

**4th International Conference on
Extractables & Leachables for Pharmaceutical Products
27-28 September 2011
The Ashling Hotel, Dublin, Ireland**



Papers will include:

Origins of extractables and leachables from polymer products

This paper reviews some of the possible sources of extractables and leachables, providing an overview of the typical examples of chemical species that may be expected from each source. A brief description of the types of analytical techniques and approaches that are used to profile extractables is included along with an illustration of the type of extractables data that can be obtained from a screening study on a polymer.

Tim Hulme & Dr Martin Forrest, Smithers Rapra, UK

PQRI research project on container closure systems used in parenteral and ophthalmic drug products – accomplishments and next steps

The talk summarizes activities of the Product Quality Research Institute (PQRI) Working Group on Extractables and Leachables in Parenteral and Ophthalmic Drug Products (PODP). The Working Group includes pharmaceutical development scientists representing industry, government and academia.

A Work Plan was approved 04 April 2008 entitled Development of Scientifically Justifiable Thresholds and Best Demonstrated Characterization Practices for Leachables and Extractables in Parenterals and Ophthalmic Drug Products (PODP). It was hypothesized that the “good science” best demonstrated practices that were established for the orally and inhaled nasal drug products (OINDP) pharmaceutical development process can be extrapolated to container

closure systems for PODP. Threshold and best practices concepts can be integrated into a comprehensive process for characterizing container closure systems with respect to leachable substances and their associated impact on PODP safety. Threshold concepts that have been developed for safety qualification of leachables in OINDP can be extrapolated to the evaluation and safety qualification of leachables in PODP, with consideration of factors and parameters such as dose, duration, patient population and additional product dependent characteristics unique to various PODP types.

The Work Plan will consider leachable thresholds for the following drug product categories based on FDA's high concern for safety relative to Package – Product interaction: Prefilled Syringes (PFS), Small and Large Volume Parenterals (SVP)/(LVP), Ophthalmics/Blow Fill Seals (BFS). Disposable systems (tank liners, storage containers, filters, tubing) should also be considered in the absence of defined and specific regulatory guidance.

The hypothesis is being tested by a team of toxicologists and chemists. The chemistry team obtained various materials representative of typical PODP dosage forms for the purpose of demonstrating best practices for acquiring extractable data. A qualitative protocol was agreed upon by the Working Group, taking into considerations multiple solvents and headspace volatiles. A comprehensive list of extractables, derived from experience and literature searches were compiled by the team of toxicologists to enable a safety concern threshold to be explored based on Small Volume Parenterals (SVP), Large Volume Parenterals (LVP), Prefilled Syringes (PFS) and ophthalmic dosage forms.

While the results of the extraction studies have been summarized and assessed in conjunction with proposed toxicological thresholds, implications of this initial result set to PODP dosage forms are currently under evaluation based on extended experimental protocols. The toxicological thresholds are proposed based on a classification strategy taking into consideration sensitizers, genotoxicants and irritants. A recommendations document will be drafted once a consensus is reached which will be submitted to the PQRI steering committee and regulatory authorities. This document is expected to result in improvement in quality and consistency of PODP and container closure characterization.

Thomas Egert, Boehringer Ingelheim Pharma GmbH & Co, Germany

The simulation study – the replacement of controlled extraction studies for PODP E&L documentation?

During the PQRI PODP E&L workshop Feb. 2011 the AAT (Analytical Applicable Threshold) and safety assessment triad was introduced by the chemistry group to overcome the dilemma of having fixed toxicological values for large volume parenterals which will result in analytical levels that can not be met by analytical chemistry. The safety assessment triad introduces the term "simulation study" as an approach to close the gap between controlled extraction studies and long term leachable studies. The presentation will elucidate why this procedure can be used for both small and large volume parenterals and why it is even more valuable adding

compared to controlled extraction studies when the goal is to get the long term leachable profile. The simulation study can fundamentally be regarded as either a simulated extraction study or as an accelerated leachable study. By introduction of an accelerated leachable study at an early development phase the risk of having critical interactions between leachables and the drug or formulation components will be observed prior to the long term leachable testing and thereby minimizing the risk for critical findings at a late phase development time point. The presentation will also describe how an accelerated leachable study can be performed for both soluble and lyophilized drug products. The presentation will furthermore describe cases of actual accelerated and long term leachables studies and how the results of such studies can be correlated.

Carsten Worsøe, Senior Research Scientist, Novo Nordisk A/S, Denmark

Closing the gap between extractables and leachables

When performing extractables studies and subsequent leachables studies, it is often observed that the identity of the extractable compounds can be different from the compounds, identified as a leachable. In addition, it may also be possible that the concentrations of leachables are higher than the concentrations found for these substances as an extractable from a material. In some cases, the reason for this discrepancy may be obvious, it will be the result of an ill-designed extractable study (e.g. consideration of secondary packaging, sterilization, processing aids...). In other cases, however, the reason for the discrepancy is less obvious. In a number of these cases, the reason of this difference in results between extractable studies and leachable studies can be explained by an evaluation of extraction kinetics in a solvent, degradation kinetics of the material and reaction kinetics between the drug product and the leachables. As a conclusion a testing strategy will be proposed on how to narrow the gap between extractable and leachable results.

