SMs. As discussed in refs 2 and 3, this topic is *commonly* presented to the regulators such as FDA during End-of-Phase 2 (EOP2) or Type C meetings, while feedback from other regulators such as the EMA may be garnered via the scientific advice process. Sponsors have found that they do not always receive consistent feedback from the agencies with regards to their proposed API SM. While there is alignment on the intent of ICH Q11,[4] there is generally less alignment on the interpretation and/or application of a control strategy (propinquity and complexity vs process knowledge and process control) to support the API SM justification.[9−11] The authors of this manuscript believe that a thorough and comprehensive justification, presented in a common framework following the guidance given by ICH Q11 is the best tool for ensuring globally harmonized results from interactions with regulatory authorities. This would require disclosure of enough information about each proposed API SM process so that impurities in the pre-GMP steps are understood. Also the agencies should have enough information on the framework of the sponsor's quality assurance practices to ensure control in the pre-GMP steps. This manuscript will propose a unified approach, based on our actual experience in justification of API SMs in regulatory filings. Several components are highlighted for further, more detailed discussion, to facilitate harmonization based upon their relative importance to the justification package. These include:

1. a detailed control strategy discussion of the final DS, particularly surrounding API SM impurities (process, mutagenic, and stereoisomeric impurities), given the potential impact these impurities may have on DS quality,
2. an approach for the management of Contract Manufacturers including a system of contractual (quality) agreements, quality management, change management, and risk management that maintains the desired state of control over future potential changes to pre-GMP processing steps.

2. DISCUSSION

2.1. Proposed Framework for the API SM Justification. Based on our experience, there are important pieces of information that support effective API SM discussions with the regulatory agencies. The proposed framework summarized in Table 1 contains our recommendations for those components to be included as part of an API SM justification package. This framework is proposed in an effort to align sponsors and regulatory agencies on the critical factors in the justification and thus help in creating a harmonized approach which will be acceptable across all jurisdictions.

Enough information should be included in the description of the API SM in the CTD to clearly communicate product and process knowledge pertaining to impurity origin, fate, and purge such that the regulatory reviewer can develop a good understanding of and confidence in the sponsor's impurity control strategy and potential risk to the patient. For API SMs closer to the DS the perceived risk may be higher. In addition, the amount of information provided *may be different* for commodity versus commercial and custom API SMs.[12] A more comprehensive data set, including manufacturing route of proposed API SM and control strategy for synthesis of the DS may be required for commercial and custom manufactured API SMs that are separated from the DS by only a few synthetic steps or for an API SM whose structure may be considered as complex. In addition it is recognized that the API SM may be manufactured internally and not at a CMO, under these circumstances the same framework would apply. A robust justification should address regulatory authority concerns about portions of the synthesis preceding the API SM.

The API SM justification package in the CTD serves as the primary means to communicate the sponsor's API SM control strategy, including key elements such as knowledge about impurity origin, fate, and purge in the chemical process as well as a comprehensive description of the control strategy. It is also an opportunity, for externally sourced API SMs, to communicate a framework regarding quality agreements, management of any contract manufacturer and change management overall. It is therefore of great value to ensure that the API SM justification package communicates this information very clearly, concisely, and logically.[13] A sound control strategy mitigates risk and assures acceptable quality of the DS. *A long synthetic route cannot compensate for an ineffective control strategy.*

2.2. Elements of the API SM Justification Package. The following subjects recommended for inclusion in an API SM justification package are more straightforward and do not require further elaboration in this manuscript: summary of proposed API

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Table 1. Recommended Content of API SM Justification[14]

subject	content[a]	value
Manufacturing route from proposed API SM(s) to DS	Flow diagram of DS synthetic route including proposed API SM(s), intermediates (nonisolated and isolated), reagents, catalysts, solvents, and points of purification	Overview of the synthetic route; basic introductory information; enables understanding of potential impurity formation and process control points of the overall DS synthesis; highlights structural differences of API SMs from final DS
Manufacturing route of proposed API SM	Flow diagram (reagents, solvents, catalysts) of the last steps of the synthesis if required to demonstrate the control strategy	Enables understanding of the process, key points for introduction of chirality, and assessment of potential impurities
Conclusions from batch analysis and stability data interpretation	Provide API SM batch analysis data; provide corresponding DS batch data from API SM batches and demonstrate comparability of DS batches from different API SM sources, as applicable; for custom materials, provide information (e.g., API SM retest information) to support supply chain stability of the API SM	Demonstrates impurity control and process capability to justify specifications; demonstrates manufacturing capability and affords indication of anticipated DS quality and variability; demonstrates ability to manufacture API SM internally or at multiple CMOs (robust, readily transferrable process(es) that meet intended acceptance criteria); illustrates material comparability from multiple suppliers, or multiple processes when appropriate; provides API SM stability
Control strategy of DS manufacturing	Discuss API SM impurities that are likely to be present and their fate/purge data in downstream chemistry; describe how stereoisomers are controlled in API SM and/or DS synthesis	Demonstrates and supports proposed control strategy including potential impact to Critical Quality Attributes (CQAs); justifies API SM and DS specifications; provides visibility to the risk associated with creating and maintaining desired stereochemistry; justifies testing (incl. IPC)
API SM specifications	Propose specification for each potential specified or recurring impurity, i.e., those that need to be controlled to ensure that CQAs of the DS are met; high level method description (e.g., HPLC); statement regarding method capability (e.g., isomer specificity)	Reflects parts of the proposed analytical control strategy
Management and change control at CMO,[b] if used	Provide framework of quality agreements, CMO management and change management; establish comparability of intermediate or DS obtained from different API SM sources, as applicable	Ensures any changes to current information in the steps used to prepare the API SM will be assessed and overall control strategy revised as required

[a]Actual content determined by sponsor and are dependent on the nature of the API SM (commercial or custom). [b]CMO = contract manufacturing organization.

