The IPEC-Americas Significant Change Guideline

ExcipientFest Workshop
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Increasing Focus on Excipients

- Growing International Interest in Excipient and Supply Chain Issues from a Regulatory, Safety and Quality by Design Perspective
  - ICH Q8, Q9, Q10, FDA’s PAT Initiatives
    - Understanding Excipient Functionality
    - Excipient Variability between Suppliers
  - Recent Issues with Out-Sourced Food and Drug Ingredients
    - Numerous safety and GMP issues in recent years
    - Huge media exposure has created much concern

Pharmaceutical Development and The Quality System:
(ICH Q8/Q9/Q10) - Foundation for Assuring Ongoing State of Control

The Materials System

- Integral to the Quality System
- Includes selection, characterizing, qualifying, and monitoring excipients and suppliers
Improved Communication is Essential Today!!!!!

- Users, Makers AND Regulators MUST take more time to understand each other’s needs and controls than was done in the past
- Changing World
  - Contaminated excipients
  - Bioterrorism
  - Counterfeiting of drugs & excipients
  - BSE/TSE, GMO’s, allergens, additives
  - Cost reduction goals
  - Continuous quality improvement – QbD/PAT
- Increased need for Supply Chain Controls and Traceability as well as Excipient Consistency!!!

What is an Excipient?

- All other components of a drug formulation other than the active drug. (Blecher)
- Excipients are any substance, other than the active drug or prodrug, that has been appropriately evaluated for safety, and are included in a drug delivery system to either aid processing of the system during manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety effectiveness of the drug delivery system during storage and use. (USP <1078>)

The Excipient Industry

- There is no Excipient Industry!
- Most excipient producers are fine chemical manufacturers
- Pharmaceutical sales may be a small part of their total output (often <10%).
  - Other major uses include
    - Food
    - Food processing
    - Agriculture
    - Industrial
- Very few excipients were designed originally for pharmaceutical use
Manufacturing methods

• Sources of excipients
  – Harvesting of natural materials
    • Vegetable
    • Animal
    • Mineral
  – Extraction from natural materials
  – Synthetic chemistry
  – Purification
    • Separation
    • Precipitation
    • Crystallization
    • Washing
    • Filtration

Types of processing

• Batch processing
  – A discrete amount of raw material and reagent passes through the whole process to produce a discrete lot of excipient that can be traced back to the discrete lots of raw material, etc.
  – Batch size is defined by the capacity of the equipment.

• Continuous processing
  – Raw material and reagents are continuously fed into the process, and at steady state, product is continuously produced.
  – There is no defined batch size.
  – Batch number relates to time during the manufacturing process, not to discrete quantities of raw materials or reagents.

Excipient Composition

• Most excipients work because they are not pure materials:
  – They contain other minor (concomitant) components that are a consequence of the raw material source, and may be:
    • Necessary of performance (desirable)
    • Undesirable
  – They may contain processing aids:
    • Carried over from earlier stages in the manufacturing process.
  – They may contain additives:
    • Deliberately added to assist with the handling and storage of the bulk excipient in some way.
    • For compendial excipients, additives may only be present if specifically permitted in the monograph.

Note: ‘Impurity’ is not the correct term for use with excipients.
Why is Excipient Performance so Important?

- Functional performance is what the excipient(s) bring to the formulation
- Excipient variability is one of the factors that contributes to product variability
  - Between batches
  - Within a batch
  - On stability
- Variation in functional performance of the excipient(s) has the potential to compromise medicinal product performance and/or integrity.

Why is Variability so Important?

- All processes and products have an inherent variability:
  - Normal (Gaussian) distribution
  - Log-normal distribution
- The patient requires that their medicine performs as needed/intended for as long as necessary.
- In order to meet the patients needs, we need to understand product variability and maintain it within an acceptable range
- We cannot eliminate variability. We need to:
  - Understand it,
  - Come to terms with it,
  - Learn to live with it!

