Regulatory Starting Materials—An FDA Perspective

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CDER Reorganization

Office of Pharmaceutical Quality
In Operation since Jan 11, 2015
Combines Former Office of Pharmaceutical Science (OPS) and Office of Compliance
THE OFFICE OF PHARMACEUTICAL QUALITY

Immediate Office PMAS Staff

- Office of Program and Regulatory Operations
- Office of Policy for Pharmaceutical Quality

- Office of Biotechnology Products
- Office of New Drug Products
- Office of Lifecycle Drug Products
- Office of Testing and Research

- Office of Surveillance
- Office of Process and Facilities
Office of New Drug Products

• Office of the Director
• Division of New Drug API: IND/NDA Drug Substance Review
• Division of Lifecycle API: DMF Staff/ANDA Drug Substance Review
• Division of Biopharmaceutics
• Division of New Drug Products I
• Division of New Drug Products II
ONDP Drug Substance Review

• **Division of New Drug API**
  – 2 Branches each aligned with 9 Clinical Divisions
  – Review of Drug Substance sections of NDAs, INDs and Meeting Packages

• **Division of Life Cycle API**
  – 3 Branches
  – Review of DMFs primarily in support of ANDAs (generics)

• Opportunities for workload backfill between the 2 Divisions
ONDP Drug Substance Review

- Reviews performed by subject matter experts
- Reviewers trained in organic/medicinal chemistry/analytical chemistry/process chemistry
  - Drug substance reviews are performed by approximately 80 reviewers (20 for New Drugs and 60 for Lifecycle)
  - Improved communication regarding starting material selection between RLD and all subsequent Lifecycle submissions
  - Improved consistency in responses to starting material and other drug substance related questions from industry
What is a Regulatory Starting Material?

– Starting point for cGMP synthesis
– Starting point for the detailed description of the synthetic process in a marketing application
– One or more starting materials possible depending on linear or convergent synthesis
– Can be a commercially available (commodity) chemical manufactured mainly for the non-pharmaceutical market
– Can be synthesized in-house or outsourced
Dilemma:
How do we balance starting material choice which impacts industry supply chain/cost with risk to quality and patient?
What is the risk to the quality of the drug substance and subsequently the risk to the patient by the proposed starting material selection?

For New Drugs:
Industry should initiate these discussions by End-of-Phase 2

A Background Package should follow the initial meeting request with details on

- Multiple routes of synthesis for the proposed starting materials observed/used during development and anticipated commercial route
- The fate and purge of impurities from the proposed starting materials to the API for each route of synthesis
- Specifications for the proposed SM
  • Justification why the specifications are appropriate when the route of synthesis of the SM is changed
Regulatory Perspective

What is the risk to the quality of the drug substance and subsequently the risk to the patient by the proposed starting material selection?

For Lifecycle API: (DMF review)
Utilize information known to the Agency regarding the innovator’s starting material selection, if possible.

• Is the starting material complex?
  – How is stereochemistry or regiochemistry established
  – Where in the process is the core of the structure formed?
• Was information provided on how the starting material is made so that the impurity profile can be adequately assessed?
• What is the justification for the SM specification?
  – Spike and purge studies at impurity limits (prospective)
  – Justified limits based on observed impurity values during process validation (retrospective)
Guidance Documents for Selection of Starting Materials

- ICH Q11
  - Guidance on drug substances with a sub-section on starting materials
- ICH Q11, Q &A (in progress)
  - Companion document to Q11 providing additional clarification
- ICH Q7A
  - Guidance for GMP from the starting material to API

Withdrawn but not forgotten:
- Drug Substance Guidance 1987
  - Many of the initial concepts still relevant
- Draft Drug Substance Guidance 2004
  - Detailed information on starting material selection
Overview of Current Guidances