SMs, proposed DS GMP synthesis, API SM manufacturing route(s), and batch analysis data. However, based on our collective experience, the following two subjects have been the source of the majority of discussions and differences in opinion between sponsors and regulatory authorities:

- appropriate control strategies for impurities present in API SMs which might impact DS quality, including stereoisomers and MIs;
- appropriate CMO management strategies to ensure that pre-GMP manufacturing steps have no impact on the final DS quality.

These two areas will be addressed in more detail through examples and discussion to highlight the elements in each which are key to defining a robust control strategy for API SMs.

2.2.1. Control Strategy for Impurities. According to ICH Q11, manufacturing steps that impact the impurity profile of the DS should normally be included in the manufacturing process described in S.2.2.[15] An obvious question is, does any step where class I solvents, toxic metals, or mutagenic compounds are used or formed, or where stereoisomers or key functional groups are introduced, need to be manufactured under GMP?

While an affirmative response might be initially expected, there are situations where the manufacturing processes are well-understood and robust controls on the API SM as well as CMOs management/oversight are installed to deliver consistent, high-quality DS material to allow an alternate response. ICH Q11 outlines how a comprehensive control strategy can be built and includes an example based upon this concept where stereochemical isomers are generated upstream of the API SM.[16] Consistent with principles of ICH Q11, the proposed API SM may be suitable if the following criteria can be demonstrated:

- impurities, including MIs, generated in the manufacturing steps of the proposed API SM, do not adversely affect the quality of the DS;
- the proposed API SM analytical procedures are sufficiently specific and sensitive for the control of actual and reasonably expected API SM impurities, including MIs, elemental impurities, Class 1 residual solvents, stereoisomers, and other structurally related impurities;
- actual impurities in the API SM are identified at a suitable level and a limit for unidentified impurities is established;
- the fate and purge of actual API SM impurities are understood and confirm a robust impurity control strategy in the subsequent GMP steps

These points mentioned above may be discussed in the context of the control strategy development (section S.2.6) or as part of the API SM justification (section S.2.3).[17] In addition to the control strategy the manufacturing processes to prepare the API SMs performed by CMOs are also subject to a quality risk management process that includes appreciable CMO oversight including CMO qualification and process change management. This has occasionally been used by sponsors to further justify an API SM designation.

A comprehensive impurity control strategy starts with consideration of the reasonably expected impurity landscape. For API SM introduced late in the synthesis of the DS (and where the synthetic route of the API SM is known), a knowledge of the last steps of synthetic route or routes associated with an API SM should lead toward a list of potential impurities likely to be present in the API SM. Additionally, identification of actual impurities observed in the API SM will enhance the applicant's understanding of potential impurities that may be generated in

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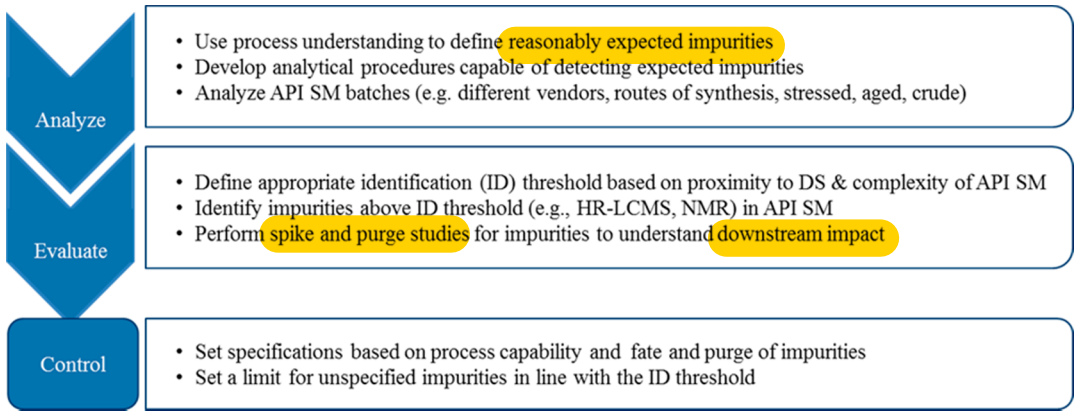

Figure 1. Summary of a typical approach for the development of an API SM to DS impurity identification and control strategy.

downstream processing steps. The identification threshold for API SM impurities can vary depending on API SM complexity and proximity to the DS. For example, in case of an API SM introduced late in the DS synthesis, lower identification thresholds, such as 0.1%, may be warranted to mitigate the risk of unknown impurities impacting DS quality. High-resolution LC-MS data are commonly used to initially propose structures of unknown impurities in API SM. Proposed impurity structures are then typically confirmed using NMR or other advanced spectroscopic techniques and/or independent synthesis.

