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

9 October 2014

IQ Symposium 2014 – “Pre-competitive Collaboration for Innovation”

# 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

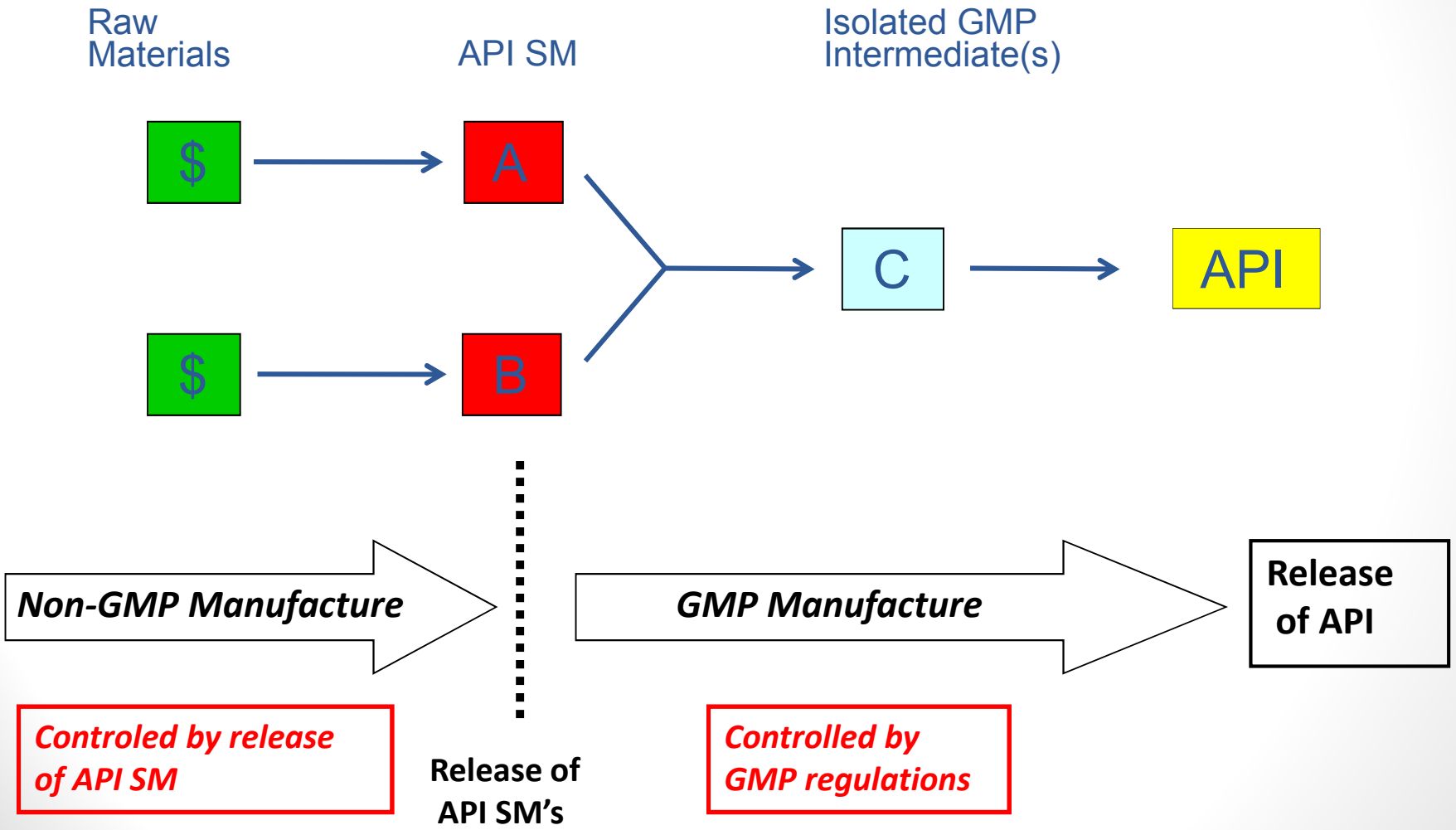
# Problem Statement & Opportunities

- 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



# 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.**
***Org. Process Res. Dev.*, 2014, *18* (5), pp 587–593**

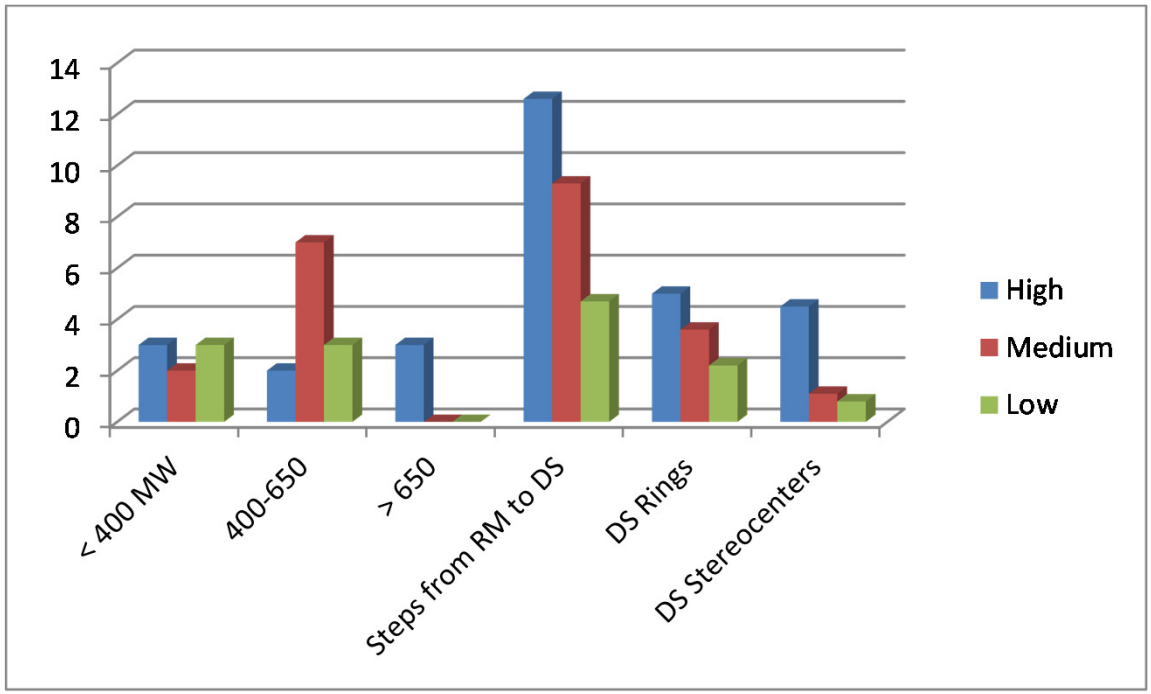
# Manuscript 2: Assessment of API SM Selection by IQ Member Companies

| DS Attributes | API SM Attributes | Control Strategy | Regulatory Strategy |
|---|---|---|---|
| • synthesis<br>• complexity<br>• historical data<br>• chiral impurities<br>• stability data<br>• impurities | • complexity<br>• manufacturing and validation<br>• sourcing<br>• propinquity<br>• impurities | • process control<br>• manufacturing<br>• propinquity<br><br><u>Analytical Control</u><br>• Control of impurities<br>• acceptance criteria<br>• analytical methods<br>• characterization<br>• fate and purge<br>• GTIs and pGTIs | • regulatory status<br>• filing structure<br>• information shared for justifications<br>• timing of final API SM strategy communication<br>• regulatory communications with US, Canada, and EU |


