ICH Quality Guideline Q11

Development and Manufacture of APIs
(An Update from the Trenches)

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Special thanks to Betsy Fritschel & Tim Watson
March 2012

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Reference to ICH Q11 as draft Guidance. Q11 is a draft until it reaches Step 4 consensus.

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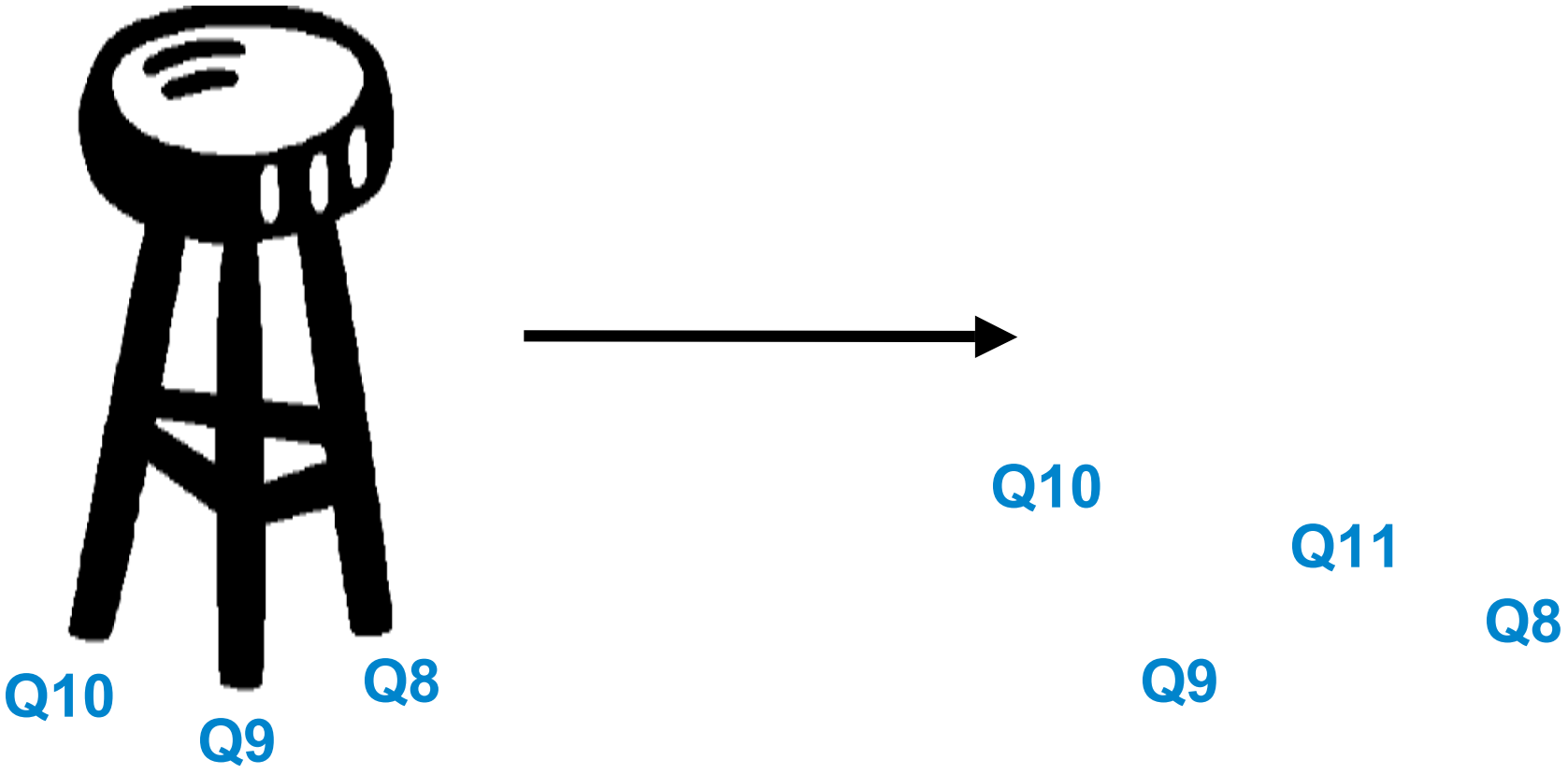
ICH Q11
Today's Agenda

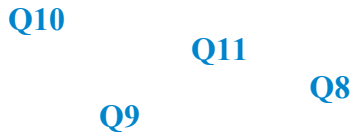
- Late breaking news
- Background and Process for Q11
- Step 2 document - highlights & controversies
- Q11 Nomenclature Quiz
  - Design Space
  - QbD development versus QbD submission
  - Platform Manufacturing
  - Control Strategy

Value of Q11



Why Q11?