Subsequently, the fate and purge of actual impurities likely to be present in API SMs should be elucidated. Impurities (if nonreactive) and their derivatives (if reactive) should be tracked through subsequent process steps (e.g., mother liquor samples or intermediates) to understand their points of removal and whether or not they have the potential to impact DS quality. Crystallizations or salt formation processes as chemical transformation steps are two of the most powerful tools chemists have to remove impurities and increase the quality of the GMP intermediates and DS. As such, understanding of purging capabilities of these downstream processing operations can be used as part of the overall justification for selection of API SMs and GMP steps. In addition, impurity removal points beyond crystallizations in isolated intermediate steps (e.g., distillations, separations, extractions) and knowledge of each of these processing operations should also be understood and communicated as part of the eventual control strategy. In other words, the number of chemical transformation "steps" is not a direct measure of the number of impurity control points in a process. ICH Q11 refers to these additional controls as "controls implicit in the design of the manufacturing process." Purge studies, which involve spiking impurities at or above specifications in API SM, are often used to help develop the control strategies for API SMs. A summary of a typical API SM related impurity identification and control strategy is provided in Figure 1.

To illustrate certain aspects of the above concepts toward development of an impurity control strategy for an API SM, an example is shown in Figure 2, the proposed registered sequence includes API SM 1 (a significant structural fragment of the DS and proposed API SM) reacting in a convergent synthesis with a Boc-protected material (compound 2) to form a Boc-protected intermediate. After isolation, the intermediate is deprotected, and the resulting DS is crystallized, washed, and dried to form the final DS material. During development, the DS was manufactured with very high purity with typically no impurity greater than the reporting threshold of 0.05%.

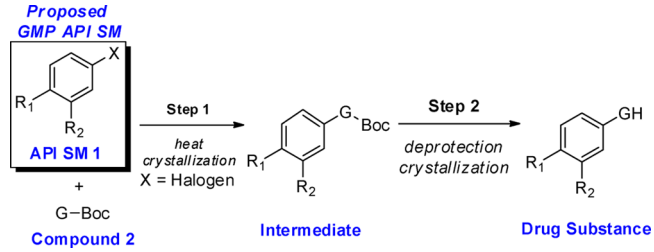

Figure 2. Manufacturing sequence from proposed API SM 1 to the DS.[18]

Upon review of the synthetic routes used to make API SM 1, several potential impurities were identified, and this information was utilized to design and develop a suitably comprehensive impurity control strategy surrounding the proposed API SM 1. API SM 1 possesses no chiral centers but has the potential to form regioisomers, and a study was completed for these impurities. Only two of the regioisomers were found to be present or likely to be present after manufacture of authentic API SM regioisomers and evaluation of API SM batches (Imp. a and Imp. b). The other regioisomers were not formed (<0.05%) under any of the synthetic conditions tested, and no further regioisomeric impurity control existed further upstream. Two additional process impurities were identified based upon synthetic schemes employed: (i) a dihalogenated impurity (Imp. c) and (ii) a compound lacking the R_2 substituent group (Imp. d). Finally, toluene is used as solvent in the last processing step.[19] No metals were used in the synthetic routes to API SM 1. Therefore, the five potential impurities listed in Figure 3 formed the basis for further studies.

Based upon the potential for the five API SM 1 impurities to exist, an evaluation was conducted to anticipate the fate of each impurity. In all instances, except that of toluene, each impurity had the potential to react in the subsequent GMP process steps to form intermediate analogues. In the case of Imp c, three potential analogues could form from coupling at either or both halogenated sites. An illustration is shown in Figure 4.

In the example, authentic samples for each of the potential API SM impurities were synthesized, along with the corresponding potential downstream analogues to facilitate fate and purge studies. Alternatively, batches with elevated impurity levels could have been used to determine fate and purge factors. Spiking studies were conducted with authentic samples of the API SM impurities spiked into the process at elevated levels relative to typical levels found in the API SM to facilitate purge factor

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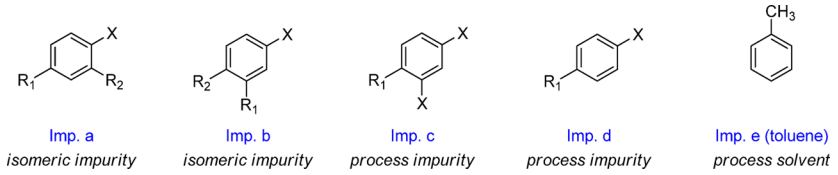

Figure 3. Potential API SM 1 impurities.

