PART A

GENERAL CONCEPTS
1

INTRODUCTION

GENERAL DISCUSSION

Materials such as plastics, glasses, and metals, are widely used in medical constructs, for example, containers, packaging systems, sets, transfer and transport systems, manufacturing systems–facilities, and devices. The physiochemical nature of these materials provides medical products with their necessary and desirable performance characteristics. A number of medical products involve constructs (objects constructed in whole or in part from materials) whose primary purpose is the generation, production, transport, storage, and/or delivery of therapeutic products that are used either directly or indirectly by patients to produce a desirable therapeutic outcome. Additionally, such constructs may be used for the same purposes with precursors of the therapeutic product. Less frequently, such constructs themselves may provide the therapeutic benefit.

While an important performance characteristic of materials (or systems) used in medical applications is chemical inertness, interactions between a material (or system) and the pharmaceutical product it contacts are well documented. Such interactions may include sorption (binding), the uptake of product components by the material, or
leaching the release of material-related components to the product (Fig. 1.1). Instances in which such an interaction can impact the therapeutic product, from either an efficacy and/or safety perspective, also have been reported. As a recent example, the leaching of a vulcanizing agent from uncoated stoppers used in prefilled syringes has been proposed as a mechanism contributing to adverse clinical events associated with EPREX®.\textsuperscript{1} Other recent examples of leachables exerting an undesirable influence on therapeutic products have also been documented.\textsuperscript{2,3} These recent examples augment a long history of instances where the safety or efficacy of a therapeutic product has been compromised by its interaction with a construct.

As outlined in relevant regulatory policies, procedures, and guidelines, any contact between a construct and therapeutic substance, which may or may not be a finished drug product, is an opportunity for that substance to be changed as a result of that contact. The purpose of a construct’s compatibility evaluation is to assess the magnitude, if any, of such a change. By convention, if little or no change occurs, then it is concluded that the construct and the therapeutic substance are compatible. A complete compatibility assessment considers numerous potential outcomes of the construct–substance interaction, as illustrated

\textbf{Fig. 1.1.} Interactions between a therapeutic product and a material (plastic) phase. Such interactions include leaching, the migration of material-related components into the product, and binding the sorption of product ingredients by the material. Both processes impact the drug product’s final composition at its time of use and thus its safety and/or efficacy. \textit{Note:} the arrows denote the direction of solute movement. The oval represents a solute molecule, which can end up in either phase at equilibrium.
in Fig. 1.2. In the most general sense, specific aspects of a compatibility assessment address either the issues of a therapeutic substance’s efficacy (does the substance perform in a manner consistent with its labeling and indication) or substance safety (does the substance produce an unanticipated and adverse user response). Considering efficacy, while drug binding (loss of ingredient from the substance due to the ingredient’s uptake by a plastic construct) is the most typically documented efficacy-impacting interaction, other types of interactions are possible and significant. For example, cross-reactivity refers to the situation in which a specific entity, leached from the construct, and a substance’s ingredient interact chemically, resulting in the ingredient’s decomposition and/or inactivation. This interaction may be direct or indirect, for example, via a catalytic action. Additionally, note that efficacy does not solely reflect a substance’s ability to deliver its specified therapeutic dose. Secondary effects reflect those instances where a property of the leached entity itself has an impact on the chemical or physical characteristics of the therapeutic substance. Examples of such secondary effects include (1) an acidic or basic leachable whose accumulation pushes a substance outside of its pH specification; (2) a leachable that either directly or indirectly causes the formation of particulate matter, and (3) a leachable whose accumulation has an adverse esthetic effect [e.g., discoloration, high ultraviolet (UV) absorbance]. In the extreme situation, the secondary effect may not be manifested in an undesirable therapeutic substance, for example, a finished drug product, but rather as an undesirable construct, which may lose its ability to perform its desired function due to the construct–substance interaction.

Also note that the accumulation of leached substances in a therapeutic substance can have ramifications outside of the context of the substance’s performance. For example, leached entities can complicate
substance analysis by producing analytical responses (e.g., chromatographic peaks) that either directly interfere with targeted analyte quantitation or indirectly complicate the interpretation of the analytical information.

While a complete compatibility assessment includes a consideration of therapeutic substance aspects other than safety, such considerations are beyond the scope of this book and are not considered in great detail herein (however, see Chapter 12 for a brief discussion of suitability for use aspects other than safety). Rather, the remainder of this book deals with the questions of (1) How does the leaching of substances from constructs impact the safety of a therapeutic substance, for example, a finished drug product and, more specifically; (2) How does one ascertain the magnitude of the impact? Compatibility assessments that deal with these questions are called safety assessments.

