DRUG SUBSTANCE: DEFINING REGULATORY STARTING MATERIALS

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INTRODUCTION
In recent years, there has been a steep rise in the number of questions asked about the choice of Regulatory Starting Materials (RSM) for Active Pharmaceutical Ingredients (APIs) from FDA as well as other regulatory agencies in the world.

Regulatory authorities are worried that the RSM is shifting more and more towards the API, which has the probability of causing significant risk to API quality, and may also lead to problems in life cycle management.

The inappropriate selection of RSM, or lack of adequate information regarding the RSM, have been show stoppers or caused significant delay in approval of numerous ANDAs.
SOME EXAMPLES TO SHOW THE SIMILARITY OF THE CONCERN OF THE REGULATORY AUTHORITIES AROUND THE WORLD

“… Per literature … (8-ACPĐ) is a process intermediate in the synthesis of the drug substance ….. However, you have listed this material as a starting material in the synthesis/manufacture of the drug substance. Since the declared starting material is a very late stage process intermediate, it is unacceptable as a starting material. Please declare an appropriate starting material for synthesis of the DS that meets the regulatory recommendations for a starting material. …”

USFDA

“…Even though the process to get TTBB is given and the specifications for this substance is very detailed, it is structurally too complex to be considered as a starting material and should be considered as an intermediate in the synthesis of drug substance ….. In the aim to show that you have control of TTBB, the starting material should be redefined several synthetic steps backwards. …”

EDQM
BACKGROUND
ICH Q7 defined an API starting material as follows:

“An “API starting material” is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials normally have defined chemical properties and structure.”

• *This definition of API starting material does not talk about multiple synthetically relevant steps that should separate the starting material and the final API.*

• *Based on this definition of API starting material, a downstream intermediate (even the crude API), manufactured under non-cGMP conditions, purchased from custom manufacturers around the world meets the ICH Q7 criteria.*
• FDA tried to address the gaps in ICH Q7 description of the API starting material in a 2004 Guidance for Industry.

• In 2004 a draft Guidance for Industry – Drug Substance - Chemistry, Manufacturing, and Controls Information was published with a list of requirements for Regulatory Starting Materials.

• The draft guidance for Chemistry, Manufacturing, and Controls of Drug Substance listed four main criteria for starting material:
  - Propinquity
  - Isolated and purified
  - Carry-over of impurities
  - Complexity of structure

• This draft was however withdrawn by the FDA in 2006.
ICH Q11, Development And Manufacture Of Drug Substances (Chemical Entities And Biotechnological/Biological Entities)

• Sections 5.1 and 5.2 of ICH Q11 talks about the selection of starting materials and source materials for APIs.

• The information in ICH Q11 regarding starting materials can be summarized as follows:
  
  ➢ For API manufacturing process, cGMP applies from starting material onwards
  
  ➢ Starting material should be a substance of defined chemical properties and structure – not a non-isolated intermediate.
  
  ➢ Starting material should contain a distinct structural fragment of the API – differentiates it from common agents for esterification, salt formation etc.
The information in ICH Q11 regarding starting materials continued:

- Commercially available chemicals, with pre-existing non-pharmaceutical market need not be justified as starting material

- Enough of API manufacturing process must be disclosed in the dossier so that the impurity fate/purge can be understood

- Manufacturing steps which impact the impurity profile of the API should be part of the process description.

- It needs to be established that the changes in material attributes/process conditions upstream (starting material manufacturing steps) may have lower potential to affect the API quality.
CONFLICTING DRIVERS
CONFLICTING DRIVERS BASED ON SELECTION OF LATE STAGE INTERMEDIATES AS API STARTING MATERIAL

Regulatory Authorities

• API quality may be at risk – unidentified impurities, contamination (non cGMP), inadequate analytical methods

• Lack of transparency - the synthetic route of the RSM, quality of reagents/solvents used is not always clear

• Problems with life cycle management - less control on any changes made to the RSM manufacturing process post approval

• The responsibility of ANDA holders - not clear regarding the RSM manufacturing sites

API Industry

• Regulatory relief – fewer supplements for upstream changes

• Economics – minimize cGMP steps, in most cases, cheaper than manufacturing in-house

• Capability – in some cases specialized handling/processing that are needed may not be available to the API manufacturer
CONFLICTING DRIVERS BASED ON SELECTION OF LATE STAGE INTERMEDIATES AS API STARTING MATERIAL

Additional Drivers:

- Fragmentation of the API supply chain – with all the globalization and outsourcing it is difficult to track quality for ANDA holders as well as the regulatory authorities

- Risk to Quality - based on significant reduction in GMP manufacturing footprint, there is risk to the drug product quality

- High level Guidelines - The ICH guidances related to this topic may be interpreted differently in different regions

- Diverse regulatory requirements – different requirements by different health authorities make it difficult of develop the same product for distribution in different parts of the world
CONFLICTING DRIVERS BASED ON SELECTION OF LATE STAGE INTERMEDIATES AS API STARTING MATERIAL – A TYPICAL SCENARIO

• **DMF Holder:**
  The late stage intermediate has a significant fragment of the API, has defined chemical structure and properties and is commercially available. The method of synthesis is provided. Thus it qualifies as a regulatory starting material.

