

_____ Symposium: Extractables in Materials for OINDP
February 13, 2007 Chicago

Clarifying Expectations:
Panel Discussion with Suppliers

_____ What does a “change” mean to you?

Material change definition from Pharma Industry point of view

Any change in raw material/ composition, manufacturing processes and/or equipment that affects material properties.

- Mechanical properties
- Chemical properties (i.e. identity, purity)
 - extractables profile
 - IR spectra or other chemical testing parameters
- Process properties
 - e.g. MFR
- Changes in production site
- All other changes affecting DMF or fulfilling regulatory requirements

_____ What does a “change” mean to you?

Material change consequence from Pharma Industry point of view

Unplanned changes might cause:

↳ Deviation in quality regarding the material properties

↳ Out of specification results (OOS)

↳ Rejection of the packaging batch

↳ **The drug product cannot be delivered to our patients.**

What does a “change” mean to you?

Material change consequence from Pharma Industry point of view

Consequences of a change notification:

- ↳ All changes in packaging materials must be justified to the regulatory body
- ↳ Any material changes may have the effect of new material/ new supplier
- ↳ Qualification process for new materials
 - Production process Safety Stability
 - Test runs - Extractables studies - Stability studies
 - Modification (e.g. tools) - Leachables studies - Compatibility tests
 - Process revalidation - Toxicological evaluation
 - Testing of component - Routine testing
- ↳ Takes several years (minimum 36 months) to qualify new materials for a critical component

What does “extractables testing” mean to you?

Material qualification process

- Container/Closure System Components – Material Selection
 - Information should be obtained on composition + manufacturing processes from the **supplier**
 - Review of composition by toxicologists for risk assessment on individual ingredients
- Controlled Extraction Studies
 - Extraction with multiple solvents, multiple analytical techniques, e.g. GC, LC
 - Identify and quantify extractables
 - Revisit **supplier** information describing component formulation
 - Evaluate extractables profiles by toxicologists to identify any potential safety concerns
 - predict a worst-case leachables profile (= substances migrating into drug product and being inhaled by the patient)
- Leachables Studies
 - part of drug product stability program on multiple batches of drug product, stored under different conditions through the intended shelf-life
 - toxicological evaluation of leachables
- Routine Extractables Testing
 - monitor **consistency in composition** incl. acceptance criteria for known and “unspecified” extractables with fully validated methods
 - quality agreement on extractables specifications with **suppliers**
 - predict and therefore avoid routine leachables testing