TRIPHASE®
Pharma Solutions, LLC

Regulatory Starting Materials- A Case Study for the Virtual Drug Company

The term "regulatory starting material" (RSM) is used to identify the starting compound(s) in the drug substance route of synthesis and is the point where current good manufacturing practices (cGMPs) begin. The development and manufacture of drug substance including the selection and justification of RSMs is governed by Q11.[1] With Q11 and the advent of quality-by-design (QbD) guidance "rules" have been replaced with "concepts" based on risk assessments. Prior to Q11 due to the clarity of the language there was a low risk of rejection and the discussion of RSMs was usually reserved for an end of phase 2 or a pre-NDA meeting. This is no longer the case. The importance of getting "buy-in" from authorities for your RSM early in the development process has become more important. Under Q11 applicants must conduct a sophisticated analysis and provide a detailed justification to assure acceptance of any custom-made RSM. The only path offered in Q11 that requires no such justification is where you start from a commodity chemical that is not custom made. Starting with such a "simple" RSM, while low risk, often requires too many synthetic steps to provide a reasonable cost of goods. In short, with Q11 and the move towards QbD the FDA has "rigged" the system requiring new drug sponsors to present their RSM and justification to authorities earlier in the development process. In this white paper we present a brief regulatory guidance history on the selection and justification of RSMs leading up to and including Q11. We then present a case study designed and executed to address responses from the FDA regarding an RSM justification provided in a recent submission package. The FDA comments and case study illustrate the high level of technical knowledge required under Q11 to provide an adequate justification for your RSM. Such resources are not commonly available to the virtual drug company who often rely on their contract vendors to oversee drug substance thus putting their NCEs at greater risk of clinical holds.

Historical Overview

Prior to Q11 the principals of Q7[2] governed drug substance and the selection of RSMs. Under Q7, a starting material;

• is a raw material, intermediate, or an API that is used in the production of an API

• is incorporated as a significant structural fragment into the structure of the API

• can be an article of commerce or a material purchased from one or more suppliers under contract or commercial agreement or produced in-house

• has a defined chemical properties and structure

The key concept of Q7 was that the RSM could be an *intermediate* made by *contract custom synthesis*. This practice was "industry standard" for over 20 years[3] until 2004 when a Draft Guidance[4] was put forth by the FDA. While the draft guidance did not prohibit the use of custom made RSMs it now required that if the RSM did *not* have "a significant non pharmaceutical market" (was *not* a commodity chemical) then it must be suitably justified and the justification should address "future changes in the manufacture process of the starting material (that) are likely to affect the safety or quality of the drug substance". The FDA's impetus behind this new draft guidance was that if a complex intermediate is being custom made under non GMP by multi-step synthesis, often in Asia, what evidence and controls did the agency have for future route changes that might affect quality and safety such as use of heavy metals, and/or potential genotoxic agents?[5] The contentious term "propinquity" was also introduced. Propinquity implies that a starting material should be separated from the final intermediate by *several* reaction steps that result in isolated and purified intermediates.[6] Collectively this draft guidance led to an outpour of protest from large pharma who had become accustomed to manufacturing complex intermediates either in-house or in Asia under non GMP conditions. While ultimately this guidance was never approved it had an indelible impact on the selection and justification of starting materials which has now become embodied in Q11. The key "new" elements for RSMs introduced in Q11 are as follows.

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to have an impact on the quality of the drug substance.
- The relationship between risk and number of steps is concerning the formation, fate, and purge of impurities.
- Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate, including whether there are appropriate controls for impurities. To conduct this 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. This will typically include

a description of multiple chemical transformation steps.

