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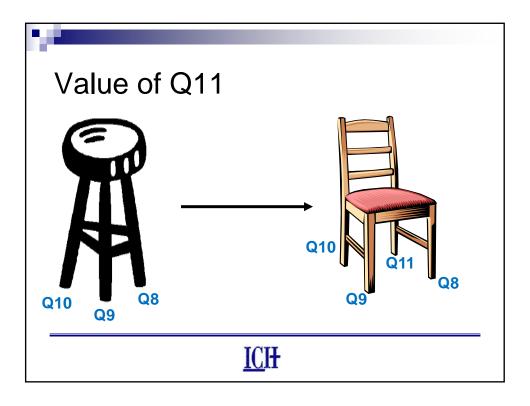
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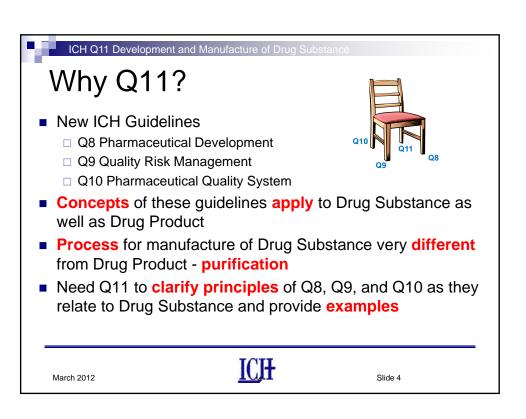
Reference to ICH Q11 as draft Guidance. Q11 is a draft until it reaches Step 4 consensus.

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter.

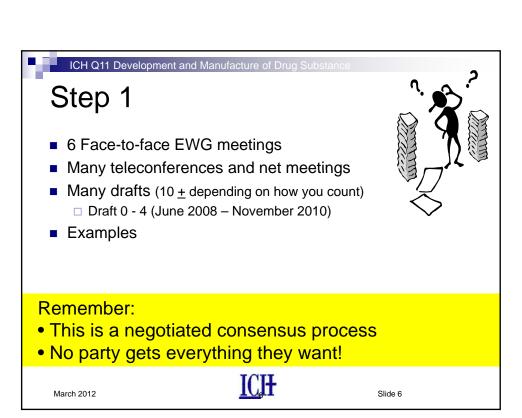
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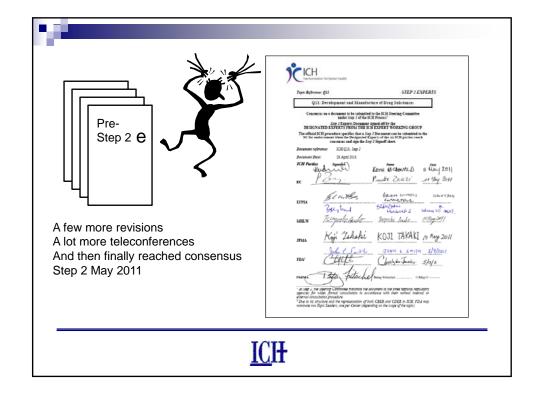