ICH Q11 – Seven General Principles

- The manufacturing route begins from the starting material and GMPs apply from there onwards;
- The changes in material attributes and process conditions at the beginning of the manufacturing process have a lower potential to impact API quality;
- Manufacturing steps that impact the impurity profile of the API should be included in the process description;
- Enough of the manufacturing process must be disclosed so impurity fate and purge can be understood;
- Starting materials should be a substance of defined chemical properties, and non-isolated intermediates are not appropriate;
- Starting materials should be a significant structural fragment and should be distinguished from reagents and solvents; and
- Commercially available commodity chemicals need not be justified as a starting material as long as these are available in the pre-existing non-pharmaceutical market.
ICH Q7A

-A multi-step GMP process is clearly implied
  -process risk inherently higher the closer the regulatory starting material is to the final API
-GMP should be applied to critical process steps which impact the quality of the API
Clarification of Q11 Principles

• ICH Q11
  - “Starting materials should be a significant structural fragment ..”
    • Should **not** be interpreted to imply close structural similarity between the proposed starting material and the API
    • Intention was to distinguish between reagents and starting materials

  – Commercially available commodity chemicals need not be justified as starting materials ...
    • Provide supporting documentation regarding the non-pharmaceutical market for these chemicals
    • High unknown impurity content
      - Why not identified? How will purge be demonstrated?
      - May require clean up prior to use
Clarification of Q11 Principles

-”Manufacturing steps that impact the impurity profile of the API should be included in the process description”

-”Enough of the manufacturing process must be disclosed so impurity fate and purge can be understood”

Is enough of the process covered under GMP that we are confident that the process can purge all impurities resulting from the starting material to the specification levels in the final API?
FDA Concerns Regarding Starting Material Designation

• Starting material is not manufactured under GMP
• Change Control and Vendor Qualification
  – Outsourcing is the norm
  – Cost benefit to industry / High risk for regulators
• Changes to manufacturing process of starting material and impact on specification
  – Risk to impurity control strategy (genotoxic, regioisomers, chirality, heavy metals, etc.)
  – Is the Quality Management System (QMS) robust for this DMF holder/Sponsor?
Common Issues with Starting Material Designation by Industry

• Proposing starting materials only one or two steps from the API in a multi-step synthesis
  – Justified by starting material contributing a “significant structural fragment”; by this logic even the final intermediate could be a starting material. Contradicts all other Q11 principles and Q7A.

• Proposing starting materials multiple steps from the API, however:
  – the steps are simple chemical manipulations e.g. esterification, removal of protecting groups.
  – The “starting material” itself is synthesized by complex reactions e.g. stereospecific reactions, complex ring systems, etc.
  – Fermentation Process: The complex/core structure generally including multiple chiral centers is proposed as the starting material
Common Issues with Starting Material Designation by Industry

• Proposal of an advanced intermediate as a starting material and making a commitment not to change the manufacturing process for it without FDA notification.
  – The ‘advanced intermediate’ should still meet all criteria for SM outlined in Q11 and Q7A
  – These types of proposals are evaluated on a case by case basis
Other Recommendations

Justification why steps prior to the starting material, which are not carried out under GMP, are not likely to affect the quality of the API should always be provided.

It is strongly recommended that industry seek FDA input and agreement on SM selection:

- For New Drugs: By the end of Phase 2
  - Multidisciplinary Meetings
  - CMC Specific meetings
  - Face to Face Meetings
  - Telephone Conferences
  - Written Responses Only Meetings

- For Generics/DMF holders: by email at
  - CDER-OPQ-QUERIES@FDA.HHS.GOV
Starting Material Selection: Take Home Message

- **All** the general principles in Q11 and Q7A for selection of starting materials should be considered rather than applying any individual one in isolation; true for both New Drugs and Generics.
- Q11 is a very flexible, high level guidance
- Deficiencies for inadequate SM are common during DMF reviews (both completeness assessment (CA) and full scientific review) and can be costly:
  - Extra review cycles
  - More work (validation/method development)
  - Risk of RTR for the referencing ANDA
Thank You