The IPEC Significant Change Guide
Content, Application and Benefit for Industry

Kevin J McGlue
Director Global Quality Assurance, Colorcon

ExcipientFest Europe
Amsterdam, 24th June 2014
The IPEC Significant Change Guide
Content, Application and Benefit for Industry

- IPEC-Americas Significant Change Guide history
- 2014 Revision overview
- Discussion of 2014 revision changes
- Benefit to Industry
- Summary

ExcipientFest Europe
Amsterdam, 24th June 2014
IPEC-Americas Significant Change Guide history
First issued in 2000 as an IPEC-Americas Guide

Adapted to USP <1195> and issued as a draft.

IPEC-Americas issued Revision 1, 2005 to include a section on Impurity Profile and certain updates

FDA reviewed USP <1195> draft and required change to make Level II changes always reportable to the excipient user.
IPEC-Americas Significant Change Guide - History

- USP issued a revised draft to <1195> incorporating FDA’s change.


- IPEC-Americas issued a revision incorporating the FDA change in 2009.

- Revision 3 (to be finalised 2014) is a complete revision to harmonise within IPEC Americas and IPEC Europe.
2014 revision overview
IPEC Significant Change Guide
2014 revision overview

- Re-worked Layout
  - Glossary and Appendices

- Significant Change Definition

- Re-worked Types of Change Categories

- Re-worked Evaluation Criteria

- Re-worked Determination of Impact on Quality and Performance
IPEC Significant Change Guide
2014 revision overview

- Reduced number of Change Risk Levels from three (3) to two (2)
- Re-worked designation of Risk Level for each Type of Change
- Added Risk Assessment Section
- Re-worked Notification Requirements
2014 revision – discussion of changes
IPEC Significant Change Guide
Definition of ‘Significant Change’

2009

- Any change by the manufacturer of an excipient that alters an excipient physical or chemical property outside the limits of normal variability, or that is likely to alter the excipient performance in the dosage form is considered significant.

2014

Definition: NSF/IPEC 363: GMP for Pharmaceutical Excipients (Publication expected 2014)

- Any change that has the potential to alter an excipient’s physical, chemical or microbiological property from the norm, and/or that may alter the excipient’s performance in the dosage form.
IPEC Significant Change Guide
Types of Change

2009
1. Site Change
2. Scale of Manufacture
3. Equipment
4. Manufacturing Process
5. Packaging and Labeling

2014
1. Site Change
2. Scale of Manufacture
3. Production Equipment
4. Production Process
5. Packaging and Labeling
IPEC Significant Change Guide
Types of Change

2009

6. Specifications
7. Multiple Changes

2014

6. Raw Materials for the Manufacture of the Excipient
7. Excipient Specification and Test Methods
8. Supply Chain
9. Multiple Changes
2009

Has there been a Δ in:
✓ Chemical Properties
✓ Physical Properties
✓ Impurity Profile
✓ Functionality
✓ Moisture Level
✓ Bioburden
✓ Origin or contact packaging

2014

Impact on:
✓ Physical Properties
✓ Chemical Properties
✓ Microbiological Properties
✓ Intended performance
✓ Composition Profile
✓ Excipient Stability
<table>
<thead>
<tr>
<th>2009</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td><strong>Δ in:</strong></td>
</tr>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td>✓ Origin, type or site of RM</td>
</tr>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td>✓ Distribution of excipient</td>
</tr>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td>✓ Origin and/or type of contact or barrier packaging</td>
</tr>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td>✓ Regulatory Status</td>
</tr>
<tr>
<td><img src="image.jpg" alt="Image" /></td>
<td>✓ Compliance to a compendia or other regulation</td>
</tr>
</tbody>
</table>
In the 2014 revision, each of the Evaluation Criteria are discussed in detail with respect to assessment of their impact on Quality and Performance.