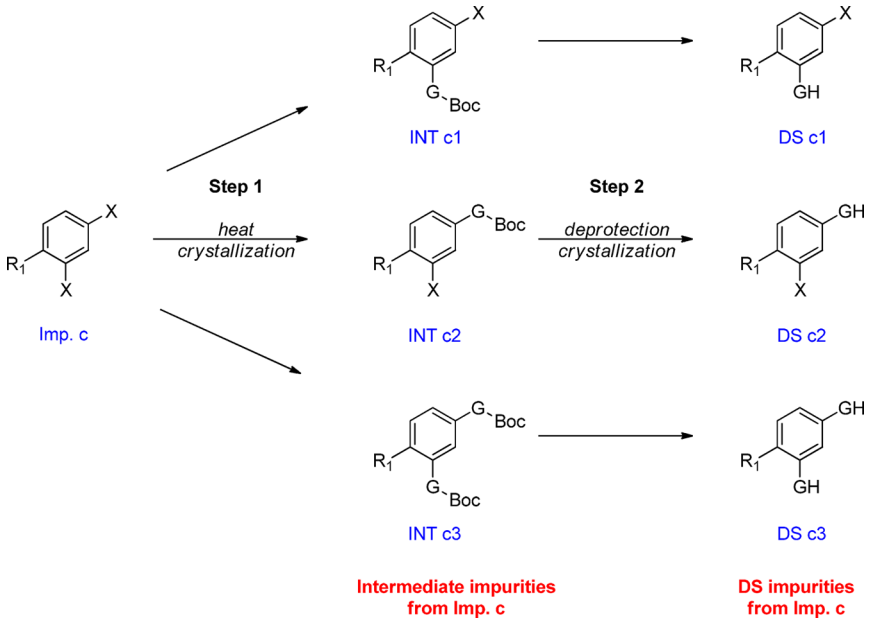

Figure 4. API starting material impurity C fate study.

Table 2. Summary of Process Knowledge[a]

API SM impurity	level of impurity spiked in Step 1	level of impurities in Step 1 product	impurity rejection in Step 1	impurity rejection in Step 2	typical impurity level in API SM	proposed API-SM specifications
Imp. a	1.0%	0.1%	90%	not studied	<0.05% (0.01−0.04%)	NMT 0.1%
Imp. b	1.0%	0.99%	0%	40%	<0.05% (<0.01−0.03%)	NMT 0.1%
Imp. c	1.0%	0.8%[b]	20%	≥50%[c]	<0.05−0.18%	NMT 0.3%
Imp. d	3.0%	0.24	92%	70%	0.8−1.1%	NMT 1.5%
Imp. e		not studied			100−500 ppm	ICH limit (790 ppm)

[a]While this example did not specifically address needs for mutagenic or stereochemical impurity control, the same strategy remains appropriate for these types of impurities, as discussed in the following sections. [b]Total of INT c1, INT c2, and INT c3 related impurities. [c]Based upon worst-case rejection of INT c1, INT c2, and INT c3 related impurities as they forward processed into DS c1, DS c2, and DS c3 related impurities.

calculations. Isolated product materials, as well as mother liquor samples, were then analyzed to assess impurity fate. It should also be noted that many of the analytical methods developed for spiking and purge studies may not be the batch release methods but instead are tailored specifically to sensitively assess impurity purge and fate in the different sample matrices.

As summarized in Table 2, API SM impurities Imp. a and Imp. d were almost completely removed to the mother liquor in the first processing step, while API SM impurities Imp. b and Imp. c carried through to the intermediate with very little to no removal in Step 1. Subsequent evaluation of the corresponding analogues in Step 2 showed partial removal. Based upon typical levels observed in the API SM together with impurity fate and purge data, appropriate analytical methods and proposed specifications were developed to ensure that API SM impurities were adequately controlled and would not adversely impact DS quality (i.e., no new API SM related impurities would be present in the DS at levels above 0.1%). Additionally, at least 8 batches of API SM made at pilot/commercial scale that contained typical impurity levels, as outlined in Table 2, were forward processed throughout development to make 14 batches of DS. In each case, no reportable impurities (≤0.05%) were found in the DS to further demonstrate the adequacy of the control strategy. In this example, although API SM Imp. a was almost completely removed in subsequent GMP processing and a high specification limit could potentially be established, a tight control was proposed since typical levels of this impurity in the proposed API SM were very low. A single specification at NMT 0.1% was proposed for any unspecified impurity which would control Imp. a, Imp. b and any potential unknown impurity in the API SM.

2.2.2. Control Strategy for Known or Potential Mutagenic Impurities. The assessment to control DNA reactive (mutagenic) impurities in the final DS is outlined in ICH M7 and follows the same principles as discussed earlier (section 2.2.1) for non-DNA reactive actual and reasonably expected impurities. ICH M7 Guidance provides the following recommendation for

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assessment of potential DS MIs which includes MIs related to API SMs:

Potential impurities in the DS can include API SMs, reagents, and intermediates in the route of synthesis from API SM to DS. The risk of carryover into the DS should be assessed for identified impurities that are present in API SMs and intermediates and impurities that are reasonably expected byproducts in the route of synthesis from API SM to DS. As the risk of carryover may be negligible for some impurities (e.g., those impurities in early synthetic steps of long routes of synthesis), a risk-based justification could be provided for the point in the synthesis after which these impurities should be evaluated for mutagenic potential. For API SMs introduced late in the synthesis of the DS (and where the synthetic route of the API SM is known) the final steps of the API SM synthesis should be evaluated for potential MIs.[20]

Following ICH M7, there are four options to development of a control strategy for MIs in the DS.