Product Consistency involves Understanding Excipient Variability

- API Variability
- Excipients Variability
- Process Variability
- Mfg. Process
- Supplier to Supplier
- Natural Sources
- Environmental
- Mfg. & Source CHANGES
Product Variability - The Reality

Sources and types of Excipients

- Naturally occurring – alginites, starches
- Semi-synthetic – modified celluloses and starches
- Synthetic – povidone, caromers, polysorbates
- Animal – lactose, gelatin, shellac
- Vegetable – cellulose, sucrose, zein
- Mineral – calcium phosphate, calcium carbonate
- Co-processed combinations
- Physical mixtures
- Solids
- Semi-solids
- Liquids
- Gases

Sources of Inherent Excipient Variability

- Scale - capacity of the equipment train
- Variability of raw materials (often of natural origin)
  - Conditions during growing season
  - Conditions at harvest
  - Variation in growing season year upon year
- Changes in raw material source due to
  - Drought
  - Flood
  - War
  - Accident
- Weather at the time of manufacture
  - Hot or cold
  - Dry or humid
Caution!!

• Don’t confuse inherent excipient variability with planned excipient changes
• Both are important to understand
• However, they are two very different things!!
• Needing different types of controls

Change!

• The paradox: Change is one of the constants in life.
  – The other two being death and taxes
  (Benjamin Franklin)
• Humans do not handle the constants in life well: we do not like death, taxes or change!
• But they are inevitable!
  – Nothing is forever!

What is Change?

• To make or become different.
  (The Merriam-Webster Dictionary)
• The process of becoming different.
  (Wikipedia)
• In GMP terms:
  – A planned move from one state of equilibrium, or control, or one set of parameters, to another state of equilibrium, control or set of parameters.
Change is not an accident

• Accidents are unplanned; change should be planned.
  – But change may be a consequence of an accident elsewhere, e.g. fire/explosion at a starting material producer.
• Change may be temporary (e.g. planned deviations).
• Change may be ‘permanent’ – long term (e.g. changing to a new raw material source)
• Change is sometimes a consequence of planning to accommodate factors beyond our immediate control.

Change is not Variability

• Variability is the variation in a set of data (e.g. inputs to a product or process) about a central point, whether controlled or uncontrolled.
• Change is not natural variation.
• Change is the movement, or the result of movement, from one central point to another central point.

Why is Change important?

• Change in excipients may compromise:
  – Pharmaceutical product integrity or performance,
  – The PATIENT!
• Change may be beyond the control of the excipient manufacturer
  – May be upstream suppliers
How do we assess change?

- We compare what we were or are doing, and what we will be doing:
  - site of manufacture
  - raw material origin or specification
  - process flow
  - equipment train
  - primary packaging origin or specification
  - excipient specification
    - In-process specification
    - Chemical, physical and microbiological attributes
    - Functional performance (model formulations)
    - Specification: The quality parameters to which the excipient, component or intermediate must conform and that serve as a basis for quality evaluation.

- Risk assessment

Excipient Specifications

- In-process specification
  - Used in the excipient manufacturing plant
  - Tighter than the sales specification
- Sales specification
  - Available to all customers
  - A public domain document
- Customer-specific specification
  - Includes either or both of:
    - Tighter limits for a particular test parameter(s), or
    - Specific extra tests and specifications not included in the sales specification.
- Monograph specification
  - The test methods and specifications set out in an official monograph (e.g. USP-NF)

Change Control

- Change control is a formal process used to ensure that changes to a product or system are introduced in a controlled and coordinated manner.
  - The goals of a change control procedure usually include minimal disruption to services, reduction in back-out activities, and cost-effective utilization of resources involved in implementing change.

- Change Control: A process for management review of proposed changes that may impact the quality or regulatory conformance of the excipient.

- Change control should be an integral part of any Quality System/Quality Management System associated with the manufacture of pharmaceutical materials and products.
Requirements for a Change Control System

• Written records of all changes, including maintenance.
• A system of checks and balances to ensure unauthorized changes are not made, and
• To ensure authorized changes are made properly and at the correct time.
• A properly functioning Quality System and Quality Management System (e.g., as required by GMP or ISO 9000) will also be necessary.

The IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients

Currently under revision to harmonize guideline within the IPEC Federation

Overview of Guideline

• Introduction and history
• Significant Change Guide – an overview
• Evaluation criteria
• Determination of significance
• Types of change
• Change risk levels
• Reporting requirements
• Decision tree
• Summary
Why a Significant Change Guide?

