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Is it safe?

Assessment of Material Changes

During the lifecycle of a drug product, there are likely to be a number of changes to the materials or components used to manufacture and store it.

This is especially true when the manufacturing processes involves single use components.

This white paper considers the key factors when undertaking material changes, including;

- Types of material changes and when they occur
- Definition of risk as it relates to extractable and leachable compounds
- Types of studies which assess materials and help us understand risk

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Introduction and Context

Material changes during a product lifecycle can occur for a number of reasons. They can be both in or out of the end user's control.

Forced changes might include;

- Suppliers making pre-planned changes to their materials
- Material quality alerts which are unplanned and often due to an unknown or uncontrolled change in the manufacturing process (i.e. unexpected changes or changes which were not expected to have an impact on the end user)

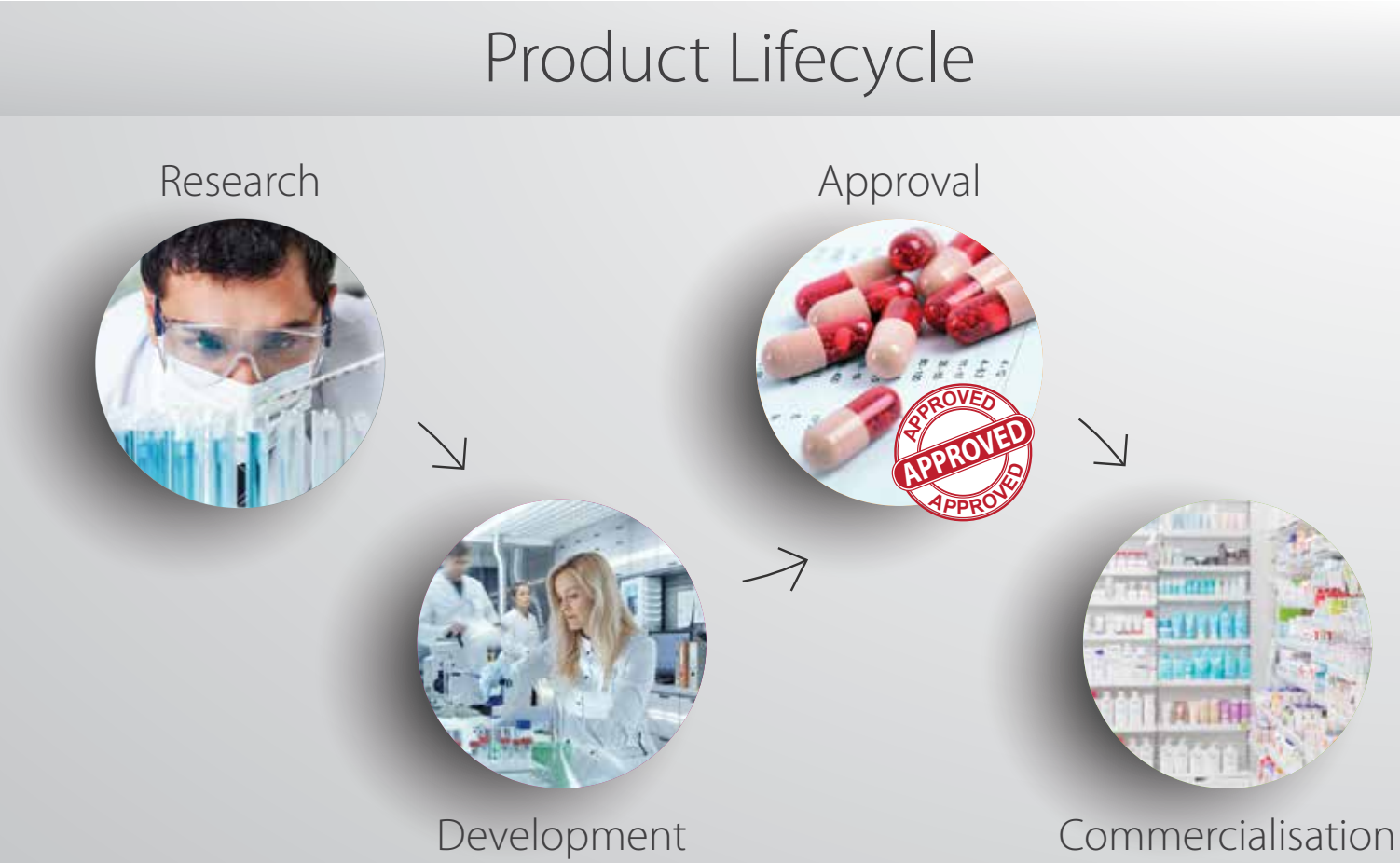
Voluntary changes might include;

- Process improvement changes
- Cost saving changes

These changes can occur at multiple stages in a product's lifecycle:

- During the R&D phase, changes are often due to process improvements and can have an impact on clinical trials or the regulatory approval of a product
- The majority of changes will happen post-approval; therefore, before these changes can be introduced, their impact needs to be carefully considered

Product Lifecycle



When a material/component change is required, there is a vital question in the qualification of the change;

Is it safe?

