Elastomers in orally inhaled and nasal drug products Part II: Control strategies

Establishing controls and managing changes in materials are key aspects of elastomer quality. This is the second of a two-part series of articles on elastomers to be published by Inhalation.

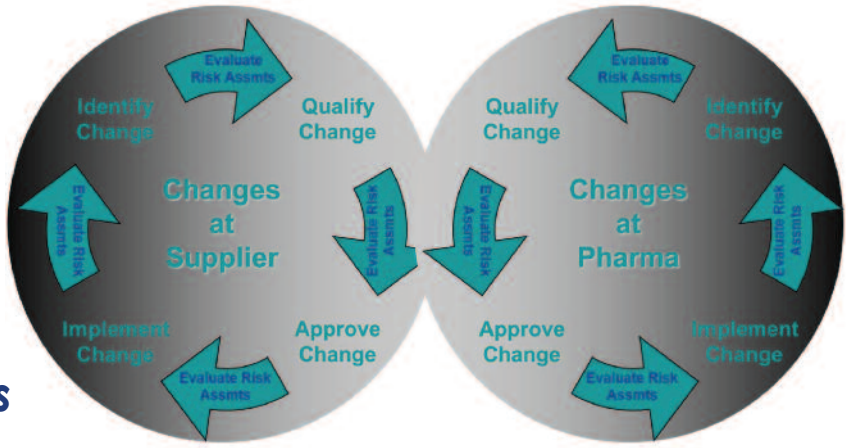

Photo courtesy of Suzette Roan, IPAC-RS Supply Chain Quality Training Course, Health Canada, Ottawa, Canada, 2009.

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I. Introduction

Establishing appropriate controls and managing changes in elastomeric materials used in orally inhaled and nasal drug products (OINDPs) are key parts of managing the overall quality of OINDP elastomers. Material selection and qualification are as well, and are addressed in the first article in this two-part series published by *Inhalation, "Elastomers in Orally Inhaled and Nasal Drug Products, Part I: Elastomer Selection and Qualification."*[1]

Acceptance criteria for the container closure system (CCS) and delivery device (DD) materials and overall product are established based on quality, safety and performance considerations. Ideally, selection and qualification of materials would be performed at the beginning of OINDP development, criteria would be set for acceptance of materials into production and these materials would remain unchanged for the life of the product. However, unexpected incompatibilities with the drug formulation or inadequate performance characteristics may necessitate a material change during development. Realistically, it is also possible that the CCS/DD materials or manufacturing processes may change over product lifecycles. Such changes need to be evaluated for impact to the product and may require additional qualification and/or additional or different acceptance criteria. It is important that such changes are performed under a well defined process of "change control," agreed upon between the material supplier and the customer. Change control is one of the most important concepts of current Good Manufacturing Practices (cGMP).

II. Control strategies: Development and implementation

After completing appropriate materials selection and qualification processes, a significant effort is required to establish appropriate controls for materials. Early in development, the efforts are focused primarily on functional and chemical characterization. Later in development, the learnings from the characterization studies are utilized to develop a control strategy. This control strategy may involve upstream control of formulation, processing, handling, facilities and equipment (ICH Q10)[2] and may be facilitated through quality agreements. Downstream controls may include additional processing steps or testing. Throughout the lifecycle of the product, it is important to ensure phase-appropriate controls are in place.

Definitions

Extractable	Chemical entities that are forcibly "pulled out" or extracted from CCS/DD components under laboratory conditions, often with application of solvents and heat. These are potential leachables.
Leachable	Chemical entities that migrate out of the CCS/DD into the drug product over the shelf-life of the drug product. These are typically, but not always, a subset of extractables.
Routine extractables test	A method by which chemical entities are extracted from materials and analyzed to quantify specific analytes, qualitatively evaluate the extractables profile and detect new compounds. This test may be used to establish, or release materials against, extractables acceptance criteria.

Identification of control attributes early in product development. A delivery device that utilizes an elastomeric component will go through several phases of testing to demonstrate that the component functions properly. Often this is an iterative process. For example, in the implementation of an o-ring to form a seal, it may be found that the position and/or size of the o-ring must be altered to adequately form the seal. On stability, it may be found that the o-ring does not maintain adequate sealing and a material with a different compression set must be selected. Closure of this stage of testing culminates in verification of the design and confirmation of the material selection. During this stage of device development, the key physical attributes of the material that correlate to functionality are identified. Attributes of elastomeric materials that may be controlled include durometer, compression set, surface finish, etc.