- New ICH Guidelines
  - Q8 Pharmaceutical Development
  - Q9 Quality Risk Management
  - Q10 Pharmaceutical Quality System



- **Concepts** of these guidelines **apply** to Drug Substance as well as Drug Product
- **Process** for manufacture of Drug Substance very **different** from Drug Product - **purification**
- Need Q11 to **clarify principles** of Q8, Q9, and Q10 as they relate to Drug Substance and provide **examples**

ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Final Concept Paper

Q11: Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)

dated 11 April 2008

Endorsed by the ICH Steering Committee on 11 April 2008

Type of Harmonisation Action Proposed

A new tripartite Technical Guidance is proposed for Active Pharmaceutical Ingredients (APIs) harmonising the scientific and technical principles relating to the description and justification of the development and manufacturing process (CTD sections S 2.2 – S 2.6) of Drug Substances including both chemical entities and biotechnological/biological entities.

This document will take into consideration and provide examples as appropriate for describing the principles and concepts which are included in ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10). However, the approaches to, and extent of, development (e.g., traditional/empirical or systematic/enhanced) will be based on the development strategy designed by each manufacturer.

This guideline is intended to provide guidance for drug substances as defined in the scope of the ICH Guideline Q6A ("SCE") and ICH Guideline Q6B ("Biotechnological/biological").

Statement of the Perceived Problem

Background and Summary:

Several aspects of technical guidance specifically related to the quality of chemical entities and biotechnological/biological drug substances have been harmonised through ICH guidelines. Although it is generally accepted that there is a strong linkage between the manufacturing process for medicinal products and their quality attributes, there is limited guidance regarding the description and justification of development and manufacturing processes for drug substances and the type and extent of information to be submitted in regulatory dossiers. During discussions at the ICH-Q Drug Substance Roundtable meeting held in Washington in September, 2007, the experts agreed that many of the principles and concepts that have been addressed in ICH guidelines Q8, Q9, and Q10 are also applicable to the development and manufacture of drug substances. The importance of an API guideline for both chemical and biotechnological/biological products was emphasized and the development of a formal concept paper and business plan was endorsed by the ICH SC in October 2007.

Therefore, it is recommended to develop a new tripartite high level Technical Guidance harmonising the scientific and technical principles relevant to the design, development and manufacture of drug substances as part of a total control strategy designed to ensure product quality and consistency. Problem Statement:

Consistent with modern global manufacturing and scientific practices (described in the ICH Quality Vision presented and endorsed in Brussels, July 2003), and economic considerations, the development and establishment of a robust manufacturing process for drug substances to deliver a product of consistent quality accounts for a significant proportion of manufacturers' resources and efforts.

Concept Paper
April 2008

Q11 EWG June 2008 Portland, Oregon

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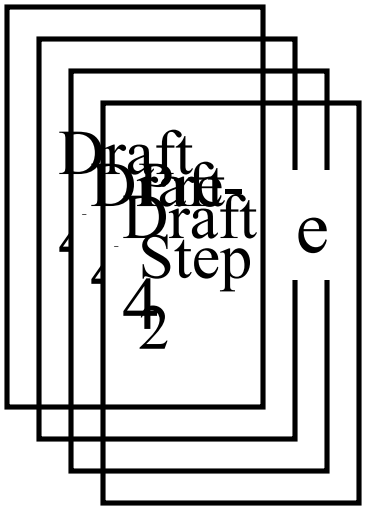
Step 1

- 6 Face-to-face EWG meetings
- Many teleconferences and net meetings
- Many drafts (10 ± depending on how you count)
  - Draft 0 - 4 (June 2008 – November 2010)
- Examples