Whilst a very simple question to ask, the answers can be surprisingly complex and will include factors such as;

- Will it have an adverse effect on patients?
  We need to understand what is in a material which could potentially have a harmful effect on a patient and how much of these harmful substances a patient might be dosed with.

- Will it affect the product's performance?
  To understand this we need to know the critical quality attributes of our product and which of these attributes might be affected by substances in the material. This may be a complex question and can often only be answered after the product has been affected by the material or something in the material.

- Will I still be able to sell my product in specific counties or regions?
  Knowledge of legislation/regulation or sensitivities over certain substances in different regions must be understood. e.g.;
  - Bis-phenol A (BPA) is banned in food packaging in several countries (including the US).
  - Phthalates are banned in children's toys
  - The European Union has a list of regulated substances (REACH regulations)
  - California also has a set of similar regulations (Proposition 65)

What these questions are really asking is;

What is the risk of making the material change?

The Risk Analogy

ICH Q9 describes risk as "... the combination of the probability of occurrence of harm and the severity of that harm."

We find it helpful to explore this interpretation using a simple analogy, so let's take the 'severity' aspect of the guidance first and use an 'ocean analogy' to investigate what this might mean;

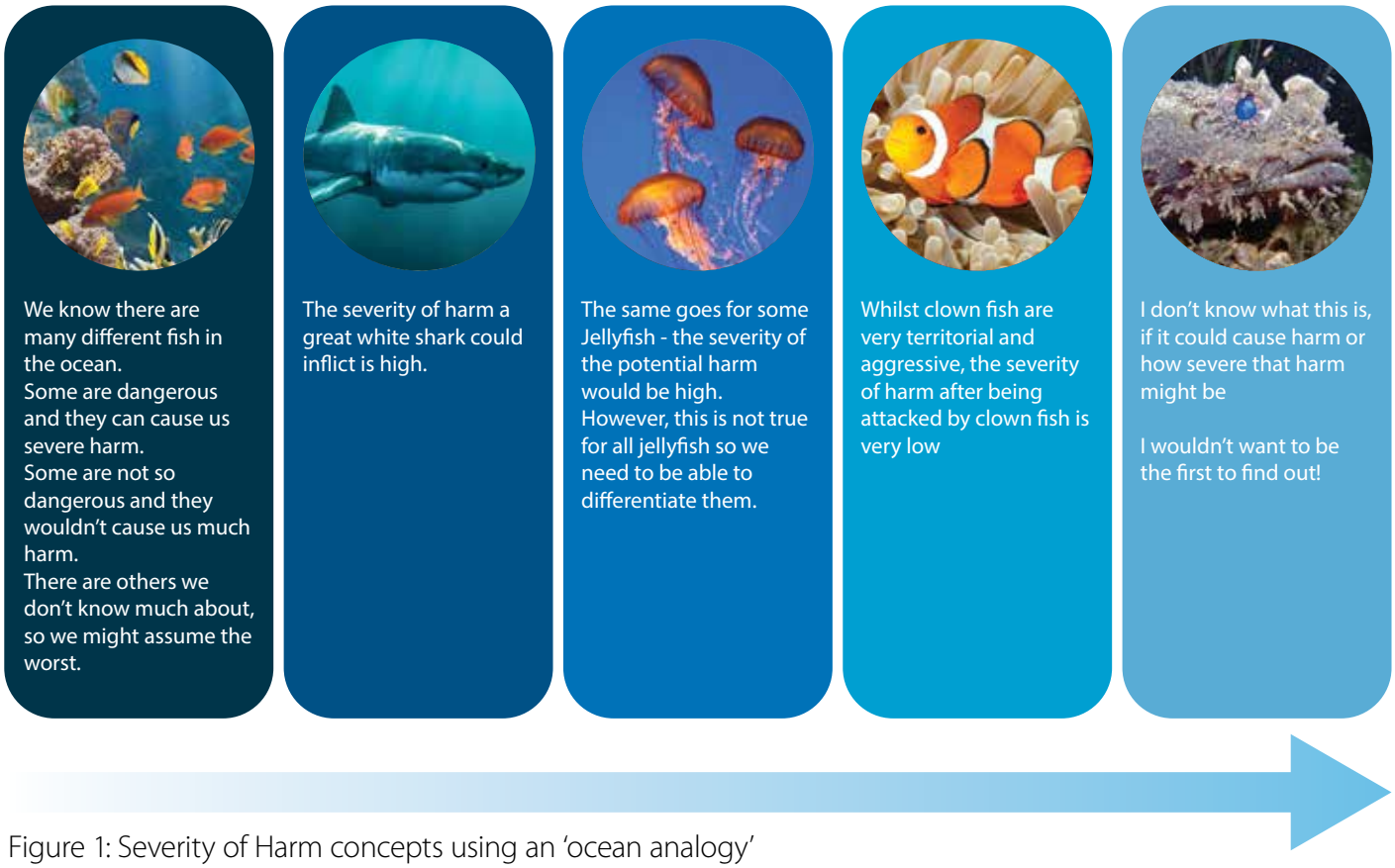


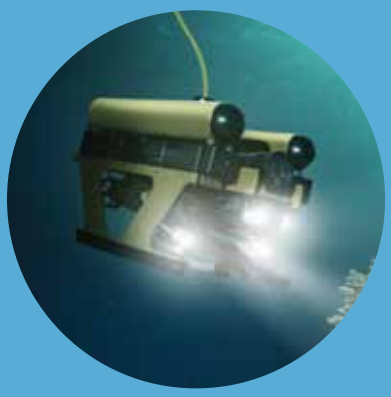
Figure 1: Severity of Harm concepts using an 'ocean analogy'

In extractable and leachable testing, this relates to the chemical substances present within the material and how harmful these substances are. In order to assess these factors, we carry out studies to evaluate the severity of the harm by characterising the component and determining the biological response.