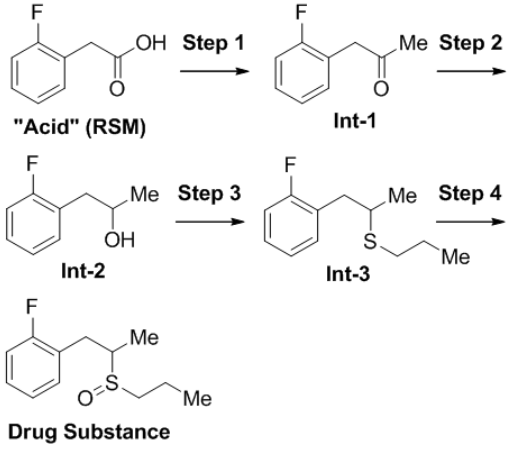
- *An applicant generally need not justify the use of a commercially available chemical as a starting material. A commercially available chemical is sold as a commodity in a preexisting, non-pharmaceutical market in addition to its proposed use as starting material. Chemicals produced by custom syntheses are not considered to be commercially available. If a chemical from a custom synthesis is proposed as a starting material, it should be justified in accordance with the general principles for the selection of starting materials outlined above.*

One should note the only "clear" element of Q11 is the last point which is a carry-over from the draft guidance such that only an RSM that is a commodity chemical can be used *without* justification. Translated, if you propose to use any custom-made RSM that is *not* a commodity chemical a justification is required and the authorities shall decide on the adequacy based upon a review. This is the key regulatory impact of Q11. Since the "rules" under Q7 are now gone a highly specialized skill-set is now required to select and adequately justify your RSM to authorities. The other take-away is that it is prudent to have this discussion early in the development process, typically in the form of Pre-IND meeting, so as to avoid any future clinical delays. Finally, as shown in the following case study, many of the required skill-sets required to generate a suitable justification are either not available or not included in the scope of work with your drug substance contract manufacturer.

FDA Responses & Case Study

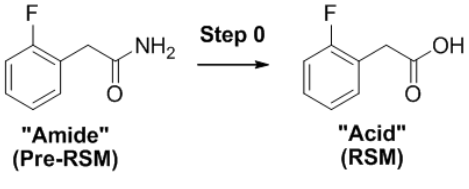
In order to illustrate the challenges to meet Q11 a case study is presented which was driven by recent comments from the FDA in response to a meeting submission package. A route of synthesis has been created to illustrate the principals while retaining confidentiality. The synthesis was a common 4-step process with three intervening isolated intermediates starting from "**Acid"** RSM as shown in **Figure 1**.

Figure 1: Drug Substance Synthesis



While the "**Acid"** was available from several manufactures it did not fulfill the requirements of a commodity chemical as defined in Q11. A rather complete summary package was provided which included specifications for the "**Acid"** covering related substances per Q3A, solvents per Q3C, and inorganics per Q3D[7]. A reference standard for the "**Acid"** had been fully characterized with proof of structure and a purity assignment for use in the specified w/w assay test. The route of synthesis for the proposed "**Acid"** was also provided as shown in **Figure 2**. The Pre-RSM "**Amide**" was available from multiple suppliers on a metric ton scale for use in the agricultural market and thus was a commodity chemical as defined by Q11. Selection of the "**Amide"** as RSM would have proceeded without need for justification however the liquid nature (and other factors) made the "**Acid"** a better choice over the "**Amide"**. Impurity tracking studies were provided in the package demonstrating the specified impurities in the "**Acid"** could be purged in the synthesis via purification steps in the intervening isolated intermediates.

Figure 2: Synthesis of RSM "Acid" from Pre-RSM "Amide"



The data package provided would have seemingly more than "checked" all the requisite boxes under Q11.[8] The following however was the FDA preliminary responses.

"An acceptance specification is required for this material that accounts for all potential impurities regardless of the supply process used by the supplier. To provide this justification, provide your analysis of potential impurities in this material, when manufactured by processes that are likely to be used in the sourcing of this material. Then provide the appropriate fate and purge studies for these impurities in your proposed commercial manufacturing process for the drug substance. Spiking studies may be used to demonstrate the purge capability of your process. You are reminded the impurity analysis should include more than just related impurities, e.g., solvent, inorganic, metallic and reaction by-product analysis is also necessary."

While the FDA's instructions were clear, the strategy of how to conform to these requests was less obvious. The following concepts were outlined.