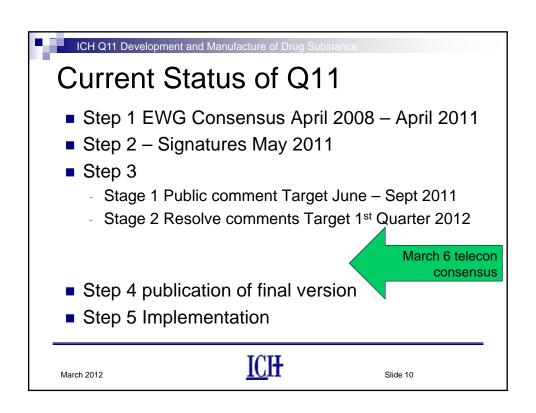














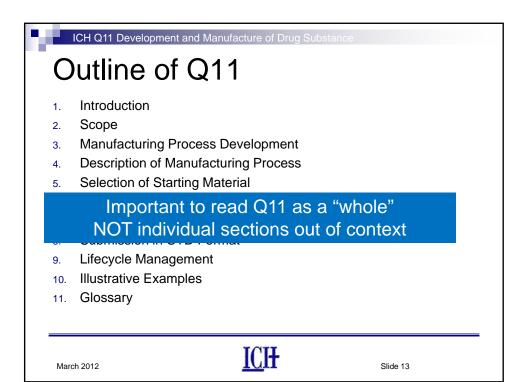
- Many different expectations
 - Traditional vs Enhanced
 - Small vs Large
 - Alignment with regional guidelines and expectations
- Many different agendas
- Team dynamics 25+ people
- Only two face to face meetings per year
- Virtual meetings ok for simple editing but not a good venue for true discussion

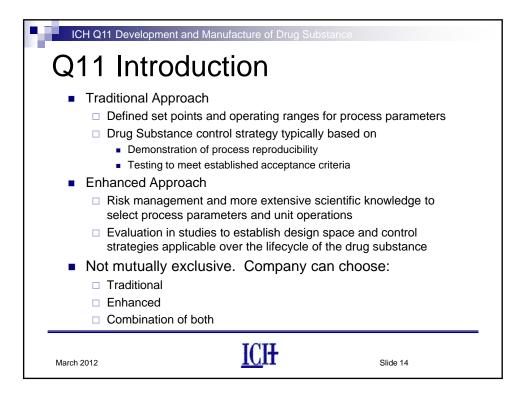


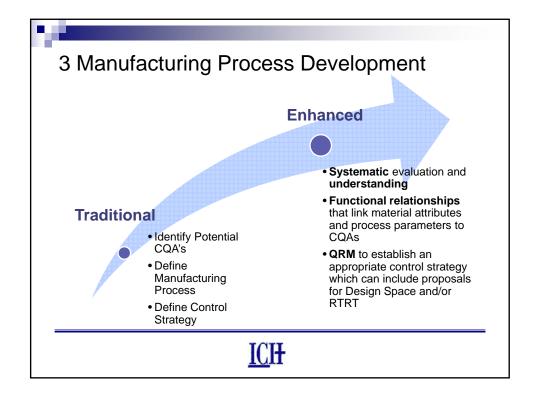
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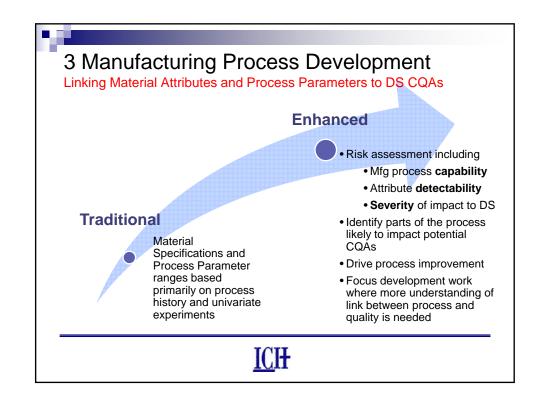














Example 1

Linking Material Attributes and Process Parameters to DS CQAs

- Illustrates
 - ☐ Traditional and enhanced approach to determination of ranges for parameters
 - Development of design space using prior knowledge and chemistry first principles
- Example 1 adapted from IWG Hydrolysis Impurity Case Study in 2010 training workshops

Note: This is a simplified example. Every company and probably every chemist and engineer could find a different approach. Focus is intended to be how to use the information, not how the process was developed.