Now, back to the ocean analogy to look at the 'probability of occurrence'. The likelihood of someone being harmed in the ocean depends on various factors.

For someone swimming in shark infested waters the probability of being harmed is fairly high

For cage divers, whilst there are sharks in the area the probability of being harmed by a shark is low
However, the probability that jelly fish can cause harm to the divers is still high



For someone in a submarine the probability of harm from fish is very low

Figure 1: Severity of Harm concepts using an 'ocean analogy'

In extractable and leachable testing, the 'probability of occurrence' relates to the likelihood of the chemical substance causing harm under in-process or in-use conditions. To understand this, we use studies to evaluate if a substance migrates from the component into the product and quantify how much of that substance migrates.

Risk Assessment

How do we assess the risk of the material change? There are various types of information which can help us to assess this risk, some of which give us a better understanding of the severity of harm and others which give us an understanding of probability of occurrence.

Various types of information that allow us to consider risk in a more informed way include;

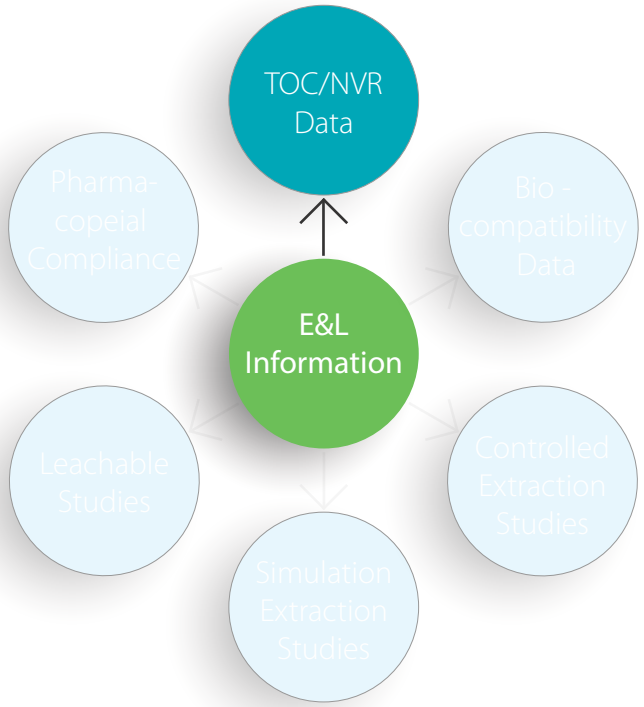
- Material identity
- Material formulation
- In-process / in-use conditions
- Biocompatibility information
- Extractable information
- Physiochemical data (Total organic content (TOC) and non-volatile residue (NVR))
- Absence Ssatements
- Food compliance
- REACH compliance
- Leachable data
- Pharmacopeial compliance

You might have some of this information from previous projects. Single-use component/system suppliers are more commonly providing some of this information as part of their certificate of analysis (CofA) or validation package.