During early development, it is also common to characterize the chemical nature of elastomeric components. This type of characterization may include pharmacopoeial physicochemical testing and Controlled Extraction Studies. Physicochemical tests are often regarded as a box-checking exercise, but may uncover unexpected processing circumstances. For example, consider an injection molded silicone component that, when tested per Ph. Eur. 3.1.9,[3] was found to fail the test for non-volatile residue and substances soluble in hexane. In this case, it was determined that the component contained a processing contaminant and was improperly cured. This suggested that a processing control was necessary. A routine extractables test was a suitable control for the attributes of cure state and chemical integrity because it can provide an oligomer profile and detect unexpected contaminants.

Development of a control strategy in mid- to late-development. Once the attributes required for a quality product are identified, it is important to establish proper controls. The control strategy will depend on several items: complexity of the supply chain, manufacturing environment, complexity of the material/production processes and supplier quality systems. In general, controls are put in place to ensure continued consistency and quality of materials over the lifetime of a product. Commonly, this is associated with minimizing change in materials once the initial material selection and qualification is complete and clinical studies are underway. A risk-based approach to the control strategy often involves a trade-off between upstream controls and downstream testing. Where downstream testing is required, acceptance criteria must be developed.

A risk-based approach would suggest that a supply chain with several layers (Figure 1) has higher risk for unexpected changes than a supply chain with only one layer. To mitigate this risk, notification of change agreements could be established at every level in the supply chain. Alternatively, incoming tests could be established at each level. Similarly, where a material and its production process are complex, it is essential that controls be placed appropriately. For example, consider the production of a metered dose inhaler (MDI) valve gasket. In this case, several steps must be considered: mixing, extrusion, calendering, curing, cooling, cutting strips, post-cure heating, die-cutting, washing, drying and bulk packaging. At several steps, the chemical composition may be affected and may impact the variability of the material. By placing strict tolerances on ingredient amounts and equipment settings at each step, variability may be minimized. Alternatively, a chemical test can be placed at the end of production to ensure chemical consistency, for example, Fourier transform infrared spectroscopy (FTIR) at the macroscopic level or extractables at the microscopic level.

At steps such as calendering or cutting, it is possible that contamination may occur if the manufacturing environment is not well controlled. Mitigations in this case may involve operator gowning, restrictions on processing aids and implementation of cleaning procedures for equipment and/or components. Alternatively, if less stringent manufacturing practices are used, an end of production test may involve routine extractables testing or microbial evaluation.

It is important to consider the general manufacturing environment for the materials and components to be used in an OINDP. For example, the presence of for-

eign particulates or ambient chemical contaminants may result in deleterious consequences for the patient but can be mitigated by maintaining a clean environment.[4] Throughout development and commercial production of pharmaceutical products, it is important to maintain traceability by regular use of lot numbers with batch production records, retention of certificates of analysis and implementation of change control.

III. The change control process

After an OINDP CCS/DD has progressed through development, the process of commercialization begins. At this point, the materials are considered final, a control strategy has been adopted and a formal system of implementing change is invoked. It is important to note that this point in time may occur very early in the overall development of the drug product and prior to marketing. It is critical that the OINDP manufacturer and the supplier agree on the parameters that constitute a change via supplier or quality agreements. One standard adopted in the pharmaceutical industry is that a change is anything that affects form, fit or function and, with respect to compliance, may include "design; components, including software; labeling and packaging; device manufacturing processes; production equipment; manufacturing materials; and all associated documentation such as quality system procedures, standard operating procedures, quality acceptance procedures and data forms, and product-specific documentation."[5] With respect to regulatory considerations, change has been more recently characterized as any change beyond established variations.[6] Most often the changes that would affect form are also those that may change the chemical profile of the material/component, as observed in extractables or leachables. Generally there are two types of changes: planned and unplanned.

"Planned changes" are those in which a change in a material or process is known in advance. In such cases, change control follows a structured process. The impact of the change is assessed, tasks are assigned to qualify the change, and upon completion, the change documentation is reviewed and approved to implement the change (Figure 2). An example of planned change is presented in Table 1.

"Unplanned changes" are those in which a change in a material or process is not known in advance. These may be due to a change in supply chain, material or process. The cause for such changes may arise as a result of a variety of circumstances, including interruption of supply due to natural disaster, unexpected business arrangements, human error, equipment malfunction or an excursion in environmental conditions. Typically, unplanned changes are characterized by no advance notification and are detected during some type of functional or chemical testing. It may not be until an out-of-specification or out-of-trend result is investigated that a change is uncovered. An example of unplanned change is shown in Table 2. These types of unplanned changes may disrupt production for several months and can significantly impact delivery of products to patients. Therefore, it is important that OINDP manufacturers carefully evaluate all manufacturing risks and mitigate them appropriately.