Dr Piet Christiaens, Scientific Director, Toxikon Europe, Belgium

How to set acceptance criteria for leachable studies - selection and toxicological evaluation of analytical targets

At the recent PQRI workshop for E&L testing in PODPs, the toxicology group introduced a staged approach to establish relevant safety concern thresholds depending on the structural class of compounds. Integration of controlled extraction studies with material knowledge gathered from the supply chain and information of prior medical application may lead to more relevant expectations for potential leachables than directly applying acceptance criteria to the extraction study.

This presentation will outline how to achieve information from controlled extraction studies and other material characterisation methods. A full strategy including selection of analytical

targets and deriving clinical relevant acceptance criteria for leachable studies will be proposed and discussed.

Carsten B. Senholt, Novo Nordisk A/S, Denmark

Current extractables/leachables thinking and its impact on the E&L approach of an elastomeric closure supplier

Several collaborate projects like PQRI/OINDP, PQRI/PODP, ELSIE, IPAC-RS, ... in recent times have given a boost to the thinking related to extractables and leachables. This evolution evidently has an impact on the practices of manufacturers of primary packaging materials. Manufacturers of the latter materials are compelled to deepen the knowledge on the materials they bring to the market and to adjust their approach in putting together the extractable data packages they offer to their customers.

This presentation illustrates how an elastomeric closure manufacturer responds to this evolution and how he aligns his approach with current thinking. At the same time a case study is given of how a forced material change is being handled in terms of extractables documentation.

Dr Renaud Janssen & Dr Bram Jongen, Helvoet Pharma, Belgium

Best practice from a seal manufacturer's view

A gasket manufacturer for the pharmaceutical industry is dedicated to high quality compounds, cleanliness and adequate consulting. The high quality compounds have to meet the requirements according to FDA and more and more according to USP Class VI chapter 87 and 88. Furthermore the compounds have to be resistant against the media used in the process. This can be aggressive CIP/SIP-cleaning agents, the API (Active pharmaceutical ingredient) itself or organic solvents needed. Therefore intensive knowledge about the behavior in this media is essential to recommend the right sealing material for a certain application. A comprehensive resistance database and the possibility to do customer specific immersion tests are the methods used to have a first look at a specific problem.

The composition and the restraints on the recipe for pharma grade compounds will be shown. To make clear how the right compound can be chosen, the results from immersion tests of different elastomers suitable for the pharma industry in typical media e.g. CIP/SIP media will be presented.

Dr Till Riehm, Freudenberg Process Seals GmbH & Co KG, Germany

Extractables/leachables from single-use systems components

This talk presents a systematic study of extractables from single-use systems into water and ethanol via novel concepts, practical design, and analytical detection using advanced techniques. In order to tackle the fairly complex systems, we first studied the individual components, which included filters, sterile connectors, flexible tubing and biocontainers. An extractables data library was then compiled, which served as a tool to perform extractables study on an integrated single-use system. This approach greatly simplified the identification of the extractable compounds from the whole systems. The test design was based on actual biopharmaceutical manufacturing process conditions using a worst-case scenario with model solvents that bracket most processes. The complete extractables results were obtained using validated analytical methods, including non-volatile residue measurement and FTIR for qualitative assessment, GC/MS for volatile/semi-volatile compounds, derivatization GC/MS for organic acids, HPLC/UV, LC/MS and LC/MS/MS for nonvolatile and heat-sensitive compounds, and ICP/MS for inorganic elemental analysis. The presentation provides a strategy for application of generic extractables data to single-use systems where appropriate, and facilitation of product-specific extractables/leachables studies where necessary. The results are beneficial to characterization of biopharmaceuticals in contact with single-use components or systems. The study can also serve as a potential guide for part of the process validation program involving single-use systems.

Dr Weibing Ding, Pall Life Sciences, USA

Extraction studies on the development of packaging materials for dialysis solutions: Presentation of a standard procedure and some results

During dialysis treatment of patients with renal failure large volume parenterale solutions in large daily quantities are used for a long time, ranging from a few days or weeks for acute treatment to life-long use in chronic renal failure. Thereby even very low concentrations in the solutions could accumulate to toxicologically relevant amounts. Therefore a careful examination in the context of extraction studies is an important aspect of the development of new packaging.

The extraction studies at Fresenius Medical Care are carried out primarily on the individual components of the container closure systems (foils, tubes, injection molding parts, etc.); increasingly also on the used polymer raw materials. The samples are autoclaved with aqueous buffer solutions with defined surface-volume ratios and the extraction solutions are examined by headspace-GC, GC-MS, HPLC-UV/DAD, HPLC-MS and ICP, with the main focus on the GC-MS investigations.