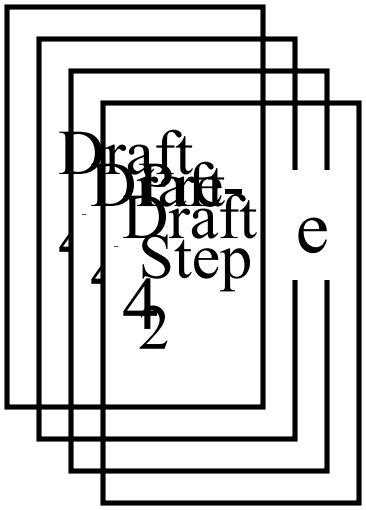
Remember:

- This is a negotiated consensus process
- No party gets everything they want!

Q11 EWG November 2010 Fukuoka Japan



A few more revisions
A lot more teleconferences
And then finally reached consensus
Step 2 May 2011



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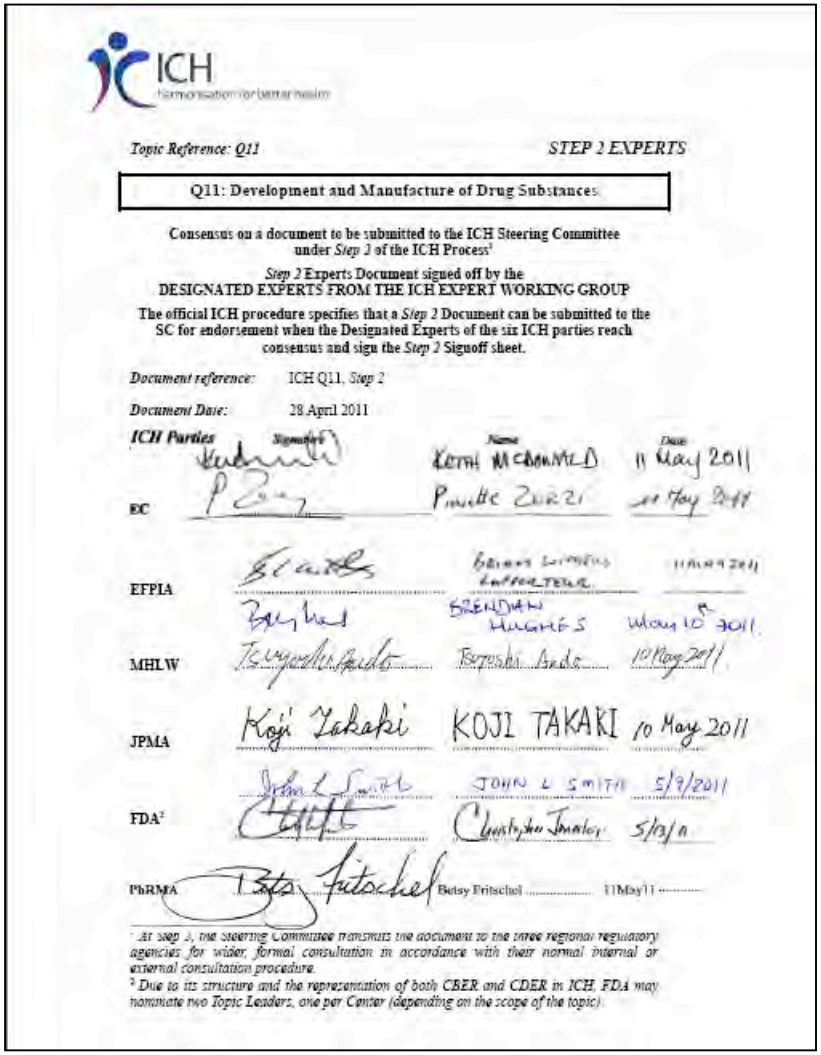

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Topic Reference: Q11 *STEP 2 EXPERTS*

Q11: Development and Manufacture of Drug Substances

Consensus on a document to be submitted to the ICH Steering Committee under *Step 3* of the ICH Process[1]

***Step 2* Experts Document signed off by the DESIGNATED EXPERTS FROM THE ICH EXPERT WORKING GROUP**

The official ICH procedure specifies that a *Step 2* Document can be submitted to the SC for endorsement when the Designated Experts of the six ICH parties reach consensus and sign the *Step 2* Signoff sheet.