So, does this information mitigate the risk of material change? Unfortunately, the answer is more complex, and we need to understand more about the data we have and what it tells us about the relative risk. This will also depend upon the way the data is generated as there are various methods to derive some of the data types mentioned in the list above.

This is the crux of this white paper — the typical extractable and leachable information which is used for assessing risk of material change in single use systems (SuS) and what this data tells us about the risk from a material change. We will consider various types of study that might be available, highlight the pros and cons for each and how they inform our knowledge of severity of harm or probability of occurrence.

Data From Total Organic Carbon (TOC) / Non-Volatile Residue (NVR) Studies



Pros

- Informs probability of occurrence
  - Quantitative data
- Data can be used for multiple projects

Cons

- Non-specific
  - Doesn't identify individual extractables meaning no saftey evaluation can be made
- Techniques have limitations
  - TOC is only suitable for aqueous samples
  - NVR only quantifies non-volatiles

The measurement of total organic carbon (TOC) gives us information regarding the total amount of organic extractables within a material, whereas von-volatile residue (NVR) gives us information regarding the total amount of non-volatile extractables within a material. These quantitative measurements help to inform us about the probability of occurrence.

This type of data can be used across multiple projects, especially when the extraction conditions used are worst case scenarios in comparison to in-use conditions. For TOC this generally only applies to aqueous formulation; therefore, conditions which use high temperatures for long periods of time, ensure the data can be applied as a worst case against a number of different situations.

Whilst these measurements give us a quantitative idea of the total amount of extractables within a material, the data is not chemically specific. As a result, we cannot make any judgements regarding safety or potential harm and a safety assessment cannot be made if the results are found to exceed the safety concern threshold (SCT) or toxicological thresholds of concern (TTC) .

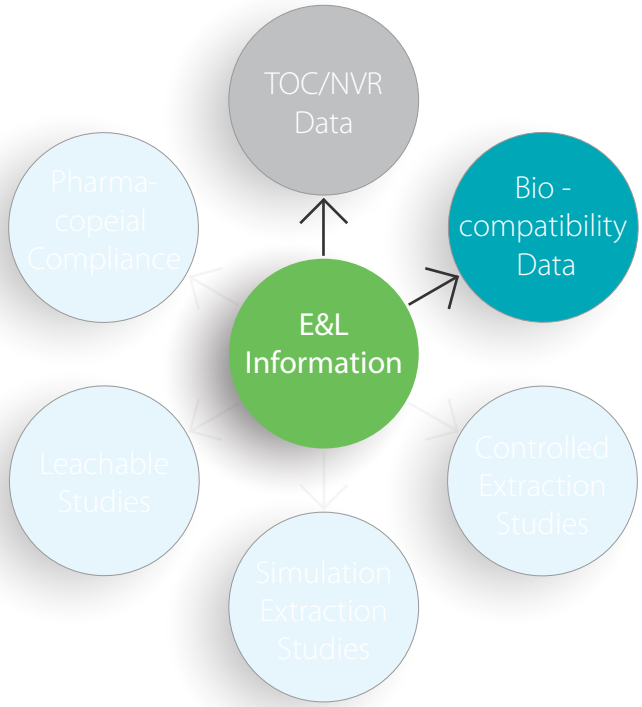
There are also further limitations with this type of data. Whilst TOC is a sensitive technique, it can only be performed on aqueous samples so, if the formulation contains organic solvents, the data may not be appropriate. Further, it is important to take account of the inorganic carbon (IC) content of the sample (typically dissolved CO2, carbonate, and bicarbonate species). Failure to do this can lead to an overestimate of the organic material present.

NVR measurements can be obtained in the presence of organic solvents but only quantify non-volatiles. Any volatile extractable materials will not be accounted for. Further, the accuracy of the technique relies upon the sensitivity of the balance used for the determination.