- In order to understand likely impurities in the RSM "**Acid"** we need to understand the "likely" routes by which Pre-RSM "**Amide"** is made commercially.
- Once we know the route(s) to Pre-RSM "**Amide"** and thus likely potential impurities to track into "**Acid"** RSM we need to design purge studies to demonstrate any newly considered impurities are purged over the 4-steps shown in **Figure 1**.
- While not specifically called out by the FDA, genotoxic impurities would be of most concern.[9]

The first step in the process was to conduct a literature search which revealed several possible routes to the Pre-RSM "**Amide"**. In order to narrow down the likely route a cost of goods analysis was conducted as shown in **Figure 3**. Based on the literature and cost analysis a "likely" route of synthesis for **"Amide"** starting from fluorobenzene (**1**) emerged as shown in **Figure 4**.

Figure 3: Cost Analysis for Pre-RSM "Amide" Synthesis

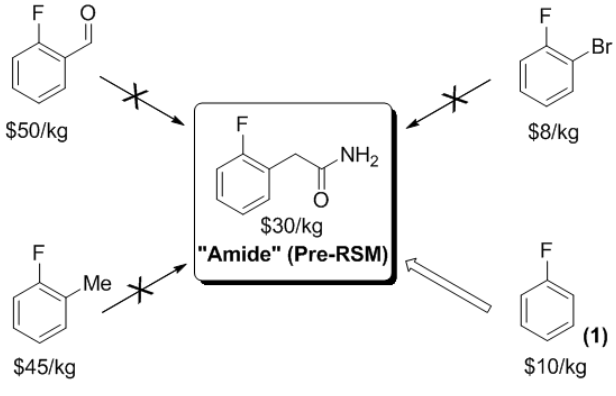
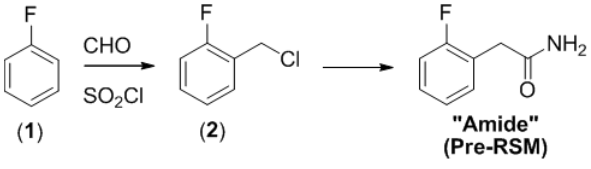
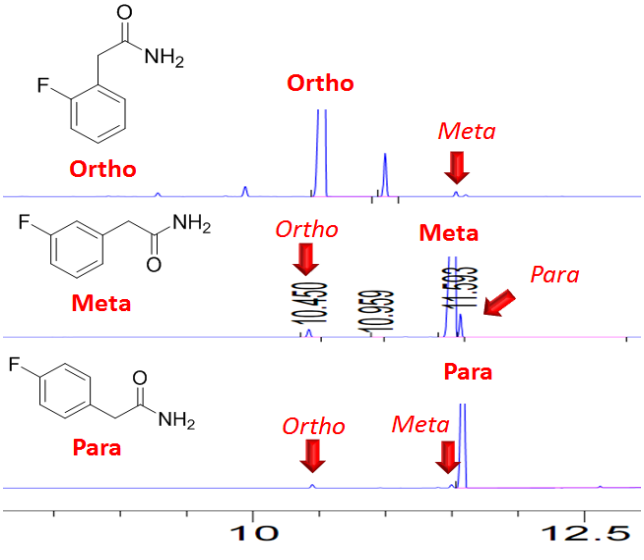


Figure 4: Proposed Route of Synthesis for Pre-RSM "Amide"



Further review of the literature indicated the process produced a mixture of isomers which were separated by bulk distillation. Analytical testing of commercial supplies of the three *para*, *meta*, and *ortho* **"Amide"** isomers were all found to contain varying amounts of the other isomers as shown in **Figure 5** indicating all samples had this likely common route of synthesis.[10]

Figure 5: GC Analysis of "Amide" Isomers



The route of synthesis for Pre-RSM **"Amide"** shown **Figure 4** indicated that genotoxic benzyl chloride (**2**) was a potential impurity. Analyses of several samples from the bulk suppliers of "**Amide"** indeed were found to contain up to 1,000 ppm of benzyl chloride (**2**). Such genotoxic impurities must be controlled in final drug substance to no more than 1.5 ppm.[9] Now that the likely route of synthesis had been identified and the potential impurities were known, purging studies were conducted to set limits for these potential impurities. Benzyl chloride (**2**) was spiked into **"Acid"** RSM at 100 ppm and shown to be <1 ppm in Intermediate-1 (**Figure 1**) so a specification limit for the **"Acid"** was chosen at 20 ppm which afforded a 5-fold buffer. The isomers, as well as other impurities identified in the **"Amide"**, were studied in spike and purge studies and specified in the **"Acid"** as appropriate. It is noteworthy that lack of this investigative work as prompted by the FDA would not have