Document reference: ICH Q11, *Step 2*

Document Date: 28 April 2011

ICH Parties	*Signature*	*Name*	*Date*
EC		KEITH MCCONNELL Pauline Zurzi	11 May 2011 10 May 2011
EFPIA		BRENDAN HUGHES	11 MAY 2011
MHLW		Tsuyoshi Ando	10 May 2011
JPMA	Koji Takaki	KOJI TAKAKI	10 May 2011
FDA[2]		JOHN L SMITH Christopher Joneles	5/9/2011 5/9/11
PhRMA		Betsy Fritschel	11May11

[1] At step 3, the Steering Committee transmits the document to the three regional regulatory agencies for wider, formal consultation in accordance with their normal internal or external consultation procedure.

[2] Due to its structure and the representation of both CBER and CDER in ICH, FDA may nominate two Topic Leaders, one per Center (depending on the scope of the topic).

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Public consultation
June - September

1300 comments across 3 regions

Regional review of comments

More telecons and Net Meetings

Almost Step 4

We called it Pre-Step 4

Q11 EWG November 2011 Seville Spain

Current Status of Q11

- Step 1 EWG Consensus April 2008 – April 2011
- Step 2 – Signatures May 2011
- Step 3
  - Stage 1 Public comment Target June – Sept 2011
  - Stage 2 Resolve comments Target 1st Quarter 2012

March 6 telecon consensus

- Step 4 publication of final version
- Step 5 Implementation

What took so long?

- Many different expectations
  - Traditional vs Enhanced
  - Small vs Large
  - Alignment with regional guidelines and expectations
- Many different agendas
- Team dynamics 25+ people
- Only two face to face meetings per year
- Virtual meetings ok for simple editing but not a good venue for true discussion

Outline of Q11 Step 2 document

1. Introduction
2. Scope
3. Manufacturing Process Development
4. Description of Manufacturing Process
5. Selection of Starting Material
6. Control Strategy
7. Process Validation/Evaluation
8. Submission in CTD Format
9. Lifecycle Management
10. Illustrative Examples
11. Glossary

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Format:
General Principles
What to Submit

Outline of Q11

1. Introduction
2. Scope
3. Manufacturing Process Development

Important to read Q11 as a “whole”
NOT individual sections out of context

7. Process Validation/Evaluation
8. Submission in CTD Format
9. Lifecycle Management
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11. Glossary

Q11 Introduction

- Traditional Approach
  - Defined set points and operating ranges for process parameters
  - Drug Substance control strategy typically based on
    - Demonstration of process reproducibility
    - Testing to meet established acceptance criteria
- Enhanced Approach
  - Risk management and more extensive scientific knowledge to select process parameters and unit operations
  - Evaluation in studies to establish design space and control strategies applicable over the lifecycle of the drug substance

Q11 Introduction

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  - Evaluation in studies to establish design space and control strategies applicable over the lifecycle of the drug substance
- Not mutually exclusive. Company can choose:
  - Traditional
  - Enhanced
  - Combination of both

3 Manufacturing Process Development

Enhanced

- **Systematic** evaluation and **understanding**
- **Functional relationships** that link material attributes and process parameters to CQAs
- **QRM** to establish an appropriate control strategy which can include proposals for Design Space and/or RTRT

Traditional

- Identify Potential CQA's
- Define Manufacturing Process
- Define Control Strategy

4 Manufacturing Description

- Description of DS manufacturing process represents applicant's commitment
- Information to adequately describe mfg process and process controls
  - Flow diagram
  - Sequential process narrative
  - In-process controls
  - Scale-factors (when process is scale dependent)
  - Any design spaces in the mfg process should be included as part of the mfg process description

Important Definition & Distinction

Design Space (Q8)

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. **Design space is proposed by the applicant and is subject to regulatory assessment and approval.** *(emphasis added)*