[1] Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

[2] ICH M7 - ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

Biocompatibility Data



Pros

- Informs severity of harm
  - Designed to identify adverse biological effects
- Data supports multiple projects

Cons

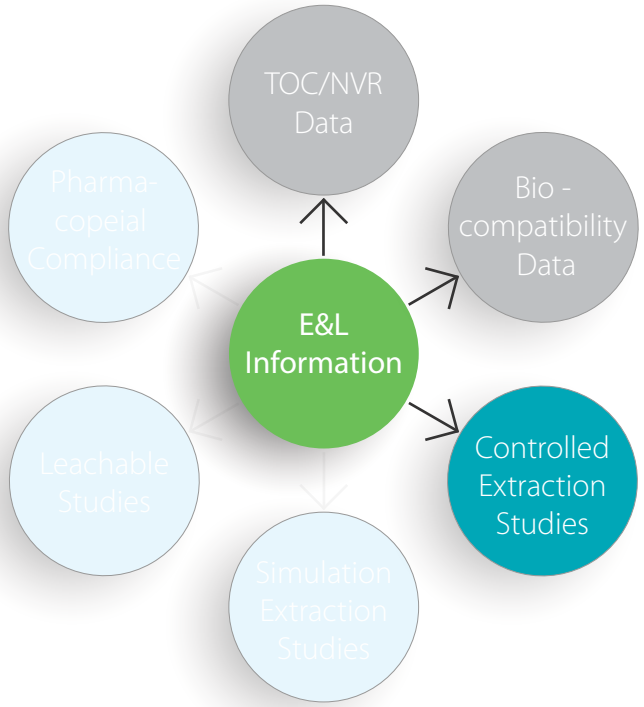
- Non-specific
  - Doesn't identify individual extractables
- Limited extraction conditions
  - May not be 'worse case than' or 'equivalent to' actual in-process conditions

Biocompatability testing determines adverse biological effects of a material or component on specific cell cultures or living organisms. The extraction conditions used to generate the data are generally not specific to one set of in-use conditions; therefore, the results can be used across multiple different projects, where the particular material under investigation is used.

This type of testing informs our decisions on potential harm from the material, but not the specific cause of this harm. Adverse effects cannot be associated with individual extractable compounds, meaning the test results are less specific.

As biological systems are used to evaluate potentially adverse effects, limited solvents can be used, meaning that decisions still need to be made about how accurately the extraction conditions reflect the process under investigation and how appropriate they are for properly assessing the potential harm.

Controlled Extraction Studies



Pros

- Informs severity of harm
  - Designed to characterise a material - aggressive solvents, time, and temperature conditions
- Data supports multiple projects

Cons

- Extreme conditions
  - Not representative of actual conditions (doesn't inform probability of occurrence)
- Difficult to perform toxicity assessment

Controlled extraction studies use vigorous extraction conditions to provide a 'worse case' scenario to characterize the maximum number of potential extractable compounds from the proposed material.

These studies are far more vigorous than 'in-use' conditions and do not generally inform what compounds are likely to migrate under in-use conditions.

There are many variables to consider when designing a controlled extraction study including;

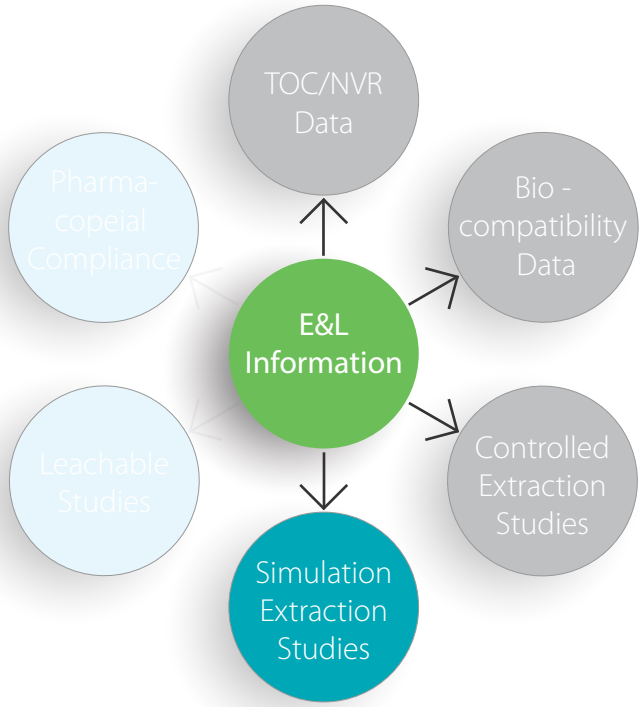
- Extraction times
- Extraction temperatures
- Extraction solvents
- Extraction methods
- Detection techniques

There is no formal guidance on controlled extraction studies; therefore, the choices of the conditions above are somewhat subjective and require knowledge of materials, extraction, and analytical techniques in order to design an appropriate study.

As the extraction conditions used are not project specific, the information can be used across multiple projects and will add to your 'knowledge base' of materials. This can be utilized whenever the material is proposed for use in future projects.

