european pharmaceutical review

Manufacturing and Packaging

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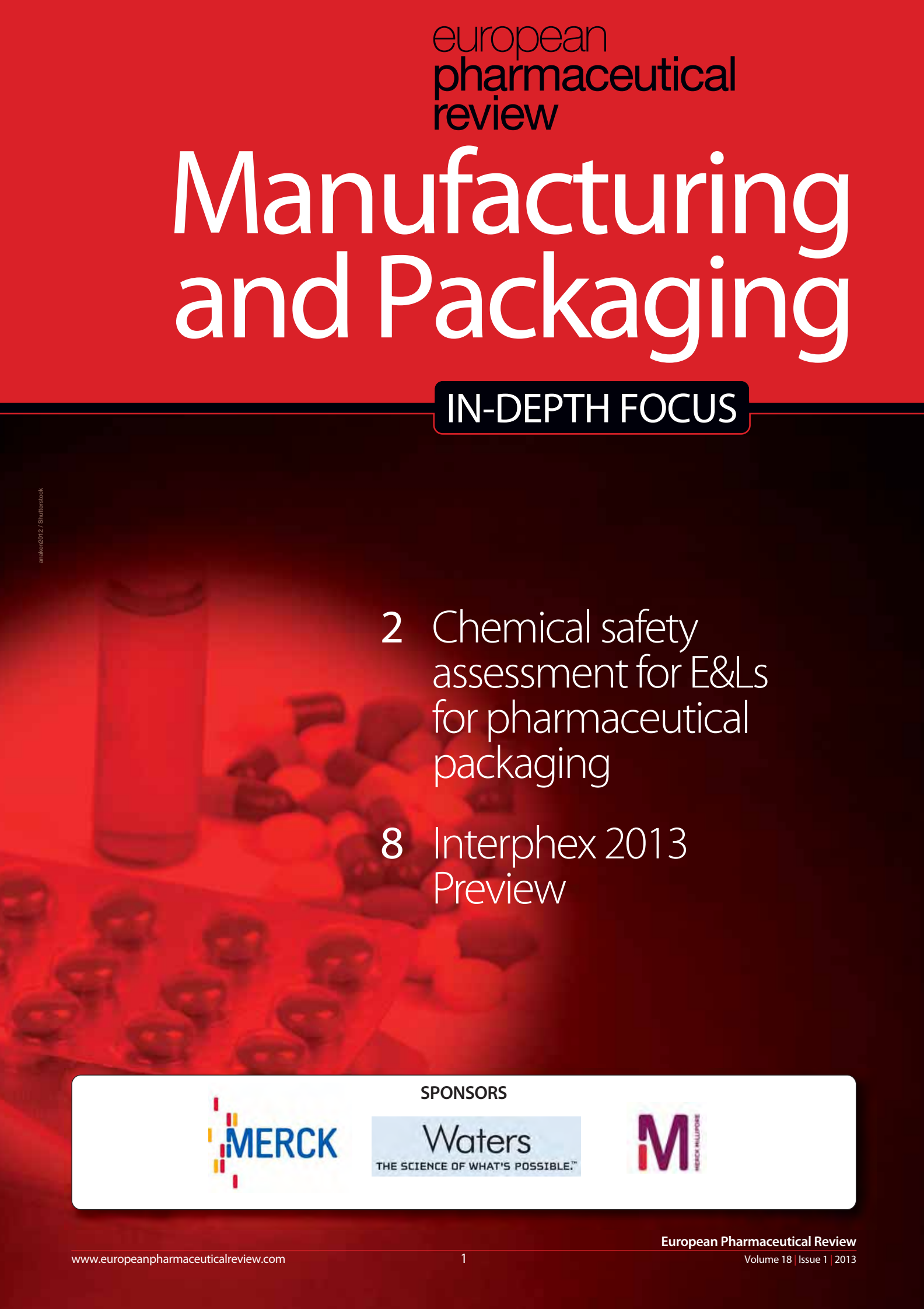

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The chemical safety assessment process for extractables and leachables associated with packaged pharmaceutical products

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Packaged pharmaceutical drug products can interact with their packaging, resulting in the migration of substances from the packaging and into the drug product. This is of concern due to the potential toxicity and/or reactivity of the migrating substances. In order to properly assess the safety risk and manage the safety hazard posed by migratory substances, it is first necessary to establish, via the application of a rigorous and extensive chemical analysis process, the identities of the migratory substances and the levels to which they will accumulate in the finished drug product. This analytical data is then evaluated by toxicologically establishing the safety hazard posed by the migratory substances, a process by which the actual user exposure to the migrating substances is balanced against a tolerable dose calculated for each migrating substance.

