



Tackling the Extractables and Leachables Challenge: Managing Extractables Along the Supply Chain

Cheryl L. M. Stults*, Barbara Falco*, Andrew Feilden‡, Bobbijo Redler‡, Matthew Coates, Jason Creasey, Daniel Dohmeier, James Mullis, Lee Nagao†, Daniel L. Norwood, Gaby Reckzuegel, Andy Rignall, Caesar Snodgrass-Pilla

INTRODUCTION

Control of extractables and leachables in orally inhaled and nasal drug products (OINDP) is a complex challenge involving OINDP developers/manufacturers and the supply chain for container closure system and device materials. *A key quality by design concept associated with extractables and leachables, is to manage these chemical entities as far back in the supply chain as is practical and possible.* This supply chain is highly complex and involves a number of different suppliers, including those providing raw materials such as resins, additives such as colorants and antioxidants, and those supplying the final packaging and device components. Additionally, molding or other forming processes can affect extractables profiles, making changes that are not obvious given the initial material composition information. The IPAC-RS OINDP Materials Working Group is interacting with different areas of the OINDP component supply chain to improve both suppliers' and OINDP manufacturers' understanding of how extractables and ultimately leachables can be best managed along this chain and within OINDP companies.

EXTRACTABLES MANAGEMENT ALONG THE SUPPLY CHAIN

Extractables management within the supply chain is critical to understanding and control of extractables and ultimately leachables in OINDP at an early stage of the pharmaceutical development process.

This approach encourages risk management and quality by design thinking and should include:

- Early and frequent communication between suppliers and OINDP manufacturers regarding materials composition information and extraction study/testing results¹
- Performance of extractables studies by suppliers and OINDP manufacturers

THE SUPPLY CHAIN

Figure 1 is an example of a supply chain for OINDP container closure systems/devices, using manufacture of plastic components as a model. Introduction of major additives is shown in yellow boxes. Areas where extractables and leachables testing could occur are also shown.

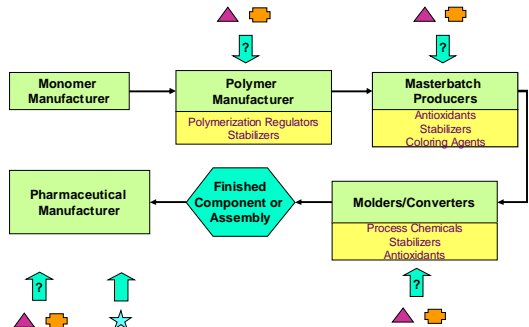


Figure 1. Points in the polymer supply chain where extractables testing could be performed. Possible introduction of additives is indicated in yellow boxes.

▲ = Controlled Extraction Studies ◻ = Routine Extractables Testing ☆ = Leachables Testing

TESTING SCENARIOS AND POTENTIAL IMPACT ON DEVELOPMENT PROCESS

Below we outline in more detail the potential roles and responsibilities regarding extractables evaluation performed by suppliers and pharmaceutical manufacturers. Communication, including sharing of composition information and extractables profiles is important.

Controlled Extraction Studies Responsibilities

Pharma Manufacturer	Supplier(s) [Potential Roles]
<ul style="list-style-type: none"> • Identify critical components and AET² • Obtain process and composition information on materials during materials selection • Obtain Controlled Extraction Study Information • Toxicological assessment • Correlate extractables to leachables • Communication across departments and with suppliers 	<ul style="list-style-type: none"> • Be aware of critical components • Provide process and composition information • Provide Controlled Extraction Study information if available • Support identification of compounds • Communication with upstream suppliers