**KEY DEFINITIONS**

**The Interacting Parties**

The number of different pharmaceutical circumstances in which two entities come in contact, one of which is either directly or indirectly used to produce a favorable therapeutic outcome and the other of which is used to facilitate the generation, transport, or storage of the first, is enormous. The scale and diversity of the pharmaceutical universe creates difficulties in terms of establishing terms that can be used to generically describe interactions that arise when two entities contact one another. For example, a well-recognized entity-to-entity couple in the pharmaceutical universe is a drug product and its associated packaging system. Clearly, a drug product and its packaging system can interact; however, it is not accurate to state that all pharmaceutically relevant interactions only occur between drug products and their packaging system. What about drug products that are administered via tubing sets? What about solutions, which may be either the drug product itself or an associated precursor, whose processing includes filtration? What about contact between a production batch and its associated manufacturing apparatus (e.g., tanks or single use systems)? What about drugs products that can be solid, liquid, or gas? What about packaging systems that may consist of plastics, glasses, metals, or combinations thereof?

There is considerable value in developing a nomenclature that deals with the general case, as opposed to individual specific cases. Such a
vernacular is based on the observation that any contact minimally involves two potentially interacting parties. In the pharmaceutical universe, one of the interacting parties is utilized to produce a favorable therapeutic outcome. The second interacting party is used, in one manner or another, to facilitate the generation or utilization of the party that provides the therapeutic benefit. Generic definitions for these parties are as follows:

**Therapeutic Substance:** A material (solid, liquid, or gas) that is used to produce a therapeutic benefit. A primary therapeutic substance is one whose use directly produces the therapeutic benefit. A secondary therapeutic substance serves as a precursor to the primary therapeutic substance. A secondary therapeutic substance is a substance that is either used and discarded to make a primary therapeutic substance and/or is further processed to produce the primary therapeutic substance. Thus, for example, a finished biopharmaceutical drug product would be a primary therapeutic substance while the growth medium in which the biopharmaceutical agent is generated is a secondary therapeutic substance.

**Construct:** An entity that is contacted by a therapeutic substance at some time during that substance’s lifecycle, which may include the substance’s synthesis, formulation, production, storage, or delivery. The contact between a construct and a therapeutic substance is typically associated with the product’s generation, storage, transport, or use.

While such a terminology offers the advantage of universal application, it is awkward in the sense that it falls well outside of common usage. To facilitate its interpretation, examples of therapeutic substances and their associated constructs are provided in Table 1.1.

**Extractables versus Leachables**

It is not uncommon to encounter the terms extractables and leachables in the context of drug compatibility assessments. Both terms are used to describe substances that migrate out of a construct when the construct is contacted with an extracting medium. While exact definitions of extractables and leachables vary slightly among the various resources that provide such definitions, these definitions all establish the same fundamental difference between these two separate, but closely related, concepts. More specifically, these terms are defined as follows:
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Leachables: Substances that are present in the primary therapeutic substance because of its interaction with a material or construct during its intended use (including production, storage transport, and/or delivery).

With this definition of leachables as our foundation, the definition of extractables is straightforward. Generally, any potential migrant is an extractable. More specifically, the following definition is given:

Extractables: Substances that can be extracted from a material or construct using extraction solvents and/or extraction conditions that are expected to be at least as aggressive as the conditions of contact between the material (or construct) and a primary therapeutic substance.

Table 1.2 is provided to further clarify the difference between these two related classes of entities and provides guidance in terms of properly linking the correct term with specific study parameters. Relevant study parameters (dimensions) include the test article (the object that is extracted), the contact medium, and contact conditions. For example, the test article extracted in an extractables–leachables evaluation can be a specific raw material, a component of a construct or the actual construct itself. The contact medium can either be a solvent or a primary or secondary therapeutic substance (or a fully justified simulation thereof). The contact conditions can either be the total product use (or a fully justified simulation thereof) or conditions that exaggerate or accelerate total product use. The combination of these three parameters determines whether the entity that is being tested for is correctly termed an extractable or a leachable. As noted in Table 1.2 and