Pharmaceutical products are packaged in packaging systems so that they can be manufactured, distributed, stored and used. As the pharmaceutical product is in contact with the packaging system during these processes, the pharmaceutical product and packaging system can interact. Although modern packaging systems are constructed with materials and by processes that seek to minimise the extent to which interactions can occur during contact, it is nevertheless the case that neither truly inert materials and systems nor truly benign contact conditions exist. Thus, interactions with potential product quality impact frequently occur between packaging and packaged pharmaceutical products. One such interaction is the migration of substances out of the packaging and into the pharmaceutical product. When the pharmaceutical product is administered to its users, these users are exposed to such migratory substances. It is possible, therefore, that the migratory substances could adversely affect the user's health, either directly or indirectly. Thus, it is a universal expectation that packaging is constructed from materials that do not leach harmful or otherwise undesirable amounts of substances to which a patient may be exposed when being treated with the pharmaceutical product.

To comply with this expectation, the packaged pharmaceutical product and/or its packaging are tested for migrating substances. The resulting migrating substances are toxicologically assessed to establish their potential to adversely affect patient health. The comb-

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ination of chemical characterisation and toxicological interpretation is termed a chemical safety assessment.

The safety assessment process

In performing a chemical safety assessment, two distinct activities are completed:

1. Substances migrating into pharmaceutical products are discovered, identified and quantified
2. The propensity of the migrating substances to be harmful or undesirable is established.

One notes that activity number 1 is an exercise in analytical chemistry and activity number 2 is an exercise in toxicological and chemical science. As the data derived from the analytical assessment is the input to the toxicological assessment, it is the case that the analytical activity must be completed before the toxicological assessment begins. If the analytical assessment is not complete, then the toxicological assessment cannot be performed. At a very high level, the chemical safety assessment process can be broken into its analytical chemistry and toxicological components (**Figure 1**). During the chemical assessment, an extract is generated. The extracting medium may be the drug product itself, a simulating extraction solvent or another appropriate solvent. The extracted entity may be the packaging itself or its materials of construction. The extraction conditions of temperature and duration are chosen based on the purpose of the study, the nature of the drug product, the nature of the packaging system and the nature of the clinical contact between the drug product and its packaging. The resulting extract is tested for extracted substances, producing an extractables profile which establishes the identity and concentration of the extracted substances. The test results (extractables or leachables profile) are safety assessed by the toxicologist, a process that requires that the toxicologist establish and balance the calculated dose of the substances versus their individual safety thresholds.