Presented are three examples of such studies: change of catalyst of a PP material, the investigation of a polyester film and the qualification of a polyurethane adhesive for multilayer films.

Dr Michael Fünfroeken, Fresenius Medical Care Deutschland GmbH, Germany

Thermodesorption GC/MS as a powerful analytical tool for E&L screenings in pharma or medical grade polymers

Today drug development includes modern state of the art packaging, application or administration systems. Such systems – usually based on pharma or medical grade polymers - must be nearly systematically tested within the frame of “extractables & leachables” (E&L) studies to demonstrate that the nature and amount of released extractables are safe and cannot harm patients. As many components of a polymer, from oligomers to catalyst systems or stabilizers and related compounds, can be regarded as potential extractables, fast and sensitive screening analytical techniques are today key to the success of E&L studies. In this respect, Thermodesorption-GC/MS can be regarded as a very powerful tool to screen for volatiles and semi-volatiles compounds that can be released from packaging or application systems, as most compounds that are detected in thermodesorption experiments are quite similar to compounds that can be solvent-extracted. With illustrative case studies applied to pharma or medical grade polymers, the various advantages of Thermodesorption-GC/MS will be discussed.

Vincent Jeanguyot, Intertek Expert Services, Switzerland

Producing Processed Plastic Materials for Controlled Extractables Testing by the ELSIE Materials Working Group

The ELSIE consortium has put forth the many potential benefits of developing a materials extractables database. In order to do so, it is necessary that the plastics being considered for studies be processed at their upper vendor recommended thermal molding times and temperatures. It is difficult to get material suppliers to produce the small amounts of materials required for the testing; however, laboratory micro scale extruders produce insufficient amounts of materials. An intermediate that fulfilled sample requirements for the pilot program of the ELSIE materials working group was the CW Brabender -Intellitorque Plasticorder. The Brabender consists of a fusion bowl and mixing paddles and records outputs of temperature and shear with time. The materials produced are arguably identical to extruded or molded materials and the amounts (50's to 100's of grams) are ideal for laboratory testing across a suite of facilities. This paper presents data from the brabender runs used to process the PVC and PE materials used in the ELSIE pilot studies and discusses the general capabilities of the brabender.

Dr Roger Pearson & Chris Chapma, Aspen Research Corporation, USA

A control strategy for leachables in a dry powder inhaler

This paper will illustrate the development of a strategy to control leachables in an inhalation product (Relovair). It will demonstrate how an understanding of extractables and their relationship with leachables has been achieved and how this knowledge is used to inform change control procedures to control leachables throughout the lifecycle of the inhalation product.

The paper will focus on a study of the levels of extractables generated by typical variation in the materials of construction and processes employed to manufacture the container closure system. It will include details of the analytical methods used and will demonstrate how the extractable information gained when combined with outputs from leachables risk assessment can be used as a basis for a leachables control strategy. Data presented will include; leachable levels in the inhalation product showing no leachables of safety concern throughout product shelf life, corresponding levels of extractable via a data base of results from several batches showing the variation in extractable levels due to the manufacturing process for the inhaler device and primary pack.

Graham Wilson, GlaxoSmithKline R&D, UK

Characterisation of drug and drug product related contaminants - when is a leachable not a leachable?

A series of case studies are presented to illustrate the wide variety of potential sources of contaminants in pharmaceutical products in addition to those directly associated with the drug product and the immediate packaging. These include several examples of process related materials being introduced to the drug product and an investigation where a number of analytical techniques were combined in order to identify a series of by-product contaminants. Examples to demonstrate the potential application of several new technologies for extractable and leachable testing will also be presented.

Michael Ludlow, LGC, UK

Extractables & leachables for medical devices: meeting the 510(k) requirements

Recent changes in the FDA's 510(k) requirements for medical device applications have spawned many inquiries from clients on how to address the request for extractables, leachables and drug compatibility data. Meeting the expectations of the CDRH can be challenging in that any given

study design is not universally applicable to all devices. A good study design requires elements of the best practices documented in ISO-10993, the PQRI guidance for E&L testing of OINDP as well as any specific requests for drug compatibility data from CDRH.

A hybridized study design, incorporating the essential regulatory elements, has been developed and successfully implemented for variety of medical device applications. The rationale behind selection of the elements, overall experimental design strategy and interpretation of the resulting data will be presented.

Dr Kurt Moyer, NSF Pharmalytica, USA

For further information about **Extractables & Leachables for Pharmaceutical Products 2011**, including sponsorship and marketing opportunities, please contact Helen Charlesworth, iSmithers, email: hcharlesworth@ismithers.net, tel: +44 (0)1939 250383, fax: +44 (0)1939 251118 or visit www.polymerconferences.com

© Abstracts submitted by the authors for Extractables & Leachables for Pharmaceutical Products 2011, iSmithers, Shawbury, Shrewsbury, SY4 4NR, UK. Not to be reproduced without permission from the authors.