<table>
<thead>
<tr>
<th>Therapeutic Substance</th>
<th>Construct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form (solid, liquid, or gas)</td>
<td>Packaging system (bags, vials, syringes, bottles, or canisters)</td>
</tr>
<tr>
<td>Dosage form (liquid or gas)</td>
<td>Transfer tubing sets</td>
</tr>
<tr>
<td>Process reagents (growth media or buffers)</td>
<td>Sterilizing filters</td>
</tr>
<tr>
<td>Production batches</td>
<td>Manufacturing equipment (tanks or single-use system)</td>
</tr>
<tr>
<td>Process solutions (chromatographic eluents, or cleaning agents)</td>
<td>Manufacturing equipment (tubing or gaskets)</td>
</tr>
<tr>
<td>In-process intermediates</td>
<td>Storage–transport containers</td>
</tr>
<tr>
<td>Drug compound</td>
<td>Drug-eluting stent</td>
</tr>
</tbody>
</table>

TABLE 1.1. Examples of Constructs and Therapeutic Substances
<table>
<thead>
<tr>
<th>Test Conditions</th>
<th>Classification of Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material of construction (raw material or resin)</td>
<td>Secondary therapeutic substance&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Primary therapeutic substance&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Construct component (part, film, or assembly)</td>
<td>Solvent</td>
</tr>
<tr>
<td></td>
<td>Secondary therapeutic substance&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Primary therapeutic substance&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Finished construct</td>
<td>Solvent</td>
</tr>
<tr>
<td></td>
<td>Secondary therapeutic substance&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Primary therapeutic substance&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>See Ref. 4.

<sup>b</sup>Or a fully justified simulation thereof. The primary therapeutic substance is the substance whose use provides the therapeutic benefit.

<sup>c</sup>Total substance use is equal to all the activities that the coupled therapeutic substance and material experience during their contact, which could include manufacturing, processing, storage, and utilization.

<sup>d</sup>A secondary therapeutic substance is a substance that is either used and discarded to make a primary therapeutic substance or is further processed to produce the primary therapeutic substance.

<sup>e</sup>Marginal designation. There is a strong tendency to want to call these substances leachables.

suggested by the previous definition, a leachable arises only under one single set of parameters, of the 18 possible combinations, that include the critical aspects of a finished system being tested with the drug product under conditions of total product use. Rigorously speaking, the entities examined under all other parameter combinations are correctly termed extractables. Because two additional sets of parameters possess
two of the three critical aspects of a leachable, one may be tempted to
call the relevant entity a leachable. However, it is important that such
a mistake be avoided because leachables are, by strict definition and
practical necessity, properties of the therapeutic product. Extractables,
on the other hand, are properties of the construct.

The distinction between a primary and secondary therapeutic sub-
stance is very clear and illustrates the very rigorous definition of a
leachable. By definition, a secondary therapeutic substance is further
processed to generate the primary therapeutic substance whose use
provides the therapeutic benefit. For example, a bulk concentrate may
be generated via a process that includes its contacting a plastic material.
This bulk concentrate is then further processed (filtration, fraction-
ation, etc.) into an active pharmaceutical ingredient (API). This API
is further processed (e.g., formulated) into a finished drug product that
is the actual entity delivered to a patient. In this case, the bulk concen-
trate and the API are secondary therapeutic substances and the fin-
ished drug product is a primary therapeutic substance. In the general
sense, and without experimental evidence, the impact that the process-
ing of the concentrate and the API has on whether extractables in the
secondary therapeutic substance translate into leachables in the primary
therapeutic substance, is unknown. It is this uncertainty that makes it
appropriate that substances, which are present in secondary therapeu-
tic substances due to contact with a construct, are called extractables
and not leachables.

The distinction between leachables and extractables is not just a
matter of semantics, but rather reflects the need for, and utilization of,
information unique to both the construct and the therapeutic sub-
stance. Because there is some uncertainty associated with these terms,
it is possible to find oneself in the situation that one has either obtained
incomplete information and/or has used information inappropriately.
Two examples of such situations, extractables = ingredients and extract-
ables = leachables, are considered as follows:

*Extractables = Ingredients:* An investigator who has received a list
of material or construct ingredients from the construct’s sup-
plier has obtained potentially useful and relevant information.
However, the investigator must not conclude that such a list of
ingredients is in fact the same as a full and complete extractables
assessment because extractables may be unintentionally present
in a system. In addition to intentionally added ingredients, extract-
ables may arise as processing aids, process contaminants, ingredi-
ent contaminants and impurities (known and unknown), and
process-induced decomposition or reaction products of ingredients. Given such circumstances, a list of ingredients alone generally does not constitute a full and complete extractables assessment. While a list of ingredients is a useful starting point for an extractables assessment, a complete and comprehensive extractables assessment (i.e., the identification of all potentially extractable substances) can only be obtained by testing fully processed materials, components, and/or constructs.