- FDA had introduced the SUPAC Guidance documents (Scale-Up and Post Approval Changes):
  - SUPAC-IR
  - SUPAC-MR
  - SUPAC-SS
- SUPAC-IR primarily discussed quantitative level changes in excipients and grade changes.
- SUPAC-MR defined release controlling and non-release controlling excipients and indicated that different risks existed for each type of excipient.
- Excipient change was discussed in SUPAC-SS; but not extensively, and only in terms of a change in supplier of a 'structure-forming excipient'.
- Excipient manufacturers were also looking to cut costs to remain competitive and minimize customer pushback.
- Since there was no official guidance, IPEC-Americas decided to develop their own.

IPEC-Americas Significant Change Guide

- First issued 2000 as an IPEC-Americas Guide
- Adapted to USP <1195> and issued as a draft.
- IPEC-Americas issued Revision 1, 2005 to include 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.
- USP issued a revised draft to <1195> incorporating FDA’s change.
- IPEC-Americas issued a revision incorporating the FDA change in 2009.
- Being considered for an IPEC Federation Guide – working with IPEC Europe to reach consensus.

IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009

1. Introduction
2. General Guidance
3. Significant Change
4. Types of Changes
5. Reporting Requirements
6. References
Appendix 1: Glossary
Appendix 2: Change Levels
Appendix 3: Decision Tree
Appendix 4: Impurity Profile
Appendix 5: History of Revision
Note!

- One change that is typically very significant is the change from one manufacturing source/supplier of an excipient to a different source of that excipient. This can sometimes be one of the most important changes to carefully assess!!

- The current IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009 does not completely address this type of change.
  - Such a change is better addressed in the IPEC Guide: Qualification of Excipients for use in Pharmaceuticals (2008)

- Various GMP and Supply Chain Security issues must also be assessed in these cases.

What is so important about change?

- No component is added to a drug without having a reason for being in the formulation
- Every excipient used in a drug formulation has a specific intended purpose necessary to ensure the drug delivers the benefit to the patient
- Clinical trials are used to verify the efficacy of the formulation against label claims
- Change to the excipient has a potential to alter the drug product and calls into question the validity of the data from clinical trials
- Only the drug product manufacturer can evaluate the impact to the formulation from change in the excipient

Example of unintended change

- An excipient manufacturer uses carbon in the clean up process to purify the finished excipient.
- The manufacturer changed their supplier of the clean up carbon to use a supplier that offered better quality and purity.
- The carbon was from the same raw material source and made by the same type of process as the old carbon but was made in a more modern facility.
- The new carbon had less phosphate.
- This changed the buffering capacity of the excipient but phosphate and buffering capacity was not part of the specification.
- The excipient manufacture did not consider this change significant because all test showed the excipient meets the specification.
- The excipient made using the new carbon changed the pH of the user’s finished product slightly and the drug product started showing up out of spec.
Significant Change

- 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.

(IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009)

Evaluation Criteria

Seven criteria:
1. Has there been a change in the chemical properties of the excipient as a result of the change?
2. Has there been a change in the physical properties of the excipient as a result of the change?
3. Has there been a change in the impurity (composition) profile for the excipient as a result of the change?
4. Has there been a change in the functionality of the excipient as a result of the change?
5. Where applicable, has the moisture level changed?
6. Where applicable, has the bioburden changed?
7. Has there been a change in the origin of any raw materials or contact packaging?

(IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009)

Change in Chemical Properties

- Include ALL monograph and/or manufacturer specification tests.
- Assess whether any other chemical properties should be assessed based on the change being made.
- Compare pre- and post-change results to see if there is a statistically significant difference.
Change in Physical Properties

- Select the physical properties to be compared based on the physical form of the excipient.
- Any physical tests that are part of the monograph or specification should also be compared.
- For all polymeric excipients, consider impact of change on molecular weight distribution.
- Compare pre- and post-change results to see if there is a statistically significant difference.

Change in Composition Profile

- If feasible, determine if there are changes to the composition profile:
  - Identified organic impurities.
  - Unidentified organic impurities above 0.10%, whether specified or not.
  - Residual solvents.
  - Inorganic impurities, including heavy metals.
- Compare pre- and post-change results to see if there is a statistically significant difference.

