API Starting Material WG: A Strategy for Justification of API SM

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Core Team

• Mark Argentine, Eli Lilly
• Carl Busacca, Boehringer-Ingelheim
• Marjorie Egan, Infinity
• Magnus Eriksson, Boehringer-Ingelheim
• Margaret Faul, Amgen
• Zhihong Ge, Merck
• Frederick Hicks, Takeda
• William Kiesman, Biogenidec
• Ingrid Mergelsberg, Merck
• John Orr, Eisai
• Steven Pfeiffer, Kythera Biopharma
• Maciej Smulkowski, Takeda
• Gerald Waechter, Boehringer-Ingelheim
Problem Statement & Opportunities

- Lack of consistent and clear guidance from regulators on API SM selection
- Industry practices vary based on experience and interpretation of the guidelines by different agencies
- Lack of harmonized interpretation of ICH Q11 by different regulatory bodies (i.e. FDA, EMA etc.)

- API Starting Material WG established in 2011 to address these challenges
- Topic is a strong Precompetitive Opportunity that can provide value to the Industry

Sponsorship and Support by the API and Analytical LGs
Generic Chemical Process and the Advantage of API SMs

Raw Materials → API SM → Isolated GMP Intermediate(s)

$ → A → C → API

$ → B → C → API

Non-GMP Manufacture

GMP Manufacture

controlled by release of API SM

Release of API SM’s

Controlled by GMP regulations

Release of API
Value for Appropriate Designation of API SMs

- API SMs relieve manufacturers, agency reviewers and inspectors of a potentially significant burden in terms of managing early-step technical information that provides little value to overall DS quality,

- Selecting appropriate API SMs with analytical control will provide appropriate quality assurance and process control for the DS

- Rigorous adherence to GMPs should not be required before the API SM is designated in the NDA/DMF.
API SM WG Progress

- Three fundamental questions are addressed in three different manuscripts:
  - How has the regulatory perspective on API SM designation developed? – *Manuscript 1*
  - What are peer companies doing currently? – *Manuscript 2*
  - What should the industry do, if anything, to improve the current process? – *Manuscript 3*

Manuscript 1 & 2 have been published; Manuscript 3 will be published in *Org. Process R&D 2015.*
Manuscript 1: Regulatory & Industry Perspective

• First comprehensive review of all literature / perspectives published on this topic during the last 25 years
  - Summarizes current regulatory guidance's
  - Provides a perspective from industry and regulators on the most important elements regarding the justification of the API SMs

→ *No alignment on application of control strategies (propinquity vs. process knowledge / process control) to support the API SM justification*

Faul, M. M.; Kiesman, W. F.; Smulkowski, M.; Pfeiffer, S.; Busacca, C. A.; Eriksson, M. C.; Hicks, F.; Orr, J. D.
Manuscript 2: Assessment of API SM Selection by IQ Member Companies

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**Analytical Control**
- Control of impurities
- acceptance criteria
- analytical methods
- characterization
- fate and purge
- GTIs and pGTIs

Comprehensive Survey across IQ Companies: Evaluated 50 API SM & 24 Drug Substances
Part 1 & 2: DS & API SM Attributes

• Survey sought to determine if complexity of DS or API SMs was an important factor in API SM designation

• Correlations between Steps from RM to DS, Rings, and Stereocenters

• Little or No correlation with MW
Correlation between API SM Sourcing and Attributes

- Correlations noted between API SM Source and API SM attributes as with API SM Complexity
- 92% of all High & Medium complexity API SMs are custom manufactured
Part 3: API SM Control Strategy

Survey indicated common trends in how the API SM quality is controlled:

- Use of batch history data (minimum of 3 batches)
- Specifications based on use test data and resultant DS quality
- Control strategy: impurity fate and purge
- Use of Stability data
- Quality agreements (including change controls) with vendors
- Manufacturing of “high risk” API SMs under GMP
- Use of validated API SM processes
API SM Analytical Methods

- API SM methods were adequately specific and sensitive to actual and potential impurities from API SM manufacturing process (e.g., process intermediates, reagents, etc.).

- API SM methods were either validated (92%) or qualified (8%).

- To justify API SM impurity limits, fate and purge data along with batch history data from one of the following materials or combination of materials were used: API SM, GMP intermediate(s), or the DS.
Stereogenic Impurities

- 43% of API SMs contained stereogenic centers
- As number of API SM stereogenic centers increased, the percentage of potential stereogenic impurity standards prepared decreased
Control of Genotoxic Impurities

- Actual API SM GTIs controlled at TTC levels in API SMs or GMP process intermediates
- Some API SMs were genotoxic and were controlled to the TTC level in the DS
- Scientific judgment used to justify that API SM pGTIs were not present in the DS
Propinquity

• For one step GMP processes:
  - Extensive fate & purge studies conducted several steps prior to the proposed API SM
  - Tighter API SM impurity controls were implemented

• For short GMP processes:
  - Respondents strived for high purity API SM
  - Manufactured API SM under GMP until approval
  - Provided regulatory agencies with API SM manufacturing vendor quality agreement details

A 2-3 step GMP synthesis appears to be a “default standard”
Part 4: Case Studies Phase of Development

- 92% of Case Studies were post-EOP2 to inform regulatory practices and strategies employed by the IQ member companies
Data Sharing in Filings

• % Synthetic Scheme / information shared by respondents with regulatory agencies:

  • Custom API SMs 77%
  • Commercially available API SMs 50%
  • Commodity chemicals < 20%

Summary: As the complexity of an API SM increases companies provide more information to regulators about their syntheses.
Manuscript 2: Summary

- Globally there is no systematic risk-based decision framework to assess the justification and quality control for API SM selection

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Manuscript 3: The Framework

- Manuscript will:
  - provide a framework on approaches to the API SM justification process
  - establish a common language and definitions to enhance understanding of the key scientific concepts & material attributes
  - outline a proposal to create uniform API SM justification packages for future products to the regulatory agencies in compliance with ICH Q11
  - specific case study examples demonstrating how process understanding is used to justify the control strategy

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The Team Dynamics.....

What worked well.....

• Clear set of goals and deliverables defined
• Team passionate SMEs, driven to learn and publish data of value to the community
• Diverse group with different experiences (API, Analytical, regulatory, EU, FDA)
• Clear accountability within team to deliver
• Team developed trust and supportive in collaboration

Challenges.....

• Significantly complex topic with multiple aspects
• Survey had to be run twice and required months to compress into meaningful data
• Defining the right tools to assess the data
• Keeping the output simple....
Value and impact of the precompetitive Collaboration on API SMs

• Manuscript 1 & 2 were within the most cited / read articles in OPR&D in 2014

• First comprehensive review of literature on API SMs

• Significant body of data on current practices across IQ member companies

• Significant reference materials

• Strong positive feedback from community