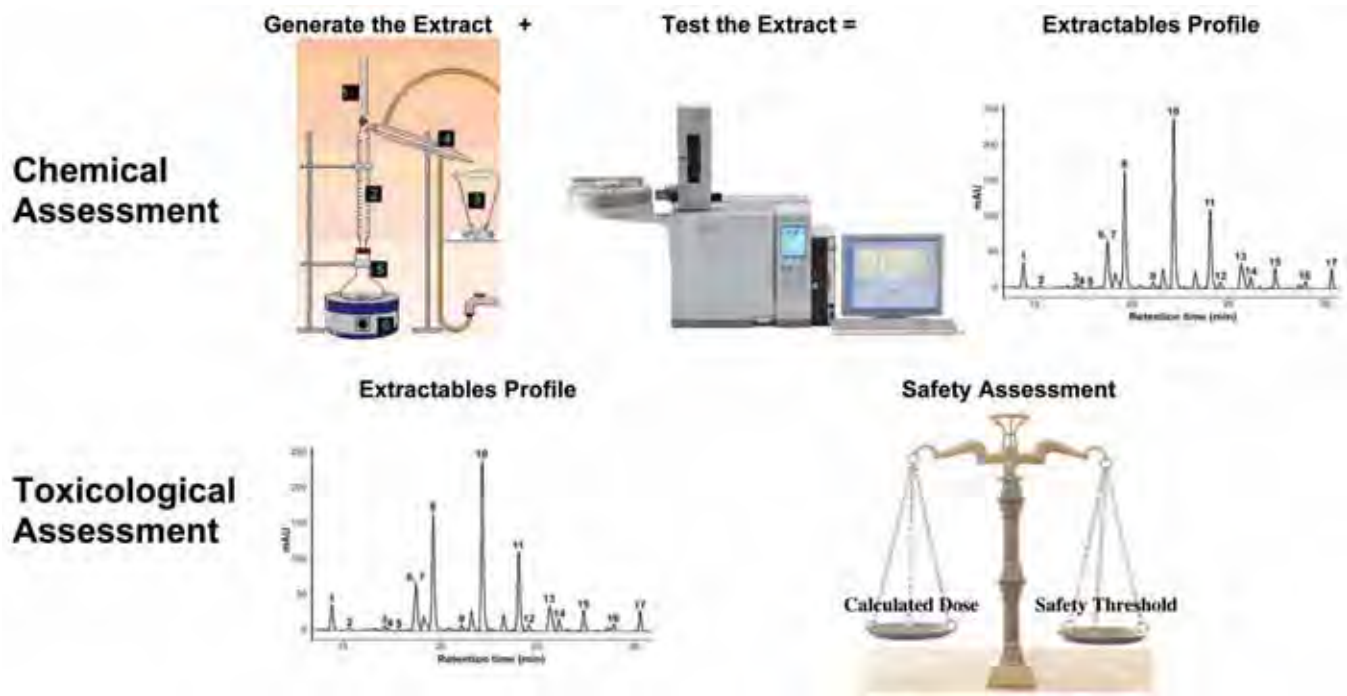

Figure 1 The process of chemical safety assessment for extractables or leachables. Although the figure refers to an extract and extractables, an analogous process is relevant for leachables. However, the 'extract' is the packaged drug product in the leachables case

> ***"Testing a pharmaceutical product for substances that have leached in to it (leachables), can be a complicated process"***

Extractables and leachables

The packaged pharmaceutical product and its packaging represent a two component system (**Figure 2**, page 6). In considering this two component system, one recognises that there are two means of establishing the nature and magnitude of migratory substances, one can test the packaging for substances that migrate out of the packaging or one can test the product for substances that have migrated into it. Both approaches have their strengths and weaknesses. Testing a pharmaceutical product for substances that have leached into it (leachables), can be a complicated process as (a) the levels of leachables in a pharmaceutical product are typically low and (b) the pharmaceutical product may be chemically complex, making it a difficult sample medium in which to discover, identify and quantify leachables. Conversely, testing a packaging system for substances which can be extracted from it (extractables) requires two steps; (1) that an extract is generated and (2) that the extract is effectively characterised with respect to extractables. Recognising the issues involved in leachables profiling, extracts for extractables assessment are typically generated so that they are analytically expedient, thereby facilitating the processes of discovering identifying and measuring the extractables. To accomplish this objective, extraction is typically performed with one or more solvents which mimic the propensity of the drug product to leach substances from packaging and is performed under accelerated or exaggerated conditions (versus actual clinical use).

While the resulting extract facilitates the

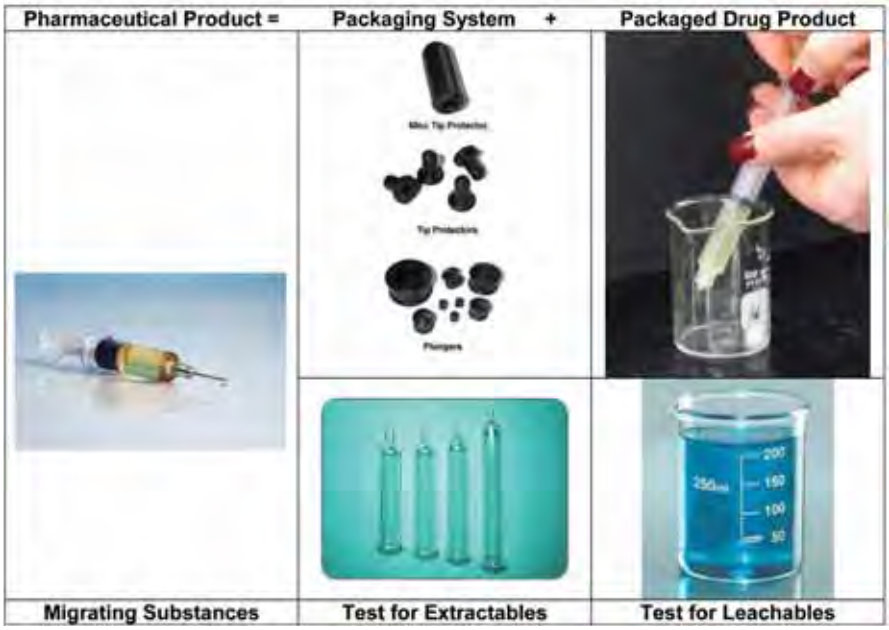

Figure 2 Use of a pre-filled syringe to illustrate the relationship between extractables and leachables. The actual pharmaceutical product is characterised for migrating substances by either testing its packaging system for extractables or its packaged drug product for leachables

analytical process of extractables profiling, it complicates the safety assessment process. Because the extraction process simulates the leaching action of the pharmaceutical product and accelerates the clinical conditions of contact, it is not necessarily the case that there is a quantitative, one-to-one correlation between extractables and leachables. Thus, while toxicological assessment of an extractable profile can infer the potential safety impact associated with the use of a packaged pharmaceutical product, such an assessment cannot always be used as the definitive measure of the actual safety impact. Clearly, the inference is the strongest when the extract's simulation of the pharmaceutical product is the most rigorous.