Routine Extractables Testing Responsibilities

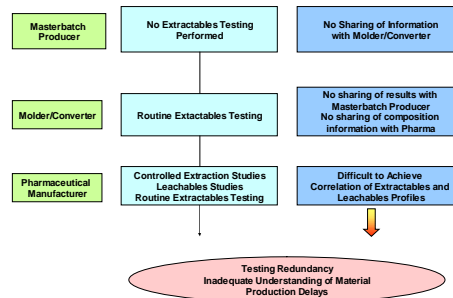
Pharma Manufacturer	Supplier(s) [Potential Roles]
<ul style="list-style-type: none"> • Ensure proper system of controls: In-process, supplier verification, routine extractables, change control • Identify targets based on safety evaluation • Ensure methods are appropriate • Establish acceptance criteria • Correlate routine Extractables testing results to Leachables acceptance criteria • Communication across departments and with suppliers 	<ul style="list-style-type: none"> • Implement controls including considerations of processing environment related to extractables • Follow change control processes • Identify targets based on composition knowledge • Support method development • Support development of or establish acceptance criteria • Communication with upstream suppliers

The goal of such communication is to increase the efficiency of the extractables/leachables program, by increasing awareness of change control, decreasing the occurrences of "surprise" leachables, and potentially decreasing the amount of extractables testing that would need to be performed on finished components.

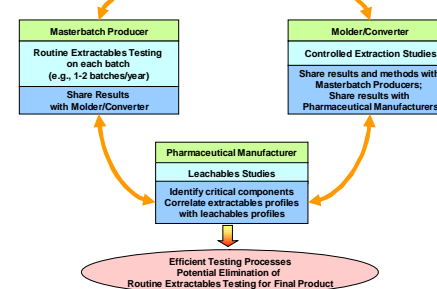
Scenario 1 illustrates a situation where there is little coordinated extractables evaluation occurring at various points in the supply chain, and little or no communication/collaboration along the chain, resulting in duplication of effort and greater potential for production delays for both pharma and suppliers.

Scenario 2 illustrates a situation where extractables evaluation occurs at various points in the supply chain and is coupled with open and frequent communication along the chain, including sharing of composition and process information resulting in the possibility of eliminating routine extractables testing for finished components. NOTE: This is only an example. Other scenarios exist depending on the type of component and the drug product.

Scenario 1



Scenario 2



SUMMARY

- A successful extractables and leachables program requires effective collaboration and early and frequent communication with suppliers throughout the supply chain.
- Extractables testing can occur at various points in the supply chain. Appropriate points for extractables testing can be determined based on component type, and structure of supply chain.
- Extractables testing within the supply chain combined with strong collaboration among suppliers and pharma could lead to significantly reduced testing, more efficient development of components and final product, and reduction in unintended changes, *increasing the safety* of OINDP components

NEXT STEPS

The Working Group is facilitating communication among pharma and suppliers through workshops and publications to encourage discussions about:

- Appropriate points in the supply chain to conduct extractables evaluation
- Sharing of extractables and composition information along the supply chain
- Ways to manage changes to the OINDP component manufacturing process
- Ways to implement the PQRI extractables/leachables best practices recommendations²

ACKNOWLEDGEMENTS AND REFERENCES

The Working Group thanks Dr. Michael Ruberto, Ciba Expert Services and Dr. Arthur Shaw, Pfizer for input on the supply chain diagram. The Group also thanks the IPAC-RS Board of Directors for support of its work.

1. See *Good Manufacturing Practices Guideline for Suppliers of Components for Orally Inhaled and Nasal Drug Products* (IPAC-RS, 2006) for more information on supplier quality systems and establishing quality agreements. <http://www.ipacrs.com/publications.htm>
2. *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products*. PQRI, 2006. http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

* Working Group Chairs. † Poster Committee
‡ Corresponding Author, lee.nagao@cbi.com
Affiliations: Stults (Nektar); Falco (Abbott); Coates (Pfizer), Creasey (GSK), Dohmeier (3M); Feilden and Rignall (AstraZeneca), Mullis, Norwood, Reckzuegel (Boehringer Ingelheim); Redler (Schering-Plough); Snodgrass-Pilla (formerly Schering-Plough)