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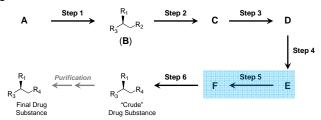


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Example 1

Linking Material Attributes and Process Parameters to DS CQAs

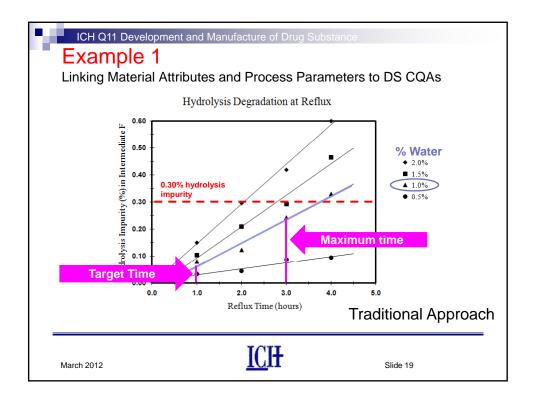


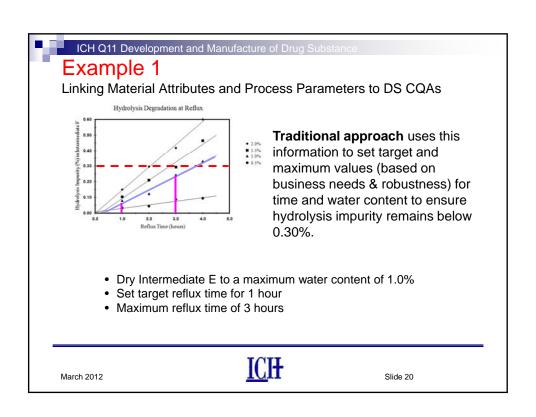
Hydrolysis impurity formed during Step 5

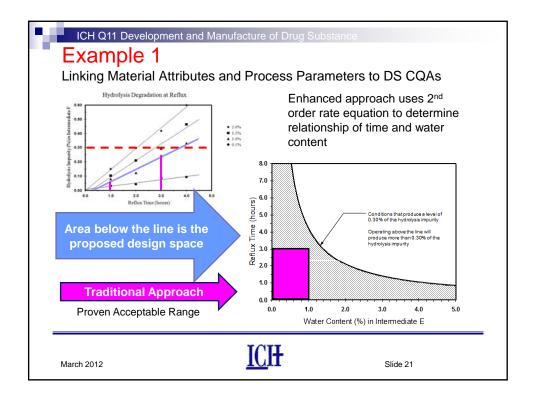
- 0.30% max at Intermediate F (based on subsequent purge)
- Formation based on time, temperature and water concentration
 - ☐ Fixed temperature (based on reflux)
 - □ Experimentation (graph) shows % impurity formed
 - 4 time points
 - 4 water concentrations

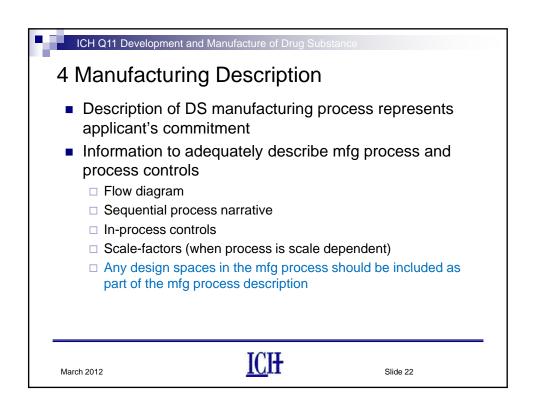
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Important Definition

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)

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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
 - 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
 - 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

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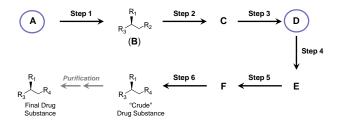
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ICH Q11 Development and Manufacture of Drug Substance

5 Selection of Starting Materials and Source Materials

- All 6 general principles should be considered rather than strictly applying each general principle
- Example 4



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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