Option 1: Control the impurity in DS with an acceptance criterion at or below the Threshold of Toxicological Concern (TTC).[21]

Option 2: Control the impurity in intermediate, API SM, or by in process control with an acceptance criterion at or below TTC. An example of such control might be confirmation of the absence of benzene (a potential impurity in toluene and other solvents, e.g., acetone), mentioned in the impurity control strategy development example above. Studies can be conducted to demonstrate the absence of benzene (e.g., <2 ppm) in the API SM with highly sensitive and selective analytical technology to mitigate risk posed by this MI.

Option 3: Control the impurity in intermediate, API SM, or by in process control with an acceptance criterion above the TTC using an appropriate analytical procedure, coupled with demonstrated understanding of fate and purge and associated process controls, that ensure the level in the DS is below the acceptable TTC limit without the need for any additional testing later in the process. An example of this approach is when the proposed API SM is itself a mutagenic substance or contains MIs exceeding the TTC level and suitable knowledge of fate and purge exist to support a higher acceptance criterion.

Option 4: Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in DS will be below the acceptable TTC limit such that no analytical testing is recommended for this impurity (i.e., the impurity does not need to be listed on any specification). Elements of a scientific risk assessment can be used to justify an option 4 approach. The risk assessment can be based on physicochemical properties and process factors that influence the fate and purge of an impurity including chemical reactivity, solubility, volatility, ionizability, and any physical process designed to remove MIs.[22] Option 4 is particularly useful for those impurities that are inherently unstable (e.g., thionyl chloride that reacts rapidly and completely with water) and for those impurities that are effectively purged.

The following example demonstrates an application of option 4. A proposed API SM was manufactured as a mesylate salt and isolated out of isopropyl alcohol. Conditions allowed isopropyl mesylate (IPM) formation from the synthetic process for the API SM, and isolation conditions and downstream processing conditions were expected to effectively remove any residual IPM to well below the TTC limit in the DS through the two-step GMP sequence. A generalized analytical method was available from the literature and used to detect a variety of potential low-molecular weight alkyl mesylates esters in the API SM, intermediate, and DS.[23]

As shown in Figure 5, the IPM impurity was typically at low levels in the API SM (<20−252 ppm). Spiking studies

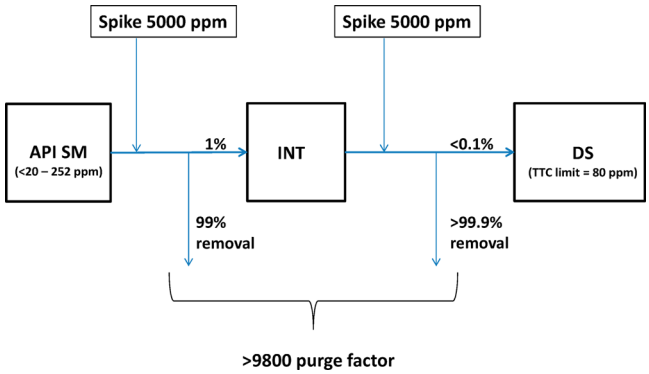

Figure 5. Assessment of overall purge factor for control of isopropyl mesylate in API SM.

summarized in Figure 5 showed that IPM was efficiently removed during downstream processing steps (>9800 purge factor). With such high removal efficiency, percent-levels of the IPM would be removed from the API SM without adversely impacting DS quality. Such data supported a plan to not include IPM in the API SM specifications.

With the potential for API SM process changes that could utilize other alcoholic solvents and result in the formation of alternate low-molecular weight alkyl methanesulfonic acid esters, similar purge data could be generated with these esters to strengthen the overall MI control strategy position for the API SM.

2.2.3. Control Strategy for Impurities: Stereoisomers. Stereogenic impurities require the same level of control as nonstereogenic impurities.[24] ICH Q11 includes a valuable example of stereochemical control for a DS with only one stereogenic center generated prior to the API SM[16] and provides guidance on how to control the undesired enantiomer in steps prior to the API SM and GMP steps subsequent to the proposed API SM. Stereochemical analytical controls are only meaningful when established at or after process stages where the stereogenic center is known to be configurationally stable. For a DS with only one or two stereogenic centers, the stereoisomeric control through chiral and achiral separation and measurement techniques is generally appropriate. However, for compounds with greater stereochemical complexity,[25] it can be quite a challenge to separate, measure, and control for all stereoisomers via an approach of testing all possible stereoisomers in the DS.

For example, 128 (2^7) stereoisomers are theoretically possible for a compound with seven chiral centers. Preparation and characterization of all of the stereoisomers may not always be possible, efficient, or practical, since some stereoisomers may be energetically unfavorable. To ensure that all potential and actual stereogenic impurities are controlled, a scientifically based control strategy can be developed justifying the exclusion of certain isomers from further study based on specifications assuming appropriate and fundamental mechanistic considerations, energy modeling, and sound development knowledge and experience. An example using this approach is outlined in Figure 6 and following discussion.