Change in Functionality

- Objective criteria are desirable to assess any change; this may not always be feasible for functionality.
- Surrogate tests such as excipient performance tests may be appropriate.
- A comparison based on small-scale, model formulations for the target market may also be appropriate.
- Compare pre- and post-change results to see if there is a statistically significant difference.
Change in Moisture Level

• The level of moisture can be critical for the performance of an excipient.
• A change in moisture level beyond the normal production range, while still within specification, may impact the stability, or performance of the excipient, or the finished drug product.
• Compare pre- and post-change results to see if there is a statistically significant difference.

Change in Bioburden

• Many changes can potentially impact the excipient bioburden.
• Compare pre- and post-change results to see if there is a statistically significant difference.
• This is particularly important for excipients that are susceptible to microbial growth and spoilage.

Change in Origin of Raw Materials

• Any change in the geographical and biological source of any raw material should be assessed, before commencing any practical evaluation, with respect to:
  – BSE/TSE concerns
  – GMO concerns
• Change in the geological origin of mineral-based excipients should be assessed with respect to the chemical and physical properties, composition profile and functional performance.
• Compare pre- and post-change results to see if there is a statistically significant difference.
Change in Origin of Contact Packaging

- Changes in contact packaging and the primary barrier packaging should be assessed with respect to protection of the excipient and leaching of components into the excipient during its shelf-life.
  - Make sure you understand ALL the components that could be present in the packaging, and that could affect the excipient in any way.

- Compare pre- and post-change results to see if there is a statistically significant difference.

- Look at the implications for shelf-life and stability

Change Risk Levels

- Three levels:
  - Level 1: Minor Change
  - Level 2: Might be Significant
  - Level 3: Always Significant

- Based on the Type of Change being made, not just whether the product actually appears to be impacted by the change to the excipient manufacturer

Level 1

- Level 1: Minor Change
  - Changes are fairly minor and considered unlikely to affect the excipient chemical or physical properties, impurity profile, or functionality. Such changes should be documented but notification to the user is not normally necessary.
  - In some cases however, it may still make sense if there is any uncertainty of impact

Level 2

• Level 2: Might be Significant
  The impact of the change should be evaluated against criteria 1, 2, and 3 (chemical properties, physical properties, and impurity profile) which often reflect the potential impact of the change on the functionality of the excipient. The user should always be informed and with as much advanced notice as possible. Where appropriate, Regulatory Authorities should also be notified.

(IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009)

Level 3

• Level 3: Always Significant
  Always Significant – This type of change should always be communicated to the user and regulatory authorities, where appropriate.

(IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009)

Types of Change

• Site change
• Scale of Manufacture
• Equipment
• Manufacturing Process
• Packaging and Labeling
• Specifications
• Multiple Changes
Site Change

- A site change can involve either manufacture or packaging.

- If the site has never been used for the manufacture or packaging of the excipient, it should be regarded as a Level 3 change.

- If the site has been used for the same processing of the excipient, but with no changes to the raw materials, etc., but not in the last 12 months; it should regarded as a Level 2 change.

- If the site has been used for the same processing of the excipient within the last 12 months, and with no changes to the raw materials, etc.; it should be regarded as a Level 1 change.

Change in Scale of Manufacture

- There are different considerations for scale-up for batch and continuous processing.
  - Scale-up in continuous processing may simply mean running the plant for longer.

- During the move from development to full commercial scale there is likely to be a change in equipment scale; particularly for batch processing.
  - Such a change is likely to be significant, and should be regarded as a Level 3 change.

- Changes in operating equipment, but using the same operating principle, should be regarded as a Level 2 change.

Change in Scale of Manufacture (cont’d)

- Optimizing the process within continuous processing, but without changing the overall process should be regarded as a Level 1 change.

- All changes should be reviewed using a comparison of pre- and post-change results. If the change does impact the properties of the excipient in any way, then the impact of the change must be carefully assessed.
  - Such changes may be considered as a higher level of risk, and should be handled accordingly.
Equipment Change

- A change in a piece of equipment, replacing like with like (replacement in kind) is a Level 1 change.
- If the new piece of equipment is not a replacement in kind, but was included in the process validation, then it would also be a Level 1 change.
- Otherwise, the change should be considered a Level 3 change.