**Comprehensive Survey across IQ Companies: Evaluated 50 API SM & 24 Drug Substances**

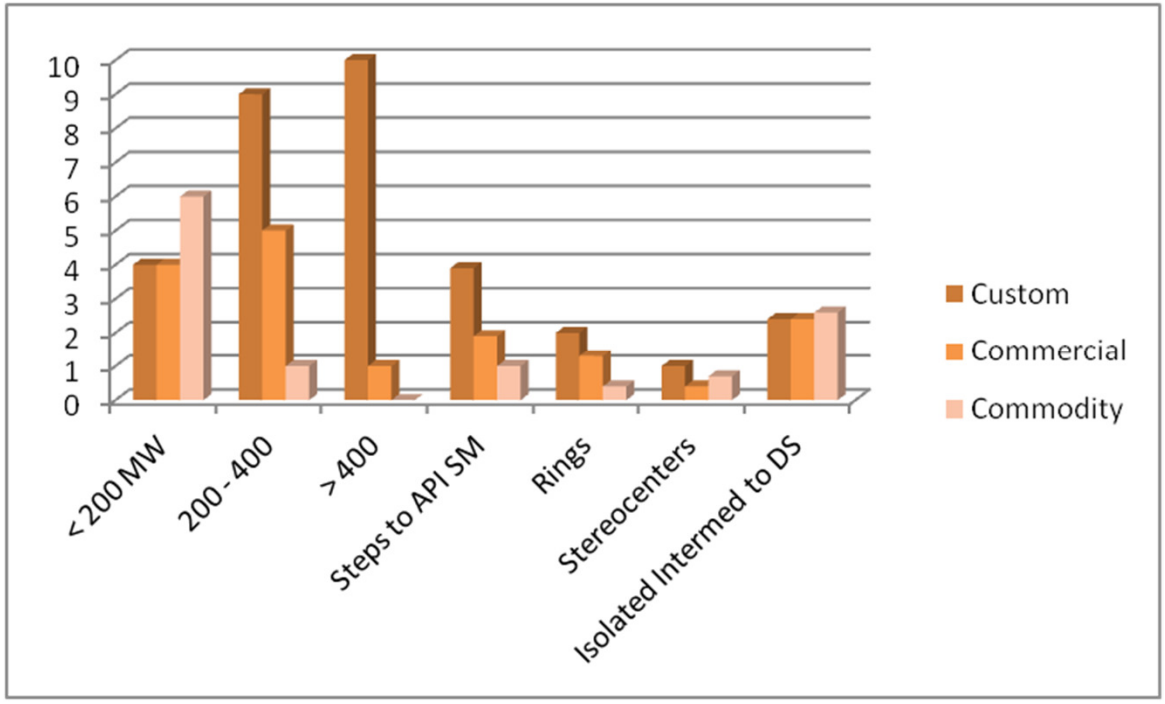
# Part 1 & 2: DS & API SM Attributes

- 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:

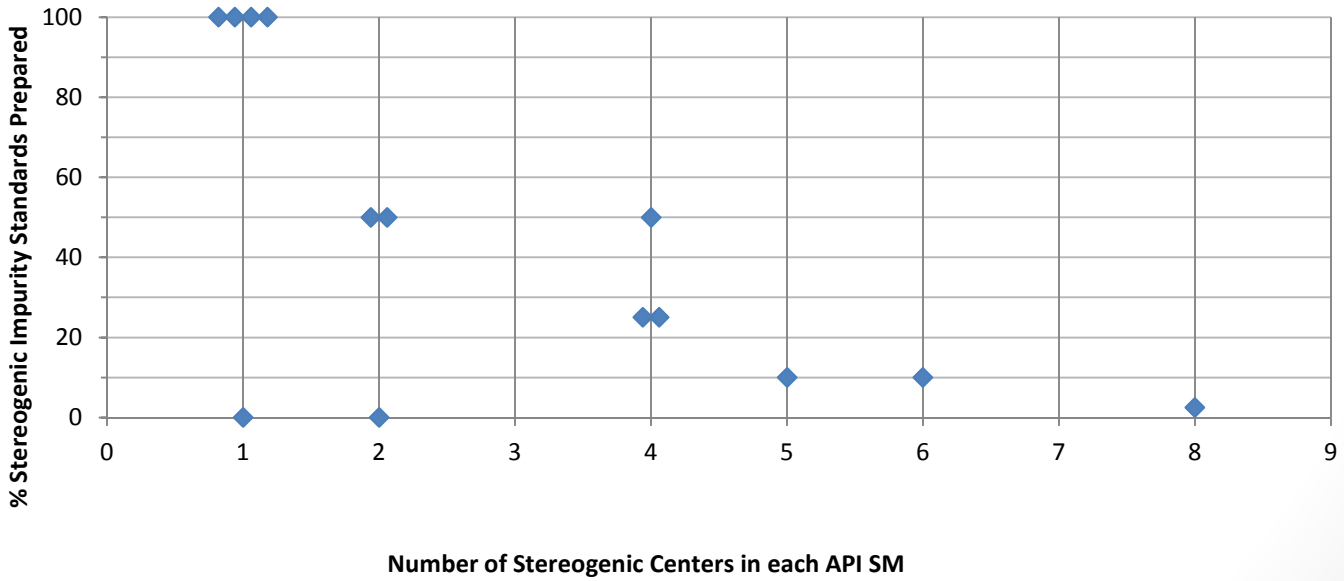
- Use of batch history data (minimum of 3 batches)
- Specifications based on use test data and resultant DS quality
- Control strategy: impurity fate and purge
- Use of Stability data
- Quality agreements (including change controls) with vendors
- Manufacturing of “high risk” API SMs under GMP
- Use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