The desired stereochemical configuration in vorapaxar sulfate was derived from the Diels−Alder reaction of Compound A to

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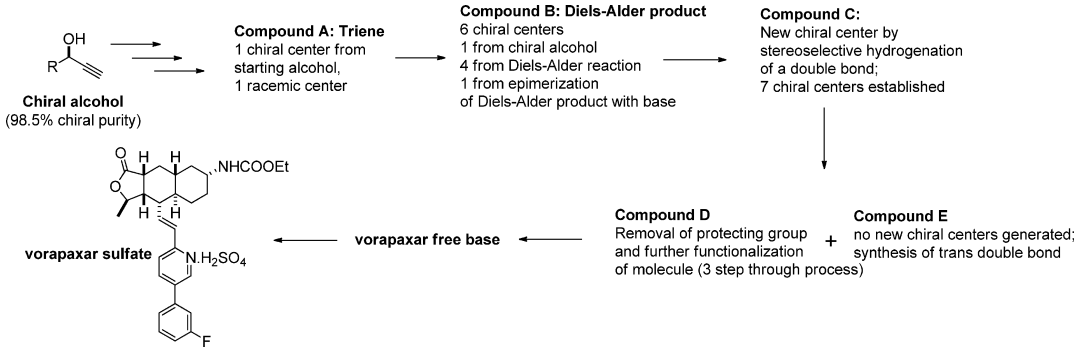

Figure 6. Vorapaxar sulfate synthesis.

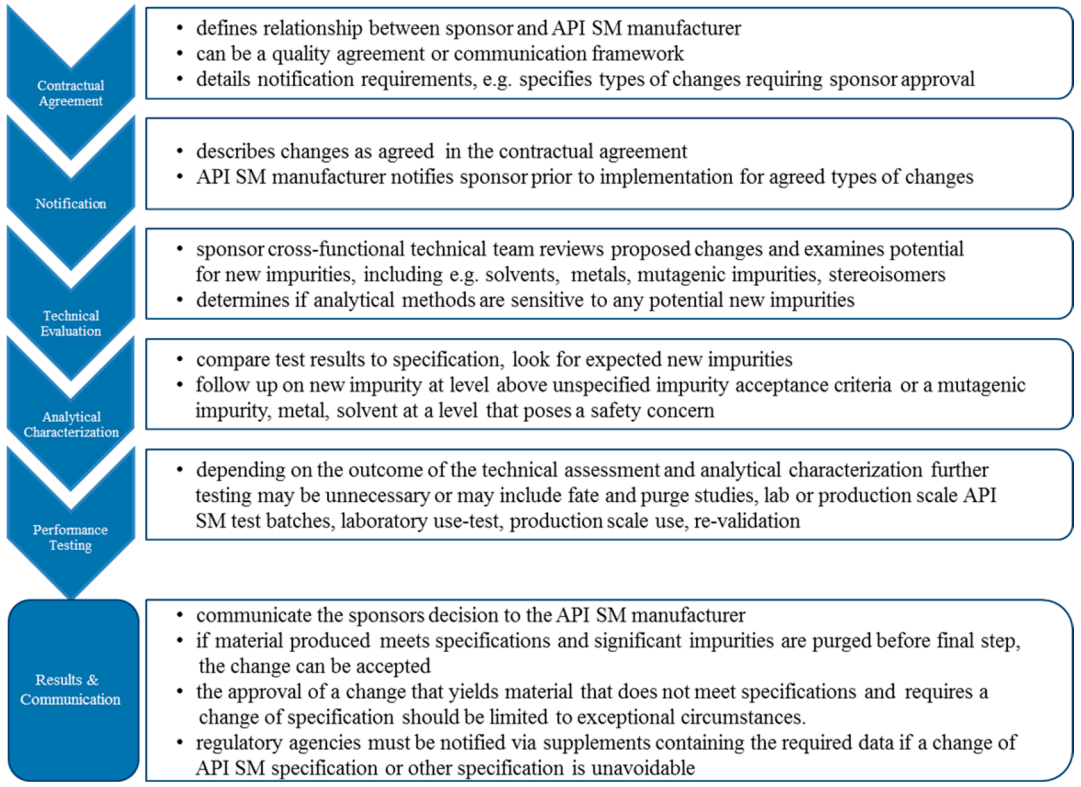

Figure 7. Management of API SM changes at CMOs.

form Compound B which is then converted to Compound C (containing seven chiral centers). In this example, Compound C is the API SM, and it serves as an effective point for ensuring suitable stereochemical purity of the DS. The chiral centers in Compound B and Compound C were controlled by

- Chirality of starting alcohol;
- Stereoselectivity in the Diels–Alder reaction;
- The catalytic hydrogenation of Compound B, where reaction stereoselectivity is dictated by the facial accessibility of the substrate.

The alcohol, a commercially available chiral precursor for the manufacture of Compound A dictated the stereoselectivity of the Diels–Alder reaction, and hence the chiral purity of the alcohol required appropriate control. However, this was an undesirable API SM as it was many steps removed from the primary portion of the synthetic sequence, and acceptable stereochemical purity was easily confirmed at later points in the process.