To overcome the shortcomings in both extractables and leachables profiling separately, it is frequently the case that a chemical safety assessment includes both extractables and leachables testing. However, it may be the case that both the extractables and leachables testing are not exercises in profiling, as profiling an extract for extractables and a drug product for leachables could be redundant in the circumstance that the extractables effectively represent the leachables. Rather, the extractables profile can be used to establish target leachables which are specifically quantified in the pharmaceutical product.

Chemical assessment

Chemical assessment is the term applied to establishing the extractables or leachables profile. As noted previously, chemical assessment is actually two processes: generating the extract and testing (i.e., characterising) the extract. Considering the extract itself, if the chemical assessment is an extractables assessment then the packaging system (and/or its materials of construction) must be extracted under the appropriate experimental conditions.

"Chemical assessment is the term applied to establishing the extractables or leachables profile"

Detailed discussions related to the specification and justification of extraction conditions are contained[1,2]. If the chemical assessment is a leachables assessment, the generation of the extract is a moot point as the extract is, in fact, the packaged pharmaceutical product.

Regardless of whether it is characterising a product for leachables or an extract for extractables, the essential challenge for the analytical chemist performing a chemical assessment is to produce a complete and accurate profile, which means that the analyst must:

1. Utilise analytical methods that are capable of producing a recognisable, unique and useful response to all extractables or leachables (discover)
2. Utilise information contained within the response to identify the extractables (or leachables) that are responsible for the observed responses
3. Process the response to quantify the extractables (or leachables) in the tested sample.

Additionally, the analyst may perform scouting analyses, which can provide useful information to facilitate the processes of discovery, identification and quantitation. For example, measuring the UV absorbance, pH or total organic content of an extract may provide useful information in terms of the quantities and general properties of organic extractables. The utility of scouting is in the guidance it potentially provides to the discovery, identification and quantitation processes. However, none of these measurements are directly relevant in terms of the safety assessment.

As the universe of potential extractables and leachables is relatively large and as it is generally the case that no single analytical method can test a sample directly and provide identities and concentrations for all analytes of interest, the analytical process of extractables or leachables profiling typically employs multiple orthogonal test methods and procedures to accomplish these objectives. In fact, the profiling exercise is most effectively and efficiently accomplished if specific analytical techniques and methods are used to accomplish the individual activities of the chemical assessment, as the activities of discovery, identification and quantitation are sufficiently different that single methods cannot effectively accomplish all three of these activities.

Figure 3 Overview of the process of toxicological safety assessment process. In this process, the toxicologist compares the patient's exposure to a particular leachable with a dose that has been established to represent an acceptable safety risk. If the exposure is greater than the permissible dose, then a potentially unsafe situation exists. If the exposure is less than the permissible dose, then an acceptable situation exists

Toxicological assessment

In its most general sense, the toxicological assessment interprets the data produced in the chemical assessment (compound identity and concentration) and produces actionable information (a statement as to the probable safety impact of the extractables or leachables).

"The essential challenge for the analytical chemist performing a chemical assessment is to produce a complete and accurate profile"

This process involves the use of the available information to identify health hazards (as manifested in leachables and inferred in extractables) and to estimate health risk (the likelihood of the occurrence of harm and the severity of that harm). Although numerous means of performing such a toxicological assessment have been proposed and published, most of these means contain certain common characteristics or steps (for example[3]), including the following:

1. The compound of interest has been identified via the chemical assessment
2. Based on the compound's identity, its associated toxicological data is obtained and is used to establish the substance's Permissible Dose (PD)
3. The compound on interest has been accurately quantified in the test sample
4. The compound's concentration in the test sample is extrapolated to clinical use of the pharmaceutical drug product to establish the Patient Exposure (PE)
5. Using well established principles of toxicology, the PD and the PE are compared to one another (**Figure 3**, page 6). In its simplest manifestation, the ratio of PD versus PE is taken. If this ratio is larger than a prescribed value (typically greater than 1), it is concluded that the risk to patient safety is acceptable. This comparison serves as the basis of the safety assessment
6. The appropriate conclusion concerning patient safety is drawn from the safety assessment of all compounds of interest.