**Leachables = Extractables:** An investigator who possesses a full and complete extractables assessment might be tempted to use that assessment to establish the safety, efficacy, and/or compliance of a primary therapeutic substance, for example, a finished drug product. While there may be circumstances where such an extrapolation is appropriate, such circumstances must be justified and not just taken on blind faith for two reasons. First, the chemical conversion of extractables under conditions of contact with therapeutic substances is well known and documented in the literature. Thus, for example, if an antioxidant present in a material or construct is oxidized during contact with a finished drug product, the more soluble oxidation product may accumulate in the drug product (and thus is the leachable) and not the extractable antioxidant. This circumstance is illustrated in Fig. 1.3. In such a circumstance, an assessment based on extractables would “miss the target” because the extractables themselves do not actually accumulate in the finished drug product. Second, an assessment based on extractables and their levels in extracts (or their total pool) may deal with a significantly overstated case because extractables, by their very nature and function in the containment system, may not be fully soluble in, or may not fully partition into, the finished drug product. Thus a final drug product, deemed to be unsafe, subpotent, or noncompliant, based on extractables information may actually be perfectly safe, effective, and compliant. While issues of leachables and extractables are appropriately and necessarily approached with caution and a conservative nature, rejecting an acceptable therapeutic substance, for example, a finished drug product, is not a desirable outcome of an extractables–leachables assessment.

The subtle differences between, and nuances associated with, extractables and leachables can be confusing and unclear. To clarify somewhat, consider an analogy between extractables and leachables and situation of the bogeyman hiding in the closet. Certainly, it is the case
Irganox 1076 (3,5-bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid, octadecyl ester); [2082-79-3], C_{35}H_{62}O_{3}, formula weight = 530.86.

![Chemical Structure of Irganox 1076](image)

Related Substance No.1, (3,5-bis(1,1-dimethylethyl)-4-hydroxy-benzenepropanoic acid); [20170-32-5], C_{17}H_{26}O_{3}, formula weight = 278.39.

![Chemical Structure of Related Substance No.1](image)

Related Substance No.2, (3,5-bis(1,1-dimethylethyl)-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-propanoic acid); [83237-15-4], C_{17}H_{26}O_{4}, formula weight = 294.39.

![Chemical Structure of Related Substance No.2](image)

Fig. 1.3. Extractables vs. leachables; Irganox 1076 (extractable) and related hydrolysis products (leachables). Extractables present in the material may not migrate into the drug product for solubility or compatibility reasons and thus are not both extractables and leachables. However, the more soluble degradation products of the extractable can accumulate in the drug product and thus are correctly termed leachables.\(^5\)

that most people would want to know that there is a bogeyman (extractable) hiding in their closet (construct). For example, one might want to be sure that they do not go into the closet so that they do not have to face the bogeyman (akin to not using the construct because of an extractable). Alternatively, they might want to put a lock on the closet to keep the bogeyman from getting out (akin to coating a construct
with a migration barrier). Finally, a person might want to consider getting help in exorcising the bogeyman from the closet so that the threat goes away (akin to processing the extractable out of the construct).

In the final analysis, however, it is possible that all the worry and activity related to the bogeyman in the closet is unnecessary. After all, the bogeyman is no real threat as long as he stays in the closet (and as long as you stay out of the closet). It is only if or when he comes out of the closet (and becomes a leachable) that we have to worry about him “getting” us.

Continuing the analogy further, most people would want to know a few things about the bogeyman in order to deal with him properly. It is not necessarily the case that the bogeyman is a real or major threat. Maybe it is only a little bogeyman and we can handle him ourselves. Maybe the bogeyman hates the light and only comes out at night. Maybe, like the movie Monsters, Inc., it is really not a bogeyman at, all but just something that is “misunderstood”. If we do not know anything about the bogeyman, it is likely that we will either under- or overestimate him or even be paralyzed by our fear of the unknown. However, if we can get some information about the bogeyman, we can analyze the threat and estimate the true risk. If the risk is small enough, maybe we let the bogeyman out and just monitor his behavior.

The role of these two independent, but related, compound populations in the various phases of safety assessment will be considered in greater detail in subsequent chapters.