Important distinction between QbD development and QbD submission

Example 1

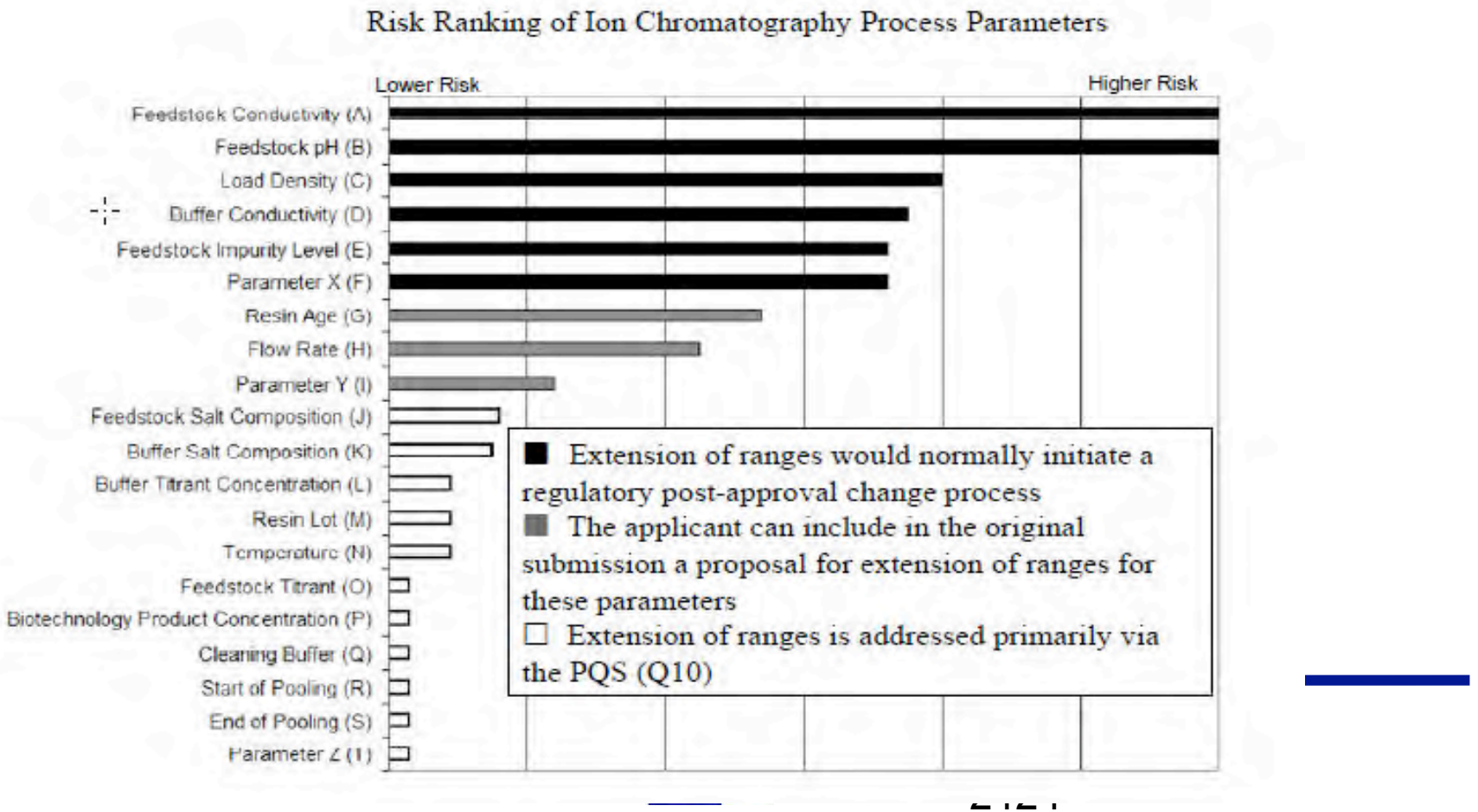
- *This example illustrates development of a design space using prior knowledge and chemistry first principles. It depicts both a traditional and enhanced approach to determination of the ranges for parameters controlling the formation of a hydrolysis impurity*
- Value: *high priority for PhRMA LDKIT*
  - Multivariate design is NOT DoE, Drug substance has many tools to develop and design space.
  - Demonstrate "fixed parameters" in MVD (eg. reflux temperature)
- Example proposed, developed, and supported by both regulators and industry
- Not a complex example, and very "basic"; BUT the intent is very valuable to the disciple of drug substance.