• **FDA:**
  It is only one de-esterification step removed from the API so it does have the significant fragment of the API structure (almost all of it) and defined chemical structure. It is commercially available from a small scale custom manufacturers only. The synthetic scheme comprises of one page of information with no control strategy or any other information. Also, being so close to the final API, there is no assurance that any impurity present in this starting material can be purged during the API manufacturing process. This is not acceptable as a regulatory starting material.

• **ANDA Holder:**
  There is a late stage intermediate declared as starting material for API??

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API MANUFACTURER’S RESPONSIBILITY
SELECTION OF REGULATORY STARTING MATERIALS FOR API

• Performing an evaluation of the role of the starting material selection, and the controls on the starting materials on the overall control strategy that mitigates risk related to the quality of the API.

• Need to interpret the ICH Q11 appropriately while selecting a regulatory starting material

• Making sure that there are adequate number of synthetically relevant steps between the regulatory starting material and the API: synthetically relevant steps involve formation or breaking of C-C or C-X bonds and preferably a few isolated intermediates

• Coming to terms with the fact that recrystallization, salt formation, chiral separation are not considered chemical transformation or synthetically relevant steps by FDA, nor are activities like milling and sieving
ANDA HOLDER’S RESPONSIBILITY
WHAT CAN AN ANDA HOLDER DO TO AVOID DELAY IN APPROVAL DUE TO API STARTING MATERIAL ISSUE?

• Reviewing the manufacturing scheme (how many steps from the RSM to the API, use or generation of genotoxic materials in the RSM manufacturing process) of the API manufacturer and anticipating the potential risks based on background search and prior knowledge.

• Evaluating the risk related to the choice of starting material supplier in life cycle management (any Quality Agreements between the API manufacturer and RSM supplier).

• Asking the API manufacturer if they have a control strategy related to the impurities, that may arise, based on their choice of RSM (metal catalysts, solvents, reagents and intermediates).
INDUSTRY’S EXPECTATIONS
FROM FDA
WHAT COULD THE FDA DO TO HELP THE INDUSTRY IN SELECTING THE RIGHT “STARTING MATERIAL’

1. Publishing of detailed guides with the FDA expectations.
   The currently available international guides on this topic are high level and open to interpretation.

2. Bringing consistency in the decisions across the board.
   Evaluation of the agency varies on a case-by-case basis, which makes it difficult for the API manufacturers to apply any general principle as to what will be acceptable to the agency as a regulatory starting material.

• 3. Increasing communication.
   To create a pathway (may be an “RSM Specific” controlled correspondence) by which a API manufacturer may be able to communicate with the FDA regarding acceptability of their regulatory starting material before making a decision.
CONCLUSION
IN SUMMARY

• Improper choice of regulatory starting material (RSM) may be a significant hurdle in the ANDA approval process

• ANDA holder should be cognizant of the risk associated with the choice of starting material by the API manufacturer

• The focus of the API manufacturer should be on establishment of good control strategy based on the selection of RSM (short synthetic routes should be exceptions rather than norm)

• Better clarification from FDA regarding the requirements for an “acceptable” RSM in API manufacturing will be of great help:
  o New FDA-specific guidances, publications
  o “RSM-specific” controlled correspondences
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<thead>
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<th>CLINICAL RESEARCH</th>
<th>MEDICAL COMMUNICATIONS</th>
<th>eCLINICAL TECHNOLOGIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Regulatory Strategy / Health Authority Liaison</td>
<td>• Bioanalytical Services</td>
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<td>• EDC</td>
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<td>• Clinical Trials Regulatory Services</td>
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<td>• Product Acquisitions, Partnering and Licensing Support</td>
<td>• Patient Recruitment</td>
<td>• Pharmacoepidemiology</td>
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<td>• Reimbursement and Market Access Services</td>
<td>• Data Management</td>
<td>• Expanded Access Programs</td>
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<td>• Biostatistics</td>
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THANK YOU