While the toxicological assessment can be accomplished via a rigorous process, it is the case that the individual steps in the process may be somewhat inexact, as the degree of protection deemed appropriate is dependent on a number of factors and the assessment itself requires that several complex factors be investigated and balanced. This is the case as it is extremely rare that definitive toxicity data, relevant for the exact conditions of clinical use and exposure for the packaged pharmaceutical product, is available for extractables and leachables.

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Biography

Dr. Dennis Jenke is a Baxter Distinguished Scientist at Baxter Healthcare Corporation. He has published extensively in analytical chemistry, environmental science and material / solution compatibility, is an expert reviewer for pharmaceutical and analytical journals, is a member of professional and standard-setting organisations related to material / solution compatibility and is a frequent speaker on this topic. He is the author of the book 'Compatibility of Pharmaceutical Solutions and Contact Materials; Safety Considerations Associated with Extractables and Leachables'.

Show PREVIEW

Date: 23-25 April 2013 · Location: New York, USA

INNOVATION + INTELLIGENCE + PASSION

INTERPHEX™ 2013

From 23-25 April, INTERPHEX, the largest annual industry exhibit for pharma/biopharma manufacturers, organised by Reed Exhibitions, will open its 2013 event at New York's Javits Center with a with a new and improved experience for 2013. This event has evolved to meet the industry's needs, including a re-engineered conference programme, expanded product categories on the show floor and additional networking opportunities.

The exhibition

Attendees will have a chance to see, touch and procure the latest new products from over 650 suppliers and 1,000 product lines in the exhibit hall. Show floor segments include: Facilities, Manufacturing & Packaging, Automation Systems & Controls and Sourcing & Services. New products and equipment will be on display from Bosch Packaging Technology, EMD Millipore Corp, IMA North America, Marchesini Packaging, MG America, and others. As a benefit of registering early for INTEPRHEX, attendees will receive bi-weekly product newsletters, based on category interests, to let them know what new and featured products exhibitors will be on display.

The exhibition will be open from 10am-5pm on Tuesday 23 and Wednesday 24 April and from 10am-3pm on Thursday 25 April.

The conference

Whatever your job function, the INTERPHEX Conference Programme has a track focused on the latest industry topics and trends just for you. With presentations given by subject matter experts, learn in-depth analysis, case studies and take-a-ways aligned to your priorities. This year, the conference will be running from 9am-5pm on Tuesday 23 and Wednesday 24 April.

This year's conference tracks include:

- Regulatory QA/QC
- Product Development
- Facility & Process Design
- Manufacturing & Packaging
- Supply Chain.

"Whatever your job function, the INTERPHEX Conference Programme has a track focused on the latest industry topics and trends just for you"

For the first time this year, a Serialisation Mini-Course will allow attendees to learn more about manufacturing intelligence, revisit the California rule and discuss the cost and benefits of a national tractability system. Rounding out the educational portion of the event are interactive case-studies and Exhibit Hall floor tours, presented by IPS-Integrated Project Services, Technical Workshops and informative Keynote sessions.

Be sure to check out our new year-round INTERPHEX Webinar Series as well, which complements the quality education programme available onsite. To view the latest schedule and archived sessions online, visit www.interphex.com/webinars.

Networking with industry colleagues

The INTERPHEX Connects Lounge will serve as the attendee and exhibitor networking hub on the show floor. Attendees and exhibitors will be able to interact with peers, share experiences and find solutions with those who share their passion.

ISPE, INTERPHEX and *Pharmaceutical Processing* magazine will join together to showcase the six category winners at the ninth annual Facility of the Year Awards (FOYA). FOYA is an annual programme which recognises state-of-the-art pharmaceutical manufacturing projects that utilise new and innovative technologies to enhance the delivery of a superior project, as well as reduce the cost of producing high-quality medicines. These category winners will be on display in the exhibition hall at INTERPHEX 2013.

Make sure you're there

Advance online exhibit hall registration is free (USD 75 if attendees wait to register onsite). Conference pricing – including discounted two- and one-day conference and single session passes – group pricing, ISPE member pricing and Government/academia pricing is all available on the website. You can also use the website to find information about travelling to the event – including discounted rates on airfare, hotels and rental cars – along with further details about registration for international attendees, and much more.

Further information

For further information on Interphex 2013, please visit: **www.interphex.com**