REGULATORY PERSPECTIVES FOR PERFORMING COMPATIBILITY AND/OR SAFETY ASSESSMENTS

The generation of safe and effective therapeutic substances and products is an obligation for companies in the pharmaceutical market. Such an obligation directly translates to organizations that generate therapeutic products that contact, at some stage in their generation, a construct. Nevertheless, it is one thing for a company to acknowledge that, “we must generate a safe product” and another thing altogether for that company to understand the process by which a product is demonstrated to be safe. It is one thing to say that “our product meets our own internally developed standards for safety” and another thing altogether to have the product declared to be safe based on an independent, scientifically rigorous and unbiased analysis of the safety assessment process and outcome. As a fundamental role of a
government is the protection of its people, it is necessarily the case that
the requirements for compatibility assessments are contained within
the context of laws, legislation and associated regulations, and that such
laws, legislation and regulations are upheld and enforced by appropri-
ate governmental authorities. In order to facilitate compliance with the
regulations, such government authorities publish and enforce guide-
lines, provide guidance, or generate standards for industry participants.
Relevant regulatory guidance in terms of such assessments is consid-
ered as follows.

The U.S. Food and Drug Administration Guidance for Industry:
Container Closure Systems for Packaging Human Drugs
and Biologics

The Federal Food, Drug and Cosmetic Act (the Act) mandates the
need for adequate information related to packaging materials. Section
501 (a)(3) of the Act states that a drug is deemed to be adulterated
“if its container is composed, in whole or in part, of any poisonous or
deleterious substance that may render the contents injurious to health
…”. In response to this Mandate, the U.S. Food and Drug Administration
(FDA) published its “Guidance for Industry: Container Closure
Systems for Packaging of Human Drugs and Biologics” in 1999.6 This
document is intended to provide guidance on general principles
for submitting information on packaging materials used for human
drugs and biologics. In general, that Guidance does not suggest specific
test methods and acceptance criteria, nor does it suggest comprehen-
sive lists of tests. Rather, it suggests that such details should be deter-
mined based on good scientific principles. The Guidance specifies that
every packaging system should be shown to be suitable for its intended
use, where suitability includes the expectations that (1) the system
should be composed of materials that are considered safe for use with
the dosage form and route of administration and (2) packaging com-
ponents will not interact sufficiently to cause unacceptable changes in
the quality of either the dosage form or the packaging component. The
guidance notes that packaging components should be constructed of
materials that will not leach harmful or undesirable amounts of sub-
stances to which the patient will be exposed when being treated with
the drug product. Consistent with this Guidance, comprehensive
assessment is appropriate for injection, inhalation, ophthalmic, or
transdermal drug products. Such an assessment involves two parts: an
extraction study on the packaging component to determine which
chemical species may migrate into the dosage form (and at what con-
centration); and a toxicological evaluation of those substances that are
extracted to determine the safe level of exposure via the label specified route of administration.

The container closure guidance contains the following definitions for establishing its scope.

*Materials of Construction:* Substances [e.g., glass, high-density polyethylene (HDPE) resin, metal] used to manufacture a packaging component.

*Packaging Component:* Any single part of a container closure system. Typical components are containers (e.g., ampoules, vials, or bottles), container liners (e.g., tube liners), closures (e.g., screw caps or stoppers), closure liners, stopper overseals, container inner-seals, administration ports [e.g., on large-volume parenterals (LVPs)], overwraps, administration accessories, and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

*Container Closure System:* The sum of packaging components that together contain and protect the dosage form, which includes primary and secondary packaging components. A packaging system is equivalent to a container closure system.

**European Medicines Agency (EMEA) Guideline on Plastic Immediate Packaging Materials**

This Guideline addresses the information that must be submitted in marketing authorization applications for plastic materials being used as immediate packaging for active substances and medicinal products. As outlined in its Scope, the Guideline is limited to plastic immediate packaging materials that are intended to be in direct contact with the active substance or medicinal product, including the container, the closure or seal, and other parts of the system. The Guideline specifically excludes elastomers and natural and synthetic rubbers from its Scope.

Considering extractables–leachables, the directives of the EMEA Guideline fall into four broad categories: (1) Section 3.2, Specifications; (2) Section 4, Extraction Studies; (3) Section 5, Interaction Studies and specifically 5.1, Migration Studies; and (4) Section 6, Toxicological Information–Documentation. An analysis of each section is as follows:
Section 3.2, Specifications: The requirements of this section are straightforward. Quoting directly from the Guideline,

... (for plastic packaging materials) reference should be made to the appropriate monographs of the European Pharmacopoeia or the monograph of the pharmacopoeia of a Member State. When referring to a monograph, compliance should be demonstrated.

If the plastic material is not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State, an in-house monograph has to be established according to the list below, taking into account the general methods of the pharmacopoeia ...

The issue of compliance to the pharmacopoeia is central to the EMEA strategy for qualifying immediate packaging materials and such compliance represents significantly more than just a matter of fulfilling the specification requirement. Considering extraction studies, for example, the Guideline notes that extraction studies are considered to be necessary “... if the material is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a member state, nor has been approved for food stuff packaging”. The implication here is that if the materials are covered by and demonstrated to comply with a relevant EP monograph and have been approved for foodstuff packaging, then extraction studies are not necessary.