Design Space Discussion for Biotech

- The development and approval of a design space for some biotechnology/biological drug substances can be challenging due to factors including process variability and drug substance complexity (e.g., post-translational modifications). These factors can affect residual risk (e.g., potential for unexpected changes to CQAs based on uncertainties related to scale sensitivity) which remains after approval of the Design Space. Depending on the level of residual risk, it may be appropriate for an applicant to provide proposals on how movements within a Design Space will be managed post approval. These proposals should indicate how process knowledge, control strategy and characterisation methods can be deployed to assess product quality following movement within the approved design space.

Example 2

- *This example illustrates how results from an iterative quality risk assessment can be used to communicate the rationale for classification and proposed future management of changes to process parameters.*



5 Selection of Starting Materials and Source Materials

- 6 general principles for consideration
- All general principles should be considered rather than strictly applying each general principle
- General principles paraphrased
  1. Changes within early steps of a given synthesis lower potential impact on API
  2. Describe enough so that reviewer can understand where and how impurities in the API are formed and why proposed Control Strategy is suitable
  3. Steps impacting impurity profile should normally be included
  4. Each branch of a convergent synthesis begins with one or more starting material
  5. Substance with defined chemical properties and structure – usually isolated
  6. Significant structural fragment

Example 4 clarifies how to use these principles

6 Control Strategy

General Principles

- Control Strategy is a planned set of controls, derived from current product and process understanding, that assures process performance and product quality
- Every drug substance manufacturing process whether developed through traditional or enhanced (or combination of both) has an associated control strategy

6 Control Strategy

General Principles (cont'd)

A control strategy can include, but is not limited to:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials for the drug substance, etc)
- Controls implicit in the design of the manufacturing process (e.g., sequence of purification steps (biotech) or order of addition of reagents (chem))
- In-process controls (including in-process tests and process parameters)
- Controls on drug substance (e.g., release testing)

6 Control Strategy

Enhanced

- More systematic identification of sources of variability
- More meaningful and efficient controls
- Iterative process as process understanding increases
- Can provide for flexibility in operating ranges for process parameters

Traditional

- Set points and operating ranges set tightly to ensure consistency
- More emphasis on assessment of CQAs at DS

Control Strategy

Is the "largest" area that contains specifications and critical quality attributes in addition to other types of controls