Figure 1

Generic example of an elastomeric component supply chain. Types of additives typically included at each stage are also noted. Entities in the supply chain are termed N (OINDP manufacturer); N-1 (component manufacturer); etc.

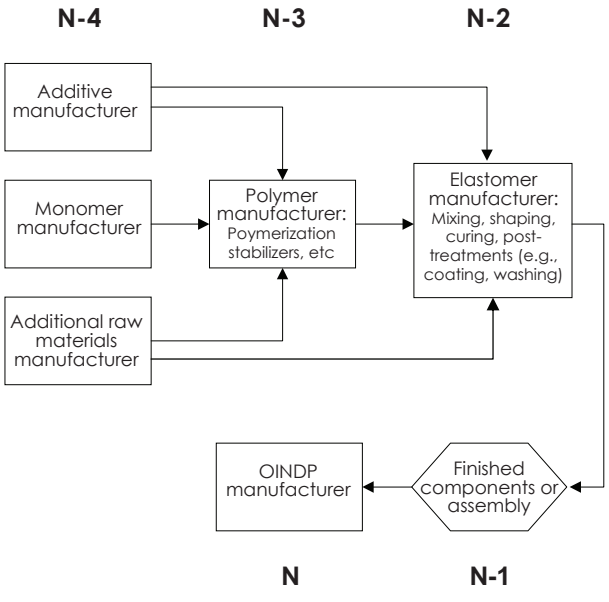

Figure 2

Change control process for pharmaceutical products

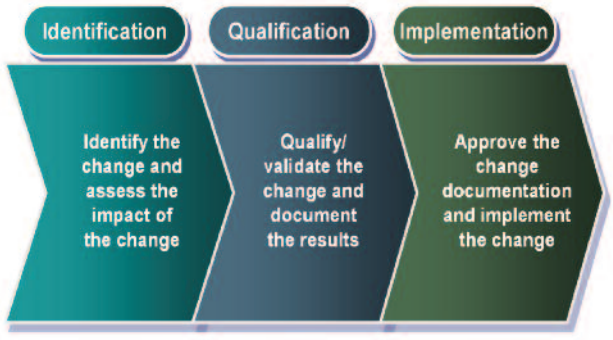

Table 1

An example of planned change: A rubber component supplier has decided to change the supplier of an un-cured rubber.

Step 1. Identification

- Supplier (N-1) notifies OINDP manufacturer (N) of intent to change their supplier (N-2)
- OINDP manufacturer details the impact:
  - New material will need to be qualified by evaluating the component manufactured– biocompatibility, physicochemical, certificates
  - Cure state may be different – check r-value (swell test), durometer
  - Function of component may be affected – check function
  - Chemical profile may be affected – evaluate extractables, leachables
  - CCS/DD performance may be affected – evaluate performance on stability
- OINDP manufacturer and supplier agree on responsibilities and timeline for implementation of change – the implementation process may take two to three years for completion

Step 2. Qualification

- Responsible parties perform tasks, complete reports
- Results show that change of supplier produces product that is not significantly different than current product
- Quality units at supplier and OINDP manufacturer review respective documentation
- Compliance and completeness of documentation confirms change is qualified

Step 3. Implementation

- Change is submitted to regulatory authorities
- Regulatory authorities confirm change is acceptable
- Change is implemented

Table 2

An example of unplanned change: A new peak is present in a chromatogram obtained during a routine extractables test for release of a drug path rubber component.

Step 1. Identification

- Lab observes new peak in chromatogram and notifies OINDP manufacturer
- Lab investigation shows lab result is real and identity of compound is high-temperature antioxidant
- OINDP manufacturer notifies rubber component supplier
- A CAPA (corrective and preventive action) process is initiated and impact assessed

Step 2. Qualification

- Further investigation/discussion with component supplier reveals:
  - Antioxidant is in an ingredient in the un-cured rubber
  - Upstream supplier of ingredient recently changed ingredient source
- Study performed to evaluate level of antioxidant in the component; toxicological assessment confirms level measured poses no harm to patient
- Engineering assessment determines there is no effect on component functionality

Step 3. Implementation

- Change documentation package is approved and routine extractables method is modified to include new representative extractables profile
- Request is made of upstream supplier to provide notification of such changes in future

IV. Conclusion

Although changes may occur at any time during development, the later in development they occur, the larger the impact due to the number of studies that may have to be repeated. In some cases, a change may not be acceptable and an entirely new material may have to be selected, qualified and implemented. Therefore, finalization of materials is encouraged early in the process. Changes in materials that comprise a marketed product may be necessary, but can be effectively addressed by coordinated efforts between the OINDP manufacturers and their suppliers. By implementing routine controls throughout the supply chain and a systematic approach to change control, many of the risks associated with minor or major changes can be minimized.

V. References

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