In the Diels–Alder reaction, four centers were stereoselectively established via the preferred *re,re-exo* cyclization pathway. The sixth stereogenic center was set during epimerization of the Diels–Alder product with base. The exo/endo selectivity of the Diels–Alder reaction was justified by relative energy transition state barriers. Key stereochemical control arguments included 1,3-allylic strain and the well-understood Diels–Alder reaction mechanism. All theoretical predictions from modeling calculations (density functional theory, DFT) confirmed the experimental observation that the single major diastereomer product was the desired Compound B and that three minor diastereomeric impurities were formed, for which reference standards were prepared.

The seventh and final stereogenic center was set by the catalytic hydrogenation of Compound B where reaction stereoselectivity was dictated by the facial accessibility of the substrate. Three isomers were potentially formed during this catalytic hydrogenation such that, in total, 15 potential stereoisomer-related impurities could have been present in

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Compound C, derived from either Compound B or its impurities and the subsequent hydrogenation. Authentic samples for each of the stereoisomeric impurities were prepared, and discriminatory analytical methodology and specifications were developed to permit the control of these impurities in Compound C. Extensive data were collected to support appropriate stereochemical characterization and control, including data on 11 batches of DS showing stereochemical control. With deep understanding and control of stereochemical identity and purity in Compound C, coupled with full knowledge of impurity fate in the subsequent process stages (including epimerization potential) to ensure stereochemical purity of the DS, this extensive process knowledge package qualified Compound C as a potential API SM to the regulatory agencies in a scientifically rigorous manner. The chiral identity of vorapaxar sulfate DS was adequately controlled by a chiral test of Compound C in which all seven chiral centers were formed.

2.3. Management of Contract Manufacturers and Change Control.[26] There are a variety of changes that take place in a manufacturing process over the lifetime of a product (from the time of initial approval through routine commercial manufacturing) in the GMP steps as well as in the synthesis to manufacture the API SM.

A thorough evaluation of these changes needs to be carried out regardless if the API SM is manufactured at a CMO or internally. Change management is applied for API SM manufactured internally and is a component of the overall system for managing CMOs. From ICH Q7 one can derive the expectation that an appropriate level of controls suitable for the production of the API SM should be applied. Quality management systems other than GMP may be applied for the steps preceding the API SM; however, the review and approval of process changes[27] are governed by the principles of GMP manufacture. These principles not only guide the evaluation of a change but also potential regulatory updates in cases where a change impacts the API SM selection, control strategy, or quality of the DS.

A relevant example would be the introduction of a new impurity observed in pre-GMP processing steps utilized to prepare the API SM. Regulators have identified the management of changes in API SM processes or CMO practices as a concern with an eye on how seemingly minor changes can negatively affect the quality of the DS. The following section describes the typical change management practices of IQ member companies and focuses on API SMs specifically. The processes employed by sponsors and their CMOs try to address the concerns of regulatory agencies and show how science-based risk analysis and clear quality management practices can reduce risks to DS quality.

It is well-understood that any changes to the DS synthetic routes, CMO, or sites employed to manufacture API SMs have the potential to introduce new impurities, solvents, catalysts (metals), or MIs into the DS process. The procedures described in the 2009 APIC[28] guidelines are widely used in the DS industry to manage process changes in steps used in the preparation of the API SM, on supplier qualification and management. They are also common practice at member companies of the IQ consortium. Figure 7 outlines the typical flow of information and the types of decisions and investigations that are part of the change control process.

Change management procedures should be designed to minimize or exclude undesired effects of synthesis/process changes on the impurity profile. Therefore, any change (major or minor) should be evaluated for its impact on API SM purity prior to its implementation to ensure the maintenance of a consistent purity of API SM batches received by the DS manufacturer. It is understood that new impurities in an API SM exceeding the acceptance limit for unidentified or unspecified impurities in the regulatory filing require a thorough evaluation of their impact on DS quality, including identification and assessment of mutagenic potential, and need to be followed up with a regulatory change application. An investigation of a new impurity that does not exceed the acceptance limit for unspecified impurities may be called for where the formation of a MI is considered likely or a carry-over to the DS is suspected. Generally, the process of evaluating a change intended by a CMO should be guided by the same principles that are applied as outlined in the section describing the Control Strategy for Impurities.

In the framework of CMO change management, scientific evaluation and analytical characterization can be used to define the actions necessary to follow up on new impurities potentially introduced by a change. However, there remains the question of whether management of the CMO can address general manufacturing issues (i.e., poor equipment cleaning). The following points should support the view that maintaining sound production practices by CMO quality management is both, expected and common practice.

- Management of the CMO is an integral part of a quality system and contributes significantly to the overall quality of the final drug product. Where DS quality is potentially affected, appropriate evaluation of suppliers is required by ICH Q7 (e.g., section 7.11 and 7.12). A recent PIC/S aide memoire (PICS/S 2009)[29] addresses CMO management as a topic for GMP inspections and highlights that this topic is the responsibility of the DS manufacturer and as such is subject of inspectional oversight.
- A detailed description of the best practices of DS manufacturers in fulfilling this responsibility is available (APIC 2009).[28] Tools for the management of an API SM manufacturer include on-site audits and the evaluation of quality systems. GMPs are not required for the production of API SM, as described above based upon ICH Q7, but the supplier may have established other quality systems (e.g., ISO 9001). An increased risk for a negative effect on DS quality is generally assumed where only a few steps separate complex API SMs from the DS. Quality management can be used as a tool to reduce this risk by placing quality requirements on API SM suppliers. For example, the risk of contaminating a DS with carry-over of production residues on equipment is reduced where appropriate cleaning procedures are in place at the API SM manufacturing site. Consideration of the quality history of a potential API SM supplier is another more general tool which contributes to ensuring sound manufacturing practices.