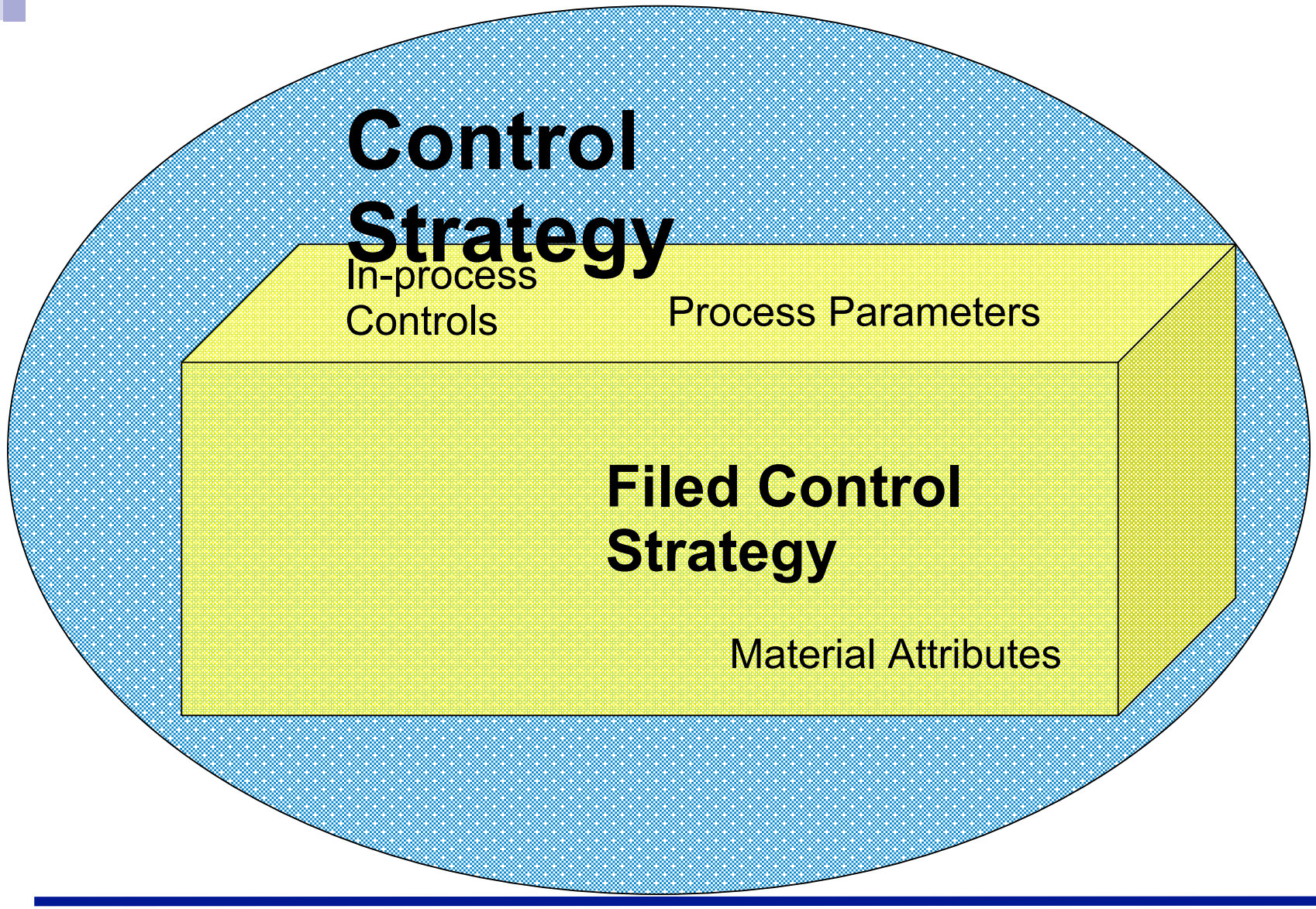
- Every specification is part of the control strategy
- There are things in the control strategy that do not have a corresponding test in the drug substance