This type of study will give us information on severity of harm; especially, when the identified extractables are subjected to a toxicology assessment.

Simulation Extraction Studies



Pros

- Informs probability of occurrence
  - Quantitative study designed to simulate actual conditions
- Data supports multiple projects

Cons

- Can be difficult to evaluate equivalence to actual process
  - Difficult to model leaching process
- Not always aggressive enough
  - May not be a worse case than or equivalent to actual in-process conditions

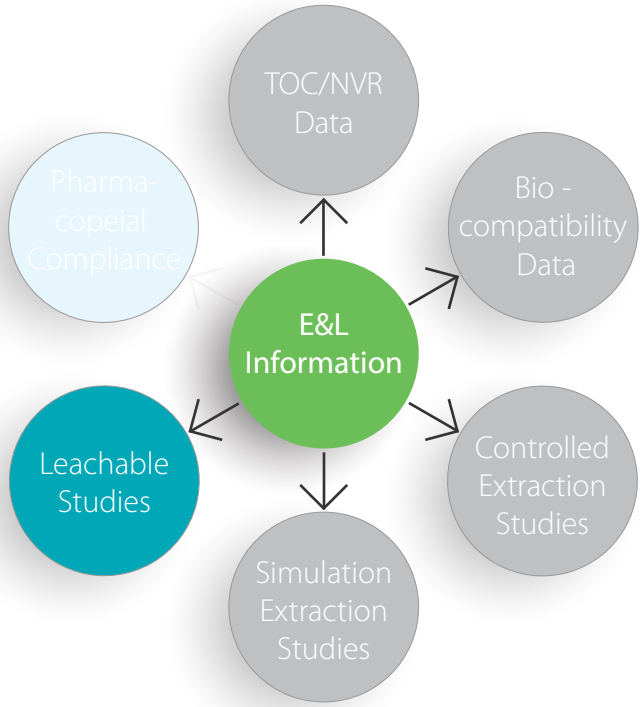
These extraction studies are designed to more closely simulate actual in-use conditions and may follow or be guided by protocols such as the BPOG recommendations or USP <665> . Because these studies are designed to simulate in-use conditions in reality, they inform probability of occurrence. Whilst the conditions more closely simulate those of the in-use situation, they might follow reasonably generic protocols; therefore, the data produced can be used across multiple projects if the in-use conditions are less aggressive than the conditions used to generate the data.

That being said, the data produced by these studies are perhaps the most difficult to interpret in terms of assessing the impact of the material change. This is particularly true when the conditions used for extraction do not match the actual in-process conditions. Interpreting data derived using a standard protocol into the in-use situation is very difficult, given the complex nature of manufacturing processes and the number of potentially different sources for the same leachables (known as the cumulative effect). It is difficult, under any set of circumstances, to assess the likelihood of any extractable compound identified to appear as a leachable under in-use conditions. This is especially true when the extraction conditions used may not represent the worse-case as seen in the actual processing situation.

However, it is possible that, using standard protocol conditions, very few extractable compounds are identified. Moreover, even fewer that are of potential toxicological concern.

[3] https://www.biophorum.com/category/resources/extractables/resources-extractables/
[4] https://www.uspnf.com

Leachable Studies



Pros

- Informs probability of occurrence
- Actual conditions

Cons

- Data is project specific
- Not always possible to generate data
- Difficult to develop methods

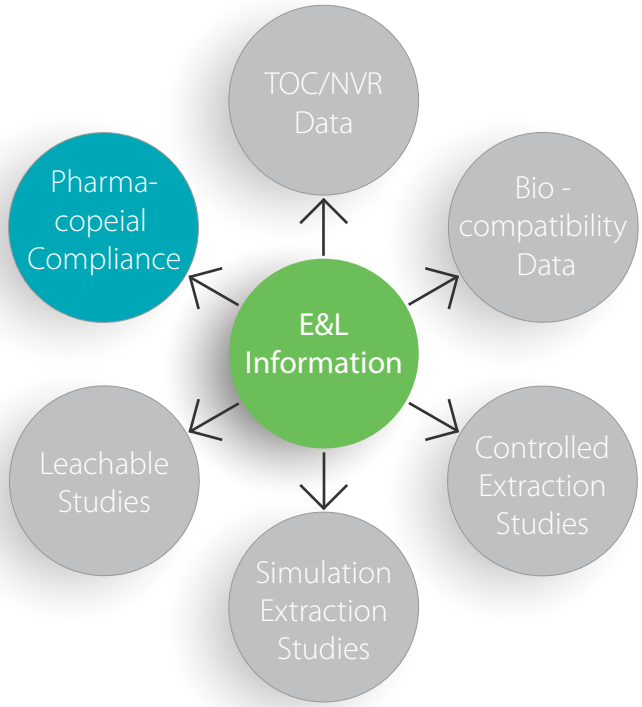
Leachable studies are possibly the most accurate ways of assessing what may be dosed to patients as they are planned to simulate the in-use conditions as closely as possible. Therefore, this gives us very good information on the probability of occurrence.