A little less clear at the moment is if inclusion of Quality Risk Management practices, Quality Agreements (QAs), and Change Management Agreements with API SM suppliers can be an added justification for API SM designations. This is a subject of ongoing discussions, and no consensus view has been reached within the industry or with regulators. With this in mind, the authors support the view that sharing some key points of quality management practices with the agencies, in particular cases where only a few steps separate complex API SMs from the DS may be helpful during the API SM justification discussions.

3. CONCLUSION

From the industry's perspective, harmonization of requirements for designation and justification of API SMs is sufficiently

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described in ICH Q11 guideline. Nevertheless, IQ member companies have experienced inconsistent interpretation of Q11 by agencies in different regions, which may in part be due to inconsistent justification of API SM designations. The authors sought to improve this situation by proposing a framework to create more uniform API SM justification packages. The outline for API SM justifications summarized in Table 1 and the examples presented in this article will facilitate common understanding and interpretation. The authors believe that many of the questions referred to in the Introduction of this paper can be addressed in this way.

In addition, we believe that improved vendor management practices and commitments should address concerns about risks in the manufacturing process prior to the API SM and support selection of more complex API SMs closer to the final DS than currently accepted by regulators.

The reliance on long synthetic routes from the API SM to the DS should be replaced with a scientifically based API SM designation process and a robust quality management of the manufacturer of the API SMs. If regulators and sponsors support this approach, both groups will be able to fully realize the spirit and guidance offered by ICH Q11 and take an important step toward regulatory harmonization

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(7) European Medicines Agency (EMA/448443/2014) CHMP and CVMP "Reflection Paper on the Requirements for the Selection and Justification of Starting Materials for the Manufacture of Chemical Active Substances", September 2014.

(8) As described in manuscript 2 of this series (ref 2), the definition of complexity is based upon the number of stereocenters, rings, and density of functional groups in the API SM mapped to the degree of justification required to demonstrate adequate control of API SM and API SM related impurities in the DS manufacturing process.

(9) As mentioned in the ICH website (www.ich.org; see section Q11 Development and Manufacture of Drug Substances, Q11 Q&As) "Experience gained with the implementation of the ICH Q11 Guideline since its finalization in 2012 shows that some clarification is needed on what information about the selection and justification of starting materials should be provided in marketing authorization applications and/or Master Files. The Q11 Implementation Working Group (IWG) is tasked to develop a Questions and Answers (Q&A) document to provide clarification of existing principles. This document will be focusing on chemical entity drug substances since that is where most of the differences of opinion have been experienced."

(10) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11, Questions & Answers: Selection and Justification of Starting Materials for the Manufacture of Drug Substances, Nov 2014.

(11) European Medicines Agency, September 2014, Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances, Explanatory note #1.

(12) Definitions used in this manuscript: *Commodity API SM* has a significant pre-existing, non-pharmaceutical market in addition to its proposed use as an API SM. *Commercially available API SM* is available from multiple vendors via Contract Manufacturer technology. *Custom API SM* is available through a limited number of CMOs using company technology.

(13) This is essential to the reviewer who has the responsibility of conducting an effective and accurate review ensuring a well-understood and well-characterized chemical process will be utilized to manufacture high quality, safe, and effective medicines for patients.

(14) Elements of this information will also be important for the EOP2 meeting with the FDA, although it is recognized that not all recommended content would be available.

(15) Common Technical Document (CTD) Section S.2.2 is a Description of Manufacturing Process and Process Controls.

(16) ICH Q11 Development and Manufacture of Drug Substances, Section 10.4; Example 4.

(17) Common Technical Document (CTD). Section S.2.6 describes the Manufacturing Process Development, and S.2.3 describes the Control of Materials.

(18) G represents an unspecified, generic, structural element. API SM 1 can be considered as relatively simple or complex in structure, depending upon the R groups; however, the impurity control strategy development concepts remain the same

(19) Benzene is a potential mutagenic impurity in toluene, and its control is discussed under "Control Strategy for Known or Potential Mutagenic Impurities".

(20) ICH M7 Assessment and Control of DNA Reaction (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 4).

(21) The Threshold of Toxicological Concern (TTC) is a concept that refers to the establishment of a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to human health. The concept proposes that a low level of exposure with a negligible risk can be identified for many chemicals, including those of unknown toxicity, based on knowledge of their chemical structures.

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(26) It is recognized that management of CMOs is a cross functional effort that includes Quality Assurance oversight of the quality systems and in particular the change control systems and processes.
(27) Changes that occur internally or at a CMO need to be evaluated within the GMP system of the DS manufacturer. Notification agreements between CMO and DS manufacturer define the scope of changes at the CMO that require evaluation by the DS manufacturer. Therefore, even process changes taking place in the pre-GMP synthesis may be subject to indirect GMP control.
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