Manufacturing Process Change

- A change in the sequence of the processing steps should be considered a Level 3 change.
- Minor changes whereby the process parameter remains within the validated range should be regarded as Level 1 changes.
- Changes where the process parameter falls outside the validated range should be regarded as Level 2 changes.

Reprocessing

- Reprocessing, if included in the process validation is not a notifiable change.
- Reprocessing of material that is not part of the process validation, but is followed by a purification step should be considered a Level 2 change.
- Reprocessing of material that is not part of the process validation, and is not followed by a purification step, should be considered a Level 3 change.
Packaging and Labeling Change

- Changes to any packaging component that is a replacement in kind should be considered a Level 1 change.
  - i.e., the replacement component is constructed from the same materials and the package is sealed in the same manner and with liners made of the same components.
- Any change that is not a replacement in kind should be regarded as a Level 3 change.
- Any change to the labeling content pertaining to the site of manufacture or testing, biological origin, additives, or storage and handling conditions should be regarded as a Level 3 change.

Changes in Specifications

- There are potentially several different specifications that can be associated with a particular excipient, including:
  - Monograph specification (e.g., USP-NF)
  - Sales specification
  - In-process specification
  - In-house specification
  - Customer specification
  - Raw material specification
  - Packaging specification

- In general, changes to raw material and packaging specifications (particularly for contact materials and barrier materials) should be regarded as Level 2 changes, unless the changes are more stringent and within the existing specification range, in which case they should be regarded as Level 1 changes.
- Any broadening of specifications that are visible to the customer should be regarded as a Level 2 change.
- Changes in specifications that are not visible to the customer should be regarded as a Level 1 change.
- If the change involves the removal of a processing aid or additive, the change is likely to be more significant and should be regarded as a Level 2 or 3 change as appropriate.
### Changes in Specifications

- Changes to in-process specifications that maintain or increase the process control within the existing specification should be regarded as Level 1 changes.

- Changes that relax the process control should be considered as Level 2 changes.

### Multiple Changes

- The highest level change will automatically influence the reporting requirements.

- Also, consider the totality of the changes:
  - For example, 4 – 5 Level 1 changes may equate overall to a Level 2 change.

### Decision Tree - Page 1
The Excipient Maker’s Responsibilities

• Plan early for changes whenever possible to maximize time for implementation (may include establishing inventories to cover change & notification timeframe)

• Perform adequate analytical and model product performance studies for intended functionality to investigate potential impact of change (include stability where appropriate)

The Excipient Maker’s Responsibilities

• Realistically evaluate the type of change and determine the change level and customer notification requirements (not dependant on results from studies)

• Notify customers appropriately based on the level of the change. Provide Executive Summary Report including results from studies and realistic assessment of the impact of the change

Must carefully evaluate interchangeability by looking beyond standard specifications: include supply chain.
The Excipient Maker's Responsibilities

- Provide adequate time between notification and implementation for customers to determine impact of the change on drug product and handle any regulatory implications.
- Better to over-communicate information on changes early to customers than to under-communicate.

Timing – Maker’s Perspective

- Give as much notice as possible!
  - The customer may have to evaluate the manufacturer’s level 2 change as a SUPAC level 3 change.
  - SUPAC level 3 changes generally require a prior approval supplement (PAS). (At the very least it will be a ‘changes being effected’ 30 day notice – a CBE 30).
- Some customers may require/desire up to 18 months of inventory to be available.
  - This takes time to organize and is not always possible.
- Emergency Changes may have to be implemented quickly to prevent out-of-stock situations.
  - Good communication is needed between the excipient manufacturer, distributors and customers in these cases to meet everyone’s needs.
- NOT EVERY CHANGE IS AN EMERGENCY!!!

Significant Change –Who to Notify

- Who do you notify?
  - All customers purchasing the excipient grade.
  - When packing product as multiple grades the customers of the excipient grade should be notified, customers of other grades are at the discretion of the manufacturer.
  - If your product is purchased by distributors for resale then notify the distributor.