The concepts of ‘risk assessment’ and ‘comparison to historical norms’ are introduced to evaluate the significance of change in certain cases.
IPEC Significant Change Guide
Change Levels

2009

- **Level 1: Minor Change**
  - User notification not necessary

- **Level 2: Might be Significant**
  - User should be informed
  - Regulatory authorities, where appropriate, should be notified

- **Level 3: Always Significant**
  - Always be communicated to the user and Regulatory Authorities, where appropriate

2014

- **Level 1 Change: Not Significant**
  - Notification not mandatory
  - Up to supplier to notify user

- **Level 2 Change: Significant**
  - Mandatory user notification
  - Mandatory Regulatory Authority notification, where appropriate
**Why change from 3 levels to 2?**

- New guide assigns changes as significant (Level 2) or not significant (Level 1)

- The determination of significance will be assessed where some types of changes will automatically be defined as Level 2 changes
  - these will require notification

- Certain types of changes will be assessed using risk assessment tools to determine the level of change and notification requirement
Why change from 3 levels to 2?

- The modification will allow for a much clearer distinction for when customer notification is required; as opposed to the current guide where some confusion has been perceived.

- Consent is no longer dictated by a level 3 change. In the current guide the customer must consent before implementation.

- A collaborative approach is recommended, based on key guiding principles, to determine the timelines for implementation for Level 2 changes.
• An entire section (4.) for *Determination of Significance/Risk Assessment* has been added

- 4.1 General
- 4.2 Guiding Principles
- 4.3 Change Management Documentation
  - 4.3.1 Testing
- 4.4 Justification for Level 1 Change
- 4.5 Supporting Data
If the level of change is not specifically defined in *Types of Changes* section then further assessment is needed

- Utilizing the concepts described in risk assessment section

Unless otherwise justified, all changes should be assumed to be Level 2

Various risk assessment tools can be utilized to determine the level of change using the *Guiding Principles*
The verbiage of this section has been re-worked based on the updated concepts of Level 1 and Level 2 changes as described.
<table>
<thead>
<tr>
<th>Year</th>
<th>Appendix 1</th>
<th>Appendix 2</th>
<th>Appendix 3</th>
<th>Appendix 4</th>
<th>Appendix 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Appendix 1 – Generic Glossary</td>
<td>Appendix 2 – Change Level Examples</td>
<td>Appendix 3 – Decision Trees</td>
<td>Appendix 4 – Impurity Profile</td>
<td>Appendix 5 – History of Revision</td>
</tr>
<tr>
<td>2014</td>
<td>Reference IPEC Glossary of Official Definitions for Excipients</td>
<td>Appendix 1 – Case Studies</td>
<td>Appendix 2 – re-worked Decision Trees</td>
<td>Appendix 3 – History of Revision</td>
<td></td>
</tr>
</tbody>
</table>
IPEC Significant Change Guide – Benefit to Industry
For the Excipient manufacturer the revised guide provides a clear definition of the types of change and how to assess them.

The revised guide introduces the concept of ‘risk assessment’ to more logically assess the impact and significance of change.

There are case studies and decision trees to give further help in assessing change.
The simplification to two levels ‘Significant’ and ‘Not Significant’ makes the decision process simpler, clearer and more logical.

There is clear guidance of when a change is notifiable to the user.
For the Excipient user the guide provides insight and understanding of the types of change that may occur in excipient manufacture.

The guide allows the excipient user to better understand what types of change they should expect notification for.

The guide can be used as a clear reference when dealing with the issue of change notification in Quality Agreements.
Summary
The IPEC Americas Significant Change Guide was first published in 2000 and since that time has been used as the key reference for the assessment of change in excipient manufacture.

It has however been predominantly US focused and lacked the concepts of the ‘risk assessment’ approach more commonly used in Europe.

It has now been subject to major revision due for publication this year.
The revised guide is truly global and merges the different concepts of change assessment employed in different territories to provide a universally acceptable approach.

The revised guide provides a more logical process and path for change assessment.

The revised guide provides a clearer outcome to the assessment of change, and hence a clearer decision as to whether a change is ‘significant’ and ‘notifiable’.
Thank you!

Kevin J McGlue
Director Global Quality Assurance, Colorcon

ExcipientFest Europe
Amsterdam, 24th June 2014