identified this potential genotoxic impurity since impurities observed at 1000 ppm (0.1%) are not subject to identification under Q3A and thus would have been overlooked. The astute reader may note that this due diligence still does not fully address the FDA's request to account for *all* potential impurities *regardless* of the supply process used by the supplier. While other routes to **"Acid"** and thus other (non accounted for) impurities could emerge, a suitable quality agreement with the RSM manufacturer was set up to ensure **"Acid"** RSM would be made via the **"Amide"** pre-RSM as shown in **Figure 2**. Should our **"Acid"** RSM justification package be rejected we are prepared to designate the **"Amide"** as the RSM, which is by definition a commodity chemical thus would require no justification.

Conclusions

This white paper provides an overview of the history of the FDAs viewpoint in the selection and justification of regulatory starting materials.[11] A case study was provided which includes recent FDA's responses followed by a justification design study used by TRIPHASE® to meet the requirements of Q11.

This study illustrates the increased knowledge in process development, organic synthesis, and analytical chemistry required to adequately address the regulatory requirements of Q11.

TRIPHASE® has managed drug substance and product development, manufacturing, and analytical chemistry & regulatory for over 50 INDs and IMPDs including pre-IND and scientific advisory meeting packages. NCEs managed include steroids, sugars, amino acids, nucleosides, oligonucleotides, peptides, and many other complex APIs for use in oral, injectable, dermal, and ophthalmic topical drugs. Please contact us to discuss your project and answer your regulatory CMC questions…

Marc W. Andersen, Ph.D., RAC
+1 919 571 8037
mandersen@CMC-SCI.Com
www.TriphasePharmaSolutions.com

[1] *ICH Q11 Development and Manufacture Of Drug Substances, Guidance November 2012. This is the guidance that governs drug substance in US and EU. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm261078.pdf*

[2] *ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, November 2000. Note that under Q11 drug substance has largely replaced the former use of API (active pharmaceutical ingredient). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf*

[3] *While Q7 was issued in 2000, it essentially embodies the principals outlined in the "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances, February 1987." http://www.ivtnetwork.com/sites/default/files/FDA%201987%20drugsub.pdf*

[4] *FDA Draft Guideline, Guidance for Industry: Drug Substance: Chemistry, Manufacturing, and Controls Information, Jan. 2004, withdrawn Fed Regist. Notice June 1, 2006. http://www.fda.gov/OHRMS/DOCKETS/98fr/2003d-0571-gdl0001.pdf*

[5] *Based on a presentation by the FDA and subsequent conversations at a "Process Research and Development Conference" circa 2001.*

[6] *Note under Q7 an API was permitted to be an RSM whereas it was now clarified that "several isolated intermediates / steps" were required and "an interconversion of a salt should not be counted as a reaction step for the purpose of evaluating propinquity". This put an end to the many "one step GMP processes" where Sponsors submitted a final crystallization as their "GMP" manufacturing process.*

[7] *See TRIPHASE® white paper titled "ICH Q3D Elemental Impurities" http://www.triphasepharmasolutions.com/Case_Study_White_Paper_ICHQ3D .*

[8] *The "adequacy" of the submission was based on experience submitting over 50 INDs most within the last 5 years without rejection of starting material or clinical hold.*

[9] *See TRIPHASE® white paper titled "Addressing Genotoxic Impurities in Drug Development" http://triphasepharmasolutions.com/Structure%20Alert%20Genotoxins.pdf*

[10] *Note also in **Figure 3** 1-Bromo-2-Fluorobenzene ($8/kg) was similar in cost to fluorobenzene and thus a potential route to Pre-RSM Amide. This route was excluded as the route from this to Pre-RSM would not have led to a mixture of isomers as observed in actual samples of Pre-RSM Amide.*

[11] *For EU references, see: http://apic.cefic.org/pub/APIC_Position_Paper_on_API_Starting_Materials_Jan2014.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500175228.pdf, https://www.edqm.eu/sites/default/files/cep_content_of_the_dossier_for_chemical_purity_microbiological_quality_september_2015_0.pdf*