Similarly, the Guideline states in Section 6, Toxicological Information/Documentation, that “if the plastic material or additives used are described in the European Pharmacopoeia, the pharmacopoeia of a member state or have been approved for use in food packaging, toxicological data may not be required”.

Thus, note that compliance with a relevant Pharmacopoeia monograph is a prime consideration in the development of an extractables–leachables strategy and that such compliance can greatly focus and simplify such a strategy. However, also note that compliance with a relevant Pharmacopoeia monograph is not, in of itself, an acceptably complete and rigorous extractables–leachables strategy. This juxtaposition is considered in greater detail in Chapter 3.

Section 4, Extraction Studies: The aim of the extraction study is to determine those additives in the material that might be extracted by the preparation or the active substance in contact with the material. The studies typically involve “exposing ... the material to an appropriate solvent system under stress conditions to increase the rate of extraction”. While the preferred extraction solvent for
a medicinal product is the product itself or a placebo vehicle, this is not a requirement and the specific direction of the Guideline is that the extraction solvent used should have the same propensity to extract substances as the active substance–dosage as appropriate.

Section 5.0, Interaction Studies: “In order to evaluate the suitability of the selected plastic packaging material for the intended use, the compatibility of the material with the active substance or medicinal product should be demonstrated.” Interaction studies, whose purpose is to demonstrate the compatibility of the material with the active substance or medicinal product, include migration studies, and sorption studies. Migration studies should demonstrate that substances do not migrate from the material under conditions representative for the intended use in such quantities as to alter the efficacy and stability of the active substance–medicinal product or to present a toxicological risk. Sorption studies address the possibility that product quality might be altered by sorption of an active substance or excipient by the packaging material.

Section 5.1, Migration Studies: The Guideline is very clear that migrations studies are a required component of the data to be provided in product registration files. Migration studies must be performed regardless of whether the materials comply with an existing pharmacopeial monograph or not. The only two circumstances that preclude migration studies are based on the outcome of extractions studies and include (1) the circumstance in which no extracted substances are identified in the Extraction Study and (2) the circumstance in which the calculated maximum amount of individual extracted substances that may be present in the active substance–medicinal product can be demonstrated to be toxicologically safe. In either circumstance, the decision not to perform migration studies needs to be justified.

Migration studies are very clearly identified as an activity to take place during the development stage of the medical product. The implication here is that monitoring of leachables during stability studies is not a requirement of this Guideline. However, if migration studies are not performed during product development then the Guideline clearly states that leachables should be monitored during formal stability studies, conducted under normal, and accelerated storage conditions.

The purpose of the migration study is to demonstrate that substances will not migrate in such quantities as to alter the efficacy
and stability of the active substance–medicinal product or to present a toxicological risk. The Guideline is very specific in terms of many aspects of migration studies, including the following: (1) the studies are necessary if extractions studies have resulted in one or several extractables; (2) the studies should be performed under conditions representative for the intended use; (3) the studies will be performed on at least one batch of the active substance–medicinal product; (4) the studies must be performed with the active substance–medicinal product, and studies performed with other test media will only be considered to provide preliminary information; (5) analytical methods used need to be either compendial methods or validated methods; (6) if the plastic material is composed of layers of different plastic materials, the possibility of migration of components from external layers to the medicinal product must be evaluated; and (7) it must be demonstrated that no components of agents applied to the outer surface of the container–closure system (e.g., adhesives or inks) will migrate into the medicinal product. Despite this clarity on the strategic levels, the EMEA Guideline does not provide tactical information, for example, specific test procedures, methods, process, or techniques.

Section 6, Toxicological Information–Documentation: The Guideline requires that toxicological data be provided for extractables and leachables, depending on their level and chemical structure. Exceptions for materials complying with pharmacopeial Monographs have been previously noted. For noncompendial materials, toxicological information is required, even if the material under consideration has been approved for use in food packaging. The Guideline provides no specific guidance in terms of how such a toxicological assessment is to be performed.

Decision Tree. A Decision Tree that defines the extent of testing required is supplied as Appendix II in the Guideline. Portions of that Decision Tree that are relevant for common nonsolid dosage forms are reproduced in Fig. 1.4.