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6 Control Strategy

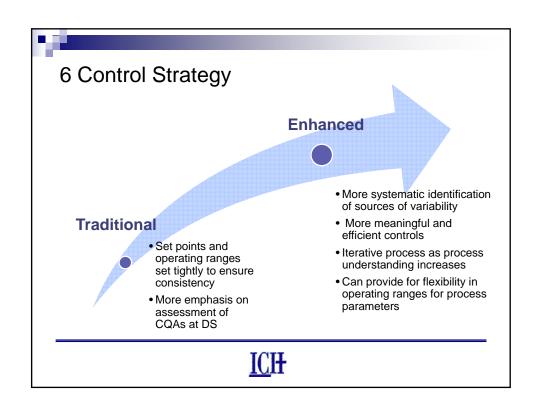
General Principles (cont'd)

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)

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Important Definitions:

Control Strategy (Q10): A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specification, and the associated methods and frequency of monitoring and control.

Critical Quality Attribute (Q8): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality

Note: bold, color and underline added for emphasis

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Specification (text below from Q6A)

- A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria....
- Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
- Specifications are <u>one part of a total control strategy</u> for the drug substance and drug product designed to ensure product quality and consistency. **Other parts** of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices; e.g, suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Note: bold, color and underline added for emphasis

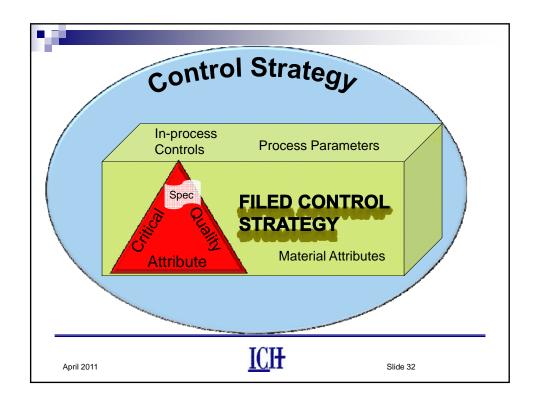
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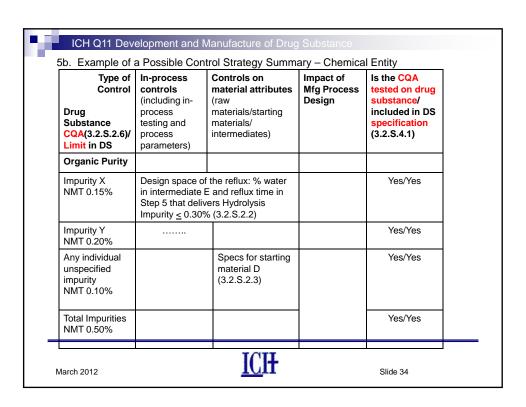


Purpose of Example 5

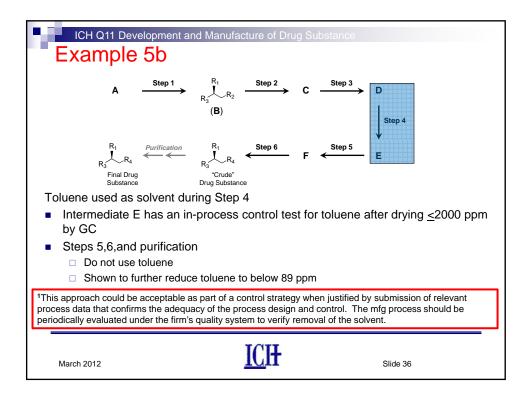
- Illustrate how <u>part of</u> a DS control strategy might be summarised in tabular form
- Not the control strategy itself, roadmap of where in the CTD to find control strategy and justification
- Multiple ways of presenting this information
 - □ 2 are shown
 - □ Amount of detail shown in the example tables is NOT related to the type of drug substance
- Not a comprehensive representation of all elements of a drug substance control strategy
- Not a template!!!