To that end, the conditions and protocol used must be very carefully designed to ensure that we accurately reflect the in-use conditions; therefore, assessing the leachables in the most accurate and appropriate manner. The data derived tends to be project specific and decisions regarding the impact of using the material under consideration in different processing conditions will not be valid if the processing conditions change.

It is important to be clear on the use of targeted and non-targeted leachables studies. Targeted studies tend to only look for compounds identified in extractables studies; however, untargeted screening is more able to identify new leachables which may be formed via interactions between the formulation and the packaging or processing materials. Obviously, the analytical methods and time taken for data processing are guided by the implementation of targeted versus non-targeted studies. Analytical methods are generally more complex due to the presence of other, potentially interfering, compounds which may be present in the drug product.

The implementation of leachables studies may not always be possible due to the time taken and/or the availability of samples (which may be required for stability storage under various conditions of temperature and humidity, for example).

Pharmacopeial Compliance



Pros

- Informs both severity of harm and probability of occurrence
- Data supports multiple projects

Cons

- Numerous tests to consider
- Large amount of data to evaluate
- Requires diverse technical expertise
- Depending on what tests have been performed further studies may be required especially if a minimal number of tests have been performed

The data derived from the various studies that make up the pharmacopeial chapters can either give us a better understanding of severity of harm and/or probability of occurrence. Generally, these studies aren't project specific, so the data produced supports multiple projects.

As there are numerous tests to consider, a diverse range of expertise is needed to generate and evaluate the data.

Due to the varying nature of the different tests within each pharmacopeia, not all of them give information on both severity of harm or probability of occurrence. As such, it is worthwhile examining each in a little more detail in order to better understand the information that might be derived from the suggested testing.

USP<661>	USP<661.1>	Draft USP<665>	USP<661.2>
• Identity (IR & DSC) • Heavy Metals • Food Additives • NVR • Resin Specific Tests • Biocompatibility (In Vitro/In Vivo) • Buffering Capacity	• Identity (IR & DSC) • Biocompatibility (In Vitro/In Vivo) • Extractable Metals • Physicochemical Tests (UV, TOC & Acidity/Alkalinity) • Resin Specific Tests • Food Additives / Plastic Additives	• Materials/ Component comply with 661.1 • Biocompatibility (In Vitro/In Vivo) • Extractable Metals • Organic Extractable • Profile and Tox Assessment	• Materials/ Component comply with 661.1 • Biocompatibility (In Vitro/In Vivo) • Physicochemical Tests (UV, TOC & Acidity/Alkalinity) • Chemical Safety Assessment (E&L and Tox Assessment)

USP<661>

Not specific to single use components (SuC) but we have seen components which claim to be compliant with USP<661>. Even though this white paper is focused on single use systems, container closure material changes also occur. Therefore, the principles discussed are also applicable.
There are some resin specific tests for polyethylene, polypropylene, polyethylene terephthalate, and polyethylene terephthalate G
USP<87>/<88> is required for high risk products (e.g. inhalation, parenteral and ophthalmic)
Buffering capacity - for liquid containers
Thermal analysis by differential scanning calorimetry (DSC)
In general, this chapter informs severity of harm, especially if USP<87>/<88> data is generated.

USP<661.1>

New 661 requirements won't come into force until May 2020; however, materials should be tested via this chapter prior to implementation.
Testing is performed on materials that make a component.
USP <88> and plastic additives are required for high-risk products (e.g. inhalation, parenteral and ophthalmics).
There are resin specific tests for polyethylene, cyclic olefins, polypropylene, polyethylene terephthalate, polyethylene terephthalate G, and plasticized polyvinyl chloride.
Plastic additives - phenolic antioxidants, nonphenolic antioxidants, copolymer of dimethyl succinate, and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol, amides, and stearates
Thermal analysis by differential scanning calorimetry (DSC)
Again this chapter informs severity of harm as the tests are designed to characterise the input materials used in a component.