FDA Guidance for Industry, Inhalation Products

In its Container Closure Guidance, the FDA identifies inhalation products as having the highest degree of concern with respect to potential container product interactions due to the route of administration and
REGULATORY PERSPECTIVES FOR PERFORMING COMPATIBILITY

For inhalation, parenteral, and ophthalmic administration

Nonsolid dosage forms

Material described in Ph.Eur. or in the pharmacopoeia of a Member State?

Yes

* General information (3.1)
* Specification (3.2)
* Interaction studies (5)

No

* General information (3.1)
* Specification (3.2)
* Extraction studies (4)
* Interaction studies (5)
* Toxicological information (6)

Fig. 1.4. Partial decision tree on the presentation of the documentation of plastic packaging materials. The decision tree establishes the information that must be included in a product’s registration dossier.7

the likelihood that an interaction will occur. Accordingly, FDA has provided Guidance for these types of products. Inhalers are addressed in the FDA Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder (DPI) Drug Products, Chemistry, Manufacturing and Controls Documentation,8 and nasal spray and inhalation suspensions are covered in the Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products—Chemistry, Manufacturing and Controls Documentation.9 Considering the level of concern associated with such products, FDA advises that “For safety considerations, materials (container closure) should be chosen that minimize leachables without compromising the integrity or performance of the drug product”. Central to both Guidance documents are the concepts of independent, but related, extraction and leaching studies. Quantitative controlled extraction studies are performed to characterize the container closure system by establishing its extractables profile. Such controlled extraction studies must include specified and justified extraction and
analyses processes (multiple appropriate solvents and methods recommended). The resulting information forms the basis of a toxicological assessment of the extractable’s product impact and serves to support acceptance criteria for container closure components.

Routine extraction studies, including discriminatory and validated test methods and appropriate and justified acceptance criteria, are used for the routine testing of incoming components of the container-closure system. Both Guidance documents note that a reduced acceptance testing schedule may be considered once the applicant establishes the reliability of the supplier’s test results and has tested multiple incoming batches.

In addition to a characterization of the container-closure system itself, both Guidance documents require the generation of leachables data (identity and accumulation) representative of the finished drug product through the end of its shelf-life. Such a leachables assessment includes not only the generation of leachables data using validated analytical methods, but also the interpretation of the data in terms of established and justified acceptance criteria. Correlating the leachables and extractables data is recommended as such a correlation may obviate the need to do leachables testing in future routine stability studies.

Medical Devices

The Association for the Advancement of Medical Instruments (AAMI), in collaboration with the International Organization for Standardization (ISO), has produced a series of guidance documents (ISO 10993 series), which address the biological evaluation of medical devices. Included in the “biological” assessment is the generation and toxicological interpretation of extractables–leachables information. Document 10993-1 (guidance on selection of tests),\(^\text{10}\) provides a useful mechanism for the categorization of medical devices. This categorization strategy, based on the nature and the duration of contact, establishes the rigor with which the device (or, most commonly, extracts thereof) is to be tested both biologically (clearly specified in the ISO 10993-1 document) and chemically (inferred through ISO 10993-1 and other members of the ISO 10993 series). Other members of the ISO 10993-series that specifically relate to the chemical aspects of a leachables assessment include ISO 10993-12, Sample preparation and reference materials;\(^\text{11}\) ISO 10993-17, Establishment of allowable limits for leachables substances;\(^\text{12}\) and ISO 10993-18, Chemical characterization of materials.\(^\text{13}\)
AN OVERVIEW OF STRATEGIES FOR PERFORMING SAFETY ASSESSMENTS

In the simplest and most general sense, the demonstration of compatibility requires testing of the construct, either by itself and/or during contact with a therapeutic product. Direct testing of the therapeutic product–construct couple to establish compatibility in general and safety in particular could be accomplished in the clinical setting via appropriate clinical trials. In fact, the FDA Container Closure Guidance notes that “for drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety”. However, such a direct approach is rarely taken without some type of prior indirect testing because of the costs, complexity, uncertainty, and risks associated with clinical testing. Simply stated, the earlier in the development process that a therapeutic product–construct interaction is identified, the less expensive (in terms of time and resources) is the process of addressing such an interaction. As the relevant clinical testing typically occurs in the later stages of the product development process, considerable resources have been spent to get to that stage of testing. Discovery of a product-construct incompatibility (safety) issue at such a late stage in the product development process would result in the potential loss of a considerable amount of value added.