The Excipient User's Responsibilities

When you receive a change notification from an excipient supplier:
1. Don't panic!
2. Don’t complain about the supplier making changes, accept the changes as continual quality improvement
3. Review the notification and the supplier’s assessment quickly,
   a. Note the deadline for any response!
4. Review your products using the excipient
   a. Classify them according to risk.
5. Consider the likely impact of the change to the excipient.
   a. If potential impact considered negligible – no further investigation is necessary.
6. Communicate promptly with your supplier.
7. Prepare an investigation plan (if necessary).

Review Notification and Supplier's Assessment

- The type of change
- Supplier’s assessment
  - Level 2, or Level 3
- Assemble an evaluation committee or team
  - Membership should include (as necessary):
    - Manufacturing
    - Development
    - Planning/Scheduling
    - Quality Control
    - Quality Assurance
    - Regulatory Affairs

Timing – User’s Perspective

- Above all respond quickly when the letter from the manufacturer is received!
  - Even if it is only to ask for more time to evaluate the change!
  - Realize this may not be possible however, depending on the situation.
- If after review, work is needed to properly evaluate the change, get back to the manufacturer as soon as possible:
  - Agree on the timeline with the manufacturer.
  - Prioritize the work to meet the desired timeline requested by the manufacturer.
  - Keep them informed of changes.
  - Do NOT keep requesting more time or inventory!
The Excipient User’s Expectations and Reality

<table>
<thead>
<tr>
<th>User’s wants</th>
<th>Reality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No variability in their raw materials (including excipients)!</td>
<td>There is always variability; no one can guarantee there will be no variability!</td>
</tr>
<tr>
<td>A validated excipient manufacturing process!</td>
<td>Not described as validated; process capability assessment.</td>
</tr>
</tbody>
</table>

The Disconnect

- The Excipient Manufacturer assesses the change and informs the customer.
- The Excipient Manufacturer has no real way of knowing the significance and impact of the change on the drug product; only the Excipient User can determine that!
  - This is why the Excipient Manufacturer is advised to give as much notice as possible, even for Level 2 changes.
- The Excipient User does not know the capabilities of the manufacturer.

Barriers to Good Communication

- Confidentiality
- NIH/NDH syndrome (Not-invented-here/Not-discovered-here)
- DOS (Desired Outcome Syndrome)
- Gatekeepers
- Language
- Jargon
- Inadequate lines of communication within an organization
**DOS – Desired Outcome Syndrome – Excipient Manufacturer**

- Excipient manufacturers sometimes try too hard to justify why a change is a Level 1 change
  - Prevents proper customer notification
  - Usually results from getting undue pushback from customers
  - Production or Marketing groups want to implement the change quickly for economic reasons and therefore try to minimize the impact of a change

**DOS – Desired Outcome Syndrome – Excipient Manufacturer**

- Human nature is to think of all changes as minor unless proven to be more significant – this can be a problem!
- Philosophy which should be used by Excipient Manufacturers:
  - All changes should start off as Level 3 changes unless there is sufficient justification to scientifically demonstrate why they can be downgraded to Level 2 or Level 1

**DOS – Desired Outcome Syndrome – Pharmaceutical User**

- Pharmaceutical companies “think” they are so important that the supplier will do what they want them to in their timeframe
  - Sometimes results in delays in evaluating the changes proposed by the excipient manufacturers
  - Requests get made to the supplier for holding inventory that are not realistic
  - Users MUST prioritize the evaluation of changes and work to the manufacturer’s realities
  - If DOS prevails, the loser will almost always be the pharmaceutical user…..and possibly the PATIENT!
Summary

- The IPEC-Americas Significant Change Guide for Bulk Pharmaceutical Excipients, 2009, provides scientifically based mechanisms for assessing the risk and impact of various types of excipient changes that may typically occur.
- Requires good communication between makers and users of excipients.
- It is recommended that this guideline be used as the basis for change control assessments included in quality and supply agreements between maker and user.

Next Steps

- Formed sub-group of IPEC-Americas and IPEC-Europe colleagues (4 from each side).
- Need to work through some fundamental differences of opinion between IPEC-Americas and IPEC Europe.
- F2F Meeting at IPEC-Americas Headquarters in July.
- Goal is to create a Bi-PEC Significant Change Guide.

Resources

- IPEC
  - www.ipecamericas.org
- Download IPEC Guidance documents
  - Available for free (do need to register)
THANK YOU!

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Discussion