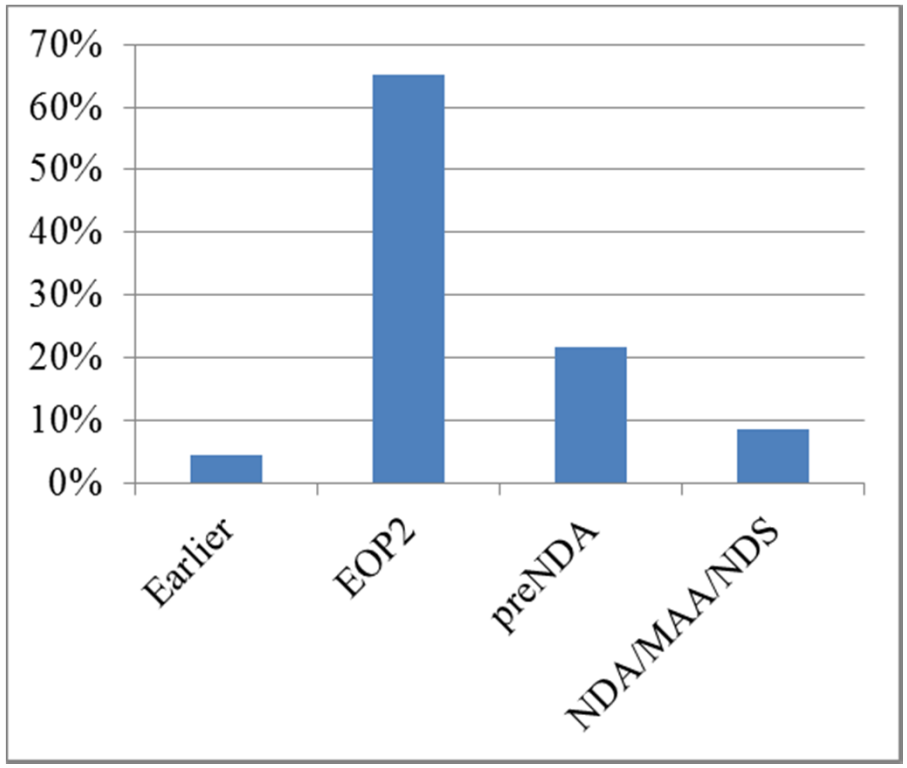
# Propinquity

- 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

**Faul, M. M.; Kiesman, W. F.; Smulkowski, M.; Pfeiffer, S.; Busacca, C. A.; Eriksson, M. C.; Hicks, F.; Orr, J. D.**
***Org. Process Res. Dev.*, 2014, *18* (5), pp 594–600**

# 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

**Faul, M. M.; Kiesman, W. F.; Smulkowski, M.; Eriksson, M. C.; Hicks, F.; Orr, J. D.; Egan, M.; Mergelsberg, I.; Ge, Z.; Waechter, G.; Argentine, M.**
***Org. Process Res. Dev.*, 2015, *Issue related to ICH Q11***

# 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