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| Type of Control Drug Substance CQA(3.2.S.2.6)/ Limit in DS | In-process controls (including in- process testing and process parameters) | Controls on material attributes (raw materials/starting materials/ intermediates) | Impact of Mfg Process Design | Is the CQA tested on DS/ included in DS specification (3.2.S.4.1) |
|--|---|--|---|---|
| Entantiomeric purity S-enantiomer NMT 0.50% | | Specs for starting material D (3.2.S.2.3) S-enantiomer ≤0.50% | Stereocentre is shown not to racemize (3.2.S.2.6) | No/No |
| Residual Solvent | | | | |
| Ethanol NMT 5000 ppm | In-process test during drying after final purification step (3.2.S.2.4) LOD ≤0.40% | | In-process results correlated to test results on drug substance (#.2.S.2.6) | No/Yes |
| Toluene NMT 890 ppm | In-process test step 4 (3.2.S.2.4) <2000 ppm by GC | | Process steps after step 4 are shown to purge toluene to levels below Q3C | No/No ¹ |



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| Toluene NMT 890 ppm | In-process test step 4 (3.2.5.2.4) ≤2000 ppm by GC | | Process steps after step 4 are shown to purge toluene to levels below Q3C | No/No ¹ |



7 Process Validation/Evaluation

- Q7 definition of validation with additional words about lifecycle approach to validation
 - □ Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a drug substance or intermediate meeting its predetermined specifications and quality attributes
 - Can include the collection and evaluation of data, from the process design stage through production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance
- No set number of batches for validation
 - Validation includes the collection of data from an appropriate number of batches
- Continuous process verification
 - □ Mentioned as an alternative to traditional process validation
 - □ Not defined still an evolving concept

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8 Submission of Manufacturing Process Development and Related Info in CTD format

- Use of enhanced approach generates information for which there is no defined location in the CTD
- Suggestions provided in Section 8
- Allows applicant to indicate where information is provided and to cross-reference

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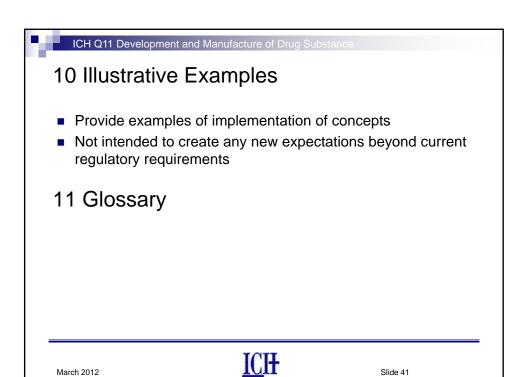
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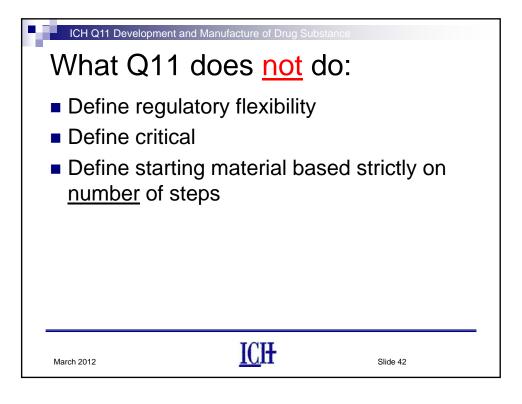
9 Lifecycle Management

- Concepts of Q10 apply to drug substance and encourage use of science and risk based approaches at each lifecycle stage
- Mfg process performance should be periodically evaluated
- Systematic approach to knowledge management
- Change management (Continual improvement)
 - □ Proposal on how specific future changes may be managed
 - □ Evaluate the impact of the change on the drug substance
 - Appropriate testing to analyse the impact of the proposed change
 - For chemical entities the appropriate testing could be on an intermediate or DS
 - □ Movement within Design Space does not require regulatory approval

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Value of Q11

- Recognizes that traditional and enhanced are not mutually exclusive
- Gives context for scientifically justifying control strategy
- Provides general principles for defining Starting Material
- Allows these SM general principles to apply to semi-synthetic processes

Disclaimer: This is MY opinion

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Is ICH worth the effort? Top Four Reasons.

- 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

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