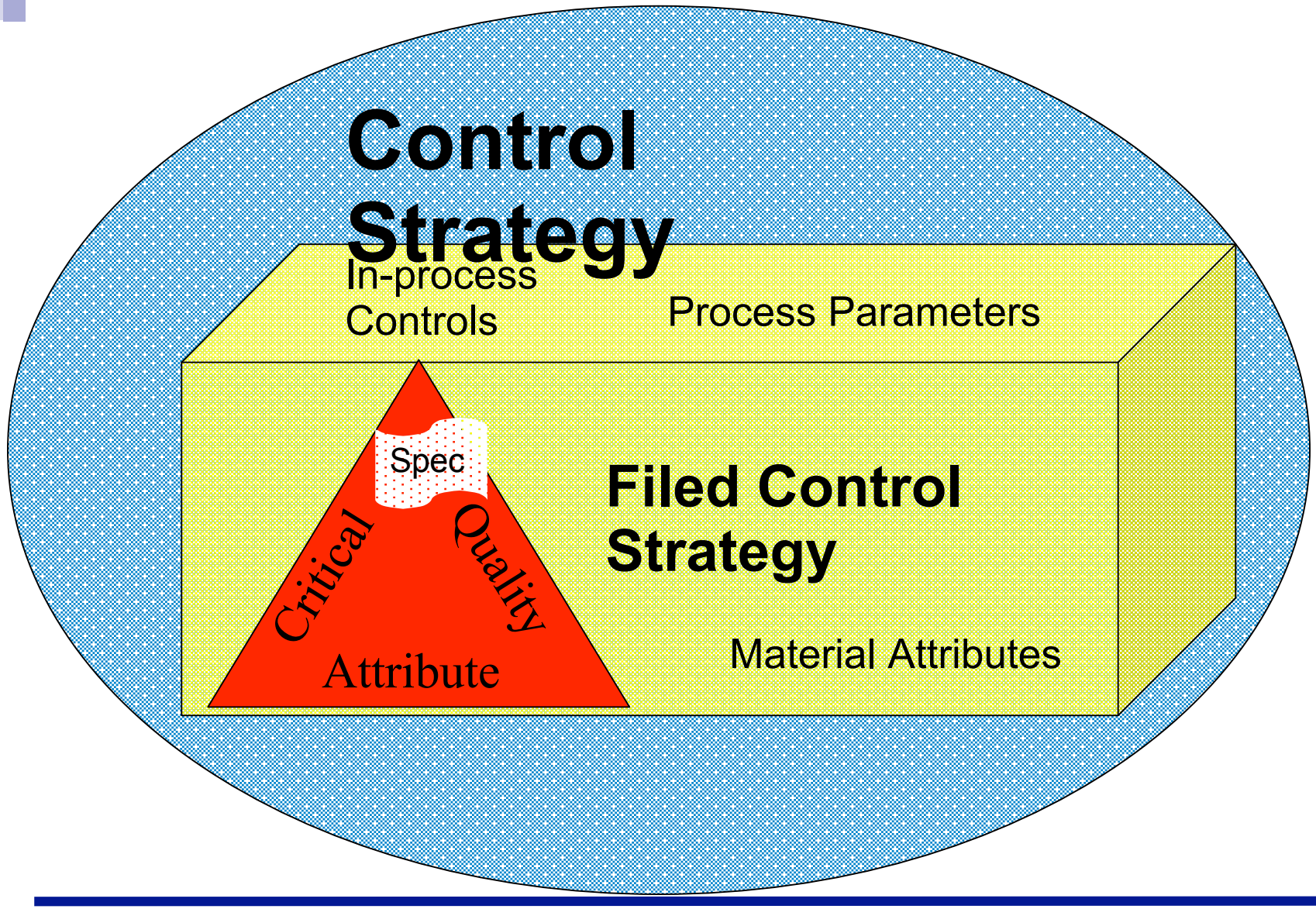
Control Strategy can also include

Material Attributes

In-process Controls

Process Parameters


Control Strategy
In-process Controls
Process Parameters
Filed Control Strategy
Material Attributes


Control Strategy
In-process Controls
Process Parameters
Spec
Critical
Quality
Attribute
Filed Control Strategy
Material Attributes

10 Illustrative Examples

- Provide examples of implementation of concepts
- Not intended to create any new expectations beyond current regulatory requirements

11 Glossary

Section 11 Glossary

New term defined:

Platform Manufacturing: The approach of developing a production strategy for a new drug starting from the manufacturing processes similar to those used by the same applicant to manufacture other drug of the same type (e.g. Mab).

What Q11 does not do:

1. Define or clarify regulatory flexibility
2. Define criticality (i.e. CPP)
3. Define starting material based strictly on number of steps
4. Clarify what goes into the manufacturing description section of CTD
5. Clarify what CPV?

Value of Q11

1. Recognizes that traditional and enhanced are not mutually exclusive
2. Gives context for scientifically justifying control strategy (provides an example of risk management for process parameters)
3. Provides general principles for defining Starting Material
4. Introduces the concept of “Platform Manufacturing”
5. Drug Substance CQA can reference a control strategy for “material attributes” upstream

Disclaimer: This is MY opinion

Is ICH worth the effort?
Top Four Reasons.

4. Allows discussion / debate of draft and proposed expectations face-to-face with regulators

3. Allows all parties to hear each other's concerns including probable unintended consequences.

2. Allows debating specific wording with regulators and hearing underlying meaning of specific words

1. Reduces regional specific guidance

Disclaimer: Also MY opinion

Special Thanks to

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Rodney Parsons	BMS	Sally Anliker	Lilly
Jonathan Walker	BMS	Mark Butchko	Lilly
Andrew Gee	Boehringer Ingleheim	John Lepore	Merck
Linda Hendricks	Centocor	John Curran	Merck
Vincent Djuhadi	Cephalon	Tim Watson	Pfizer
Carly Evans	Genzyme	Zareen Ahmed	Sanofi
Clive Meerholz	GSK		

Thank you