Draft USP<665>

For components to comply with 665 they or their materials of construction must also comply with 661.1.
Additionally, components are tested via USP<87>/<88>, extractable metals and organic extractable profile depending on how the components are used in the manufacturing process.
As well as informing severity of harm, this chapter begins to inform probability of occurrence through the organic extractable profile test.

USP<661.2>

Again 661.2 isn't specific to SuC.
For components to comply with 661.2 they must also comply with USP<661.1>.
Additionally, components are tested via USP<87>/<88>, physiochemical tests, and chemical safety assessment — depending on the route of administration. New 661 requirements won't come into force until May 2020; however, companies are starting to comply to this chapter.
Like the draft USP<665> this chapter informs 'severity of harm' and, depending on the other studies, can inform 'probability of occurrence' through the chemical safety assessment.

[1] https://www.uspnf.com/

Risk Evaluation

As has been highlighted, not all studies are created equal and the data produced informs us about different aspects of risk associated with material changes — especially when assessing probability of occurrence and severity of harm. So, we can categorise data from different studies based on how well they inform us of these two critical aspects and, as a result, the value we give different data when assessing a material.

An example of how one might weight different information which informs severity of harm or probability of occurrence is shown in Table 1. Studies and information at the bottom of the table provide less (or less useful) information than those at the top of the table with respect to the probability of occurrence or severity of harm of a component.

This list is ordered based on the risk to patient safety and may be re-ordered if considering the risk to product quality or one's ability to sell a product in a particular geography or legislative region.

It should also be pointed out that this is OUR OPINION, and others may have a differing opinion with regard to the usefulness of the information (hence our earlier comments regarding the subjective nature and difficulty of assessing risk associated with material change).

Table 1: Information 'Value' from a Variety of Testing Types

Severity of Harm (multi–project qualitative data)	Probability of Occurrence (project specific quantitative data)
Controlled Extraction Studies and toxicity assessment	Leachable Studies
Pharmacopeial Compliance (USP<665>, USP<661.2>)	Simulation Studies (e.g. USP<665>, BPOG)
Biocompatibility (USP<88>, USP<87>, ISO 10993) or Pharmacopeial Compliance (USP<661.1> on component)	Previous experience or Process knowledge or TOC
Food Compliance or Pharmacopeial Compliance (USP<661> and USP<661.1> on material)	
Material Formulation	
REACH Compliance or Physiochemical Tests	
Absence Statements or Identity tests	Controlled Extraction Studies or NVR

Note: we have assumed that all tests required by the pharmacopeial chapters for high risk routes of administration and use have been completed and that the usefulness of some studies will depend on how appropriate the conditions are to in-use conditions in reality.

Combining information from multiple studies will allow us to make more informed decisions on probability of occurrence or severity of harm. For example; in isolation, data from biocompatibility studies are not placed at the top of the Table 1 as they may not be closely comparable to the effects in human subjects. When combined with other studies, however, they are better able to inform severity of harm. Absence statements are at the bottom of the list because they tell us what is NOT in the component rather than what MAY be present as a potential extractable or leachable. Simulation studies may give a close approximation of what might leach into the product but will not truly mimic the leaching process, let alone identify drug and material interactions.

Summary

The assessment of extractables and leachables to inform the risk of material change should never be a tick box exercise. It should be informed by various appropriate studies and sources of information.

We have described how information available from various sources can help to build an informed risk management decision based on probability of occurrence and severity of harm. If this information isn't available, the approach described helps to pinpoint what testing should be performed to determine the risk from a given material. As well as helping with information gathering, risk assessment (via failure mode effects Analysis (FMEA)) helps to identify gaps in knowledge and is a structured method of documenting the rationale for the E&L testing strategy.

No single study or information source is likely to give us enough information to properly qualify the risk from a material or component and data from several appropriate sources or studies will need to be considered holistically in order to make appropriately informed decisions.

Finally, it is important to state that if the data has not been generated in-house then the conditions used in each of the studies will need to be understood in order to fully understand its applicability to your in-use situation.

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Specialists in extractables and leachables

Our vast experience helps you:

- Devise the best E&L strategy for your product
- Tailor E&L testing strategies for complex devices/processes using FMEA risk assessments
- Design the most appropriate extractable or leachable studies, aligned to relevant guidelines, using a range of techniques including, but not limited to - GC-MS, LC-DAD-HRMS and ICP-MS
- Develop and validate extractable and leachable methods
- Form structural elucidation of unknowns
- Perform toxicological assessments (through 3rd party partner) of data
- E&L regulatory support - including authoring of appropriate sections and responding to regulatory questions
- Bespoke studies designed to support material selection, patient safety, product quality and change/lifecycle management

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