Thus most safety assessments for product-construct compatibility are indirect in nature. That is, the construct is tested in a manner or by a process that simulates, approximates, or estimates the clinical outcome. For example, the construct (or an extract there of) may be tested by in vivo or in vitro biological methodologies that seek to mimic or recreate the clinical response. Such testing is termed biological testing and is outlined in various standards, for example, the ISO 10993-series and USP <87> and <88>. Such testing is not based on a characterization of the construct, but rather on the construct’s ability to illicit a biological response under rigorously defined test conditions. Alternatively, extracts of the construct can be fully and completely characterized in the sense that their composition is established both qualitatively (identification) and quantitatively (concentration). The safety impact of the extracted substances is estimated by correlating the identity, concentration, and ultimately dose information with available substance-specific toxicological data. As such an approach involves chemical analyses to establish identities and concentrations, it is commonly referred to as chemical testing.
It is inappropriate to consider biological and chemical testing as mutually exclusive or competing. Both approaches have their conceptual and practical strengths and shortcomings and it is generally recognized that neither approach alone unilaterally provides the required level of risk management. The chemical assessment process, while based on quantitative data of known (or knowable) quality and integrity, is hampered by the many approximations and assumptions that are utilized in the interpretation phase of such assessments. As it is rare that exactly relevant and applicable toxicological data exists for a particular circumstance, the toxicological assessments contain multiple factors that account for variables, for example, differing species and differing routes of administration. Thus while the chemical assessment is an effect tool for identifying extremes in behavior (grossly unsafe or generally safe), it has difficulty providing a clear outcome in situations that are “too close to tell”. While biological assessment methods provide interpretable outcomes, they suffer from several shortcomings including high cost and long lead times, lack of sensitivity, lack of clarity in and consistency of results, uncertain scientific merit, lack of a definitive endpoint, and public disfavor. As was the case with chemical testing, biological testing is also a rather blunt tool, providing clarity in extreme situations and uncertainty at the borderline.

Chemical and biological testing are complementary in that one type of testing may provide insights into the results of the other type or that the results of one type of testing may suggest appropriate testing strategies for the other type. For example, if an effect is observed in a biological test, a chemical assessment may identify the specific substances responsible for that effect. Alternatively, the identity of a leached substance may suggest what biological testing is most appropriate to perform. A strong, authoritative, and comprehensive safety assessment leverages both chemical and biological information to definitively delineate the safety risk associated with a drug product–container closure interaction (Fig. 1.5). Nevertheless, the focus of this book is on the chemical assessment of safety and compatibility.

THE GENERALIZED STRATEGY FOR SAFETY ASSESSMENTS

Entities leached from materials of contact can impact the safety and/or efficacy of therapeutic substances in ways that may and may not be readily anticipated. Thus a full and complete assessment of a material–substance interaction involves an extensive investigation that is
oftimes performed at the limits of methodological and interpretative capabilities. As the universe of pharmaceutical products and therapeutic substances is vast and the conditions of material–substance contact are varied, it is difficult, if not impossible, to provide comprehensive guidelines in terms of how a complete and efficient impact assessment is conducted for all possible situations. Nevertheless, global regulatory agencies have communicated a consistent, high-level strategic outline for the safety portion of such assessments. Components of such a high level strategy include the following:

1. **Composition and Production:** It is expected that the petitioner fully specify the contact materials. Furthermore, it is expected that the petitioner be able to delineate, at least in a general sense, the composition of the contact materials. Finally, it is expected that the petitioner specify those aspects of the manufacturing process, for both the contact materials and pharmaceutical product, in which the system or the product may be contacted by potentially contaminating chemical agents.

2. **Compliance:** It is expected that the contact materials be tested by, and be in compliance with, appropriate compendial and pharmacopoeia requirements.

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**Fig. 1.5.** Relationship between chemical and biological test methods for assessing construct–product interactions. The combination of biological and chemical testing, along with the toxicological evaluation of the chemical results, produces a complete and comprehensive safety assessment.⁴

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⁴ For a detailed explanation of the strategy and methodology involved in safety assessments, see the relevant sections in the regulatory guidelines and standards.
3. **Extraction Study:** It is expected that the petitioner will be able to provide a full and complete enumeration of the substances that can be extracted from the contact materials.

4. **Migration Study:** It is expected that the petitioner will be able to provide a full and complete enumeration of what substances will accumulate in the finished drug product and what their accumulation levels will be under product use conditions. It is very clearly communicated in all regulatory Guidelines and Guidance that it is expected that such an assessment be performed in the exact drug product and under the exact conditions of use and that if this is not the case that the petitioner faces the considerable burden of justification of their choice for the conditions under which the migration study was performed.

5. **Interpretation of Migration and/or Extraction Study Data (Toxicological Assessment):** It is expected that the petitioner interpret the migration and/or extraction study data in terms of the toxicological impact of the leached substances present in the pharmaceutical product at their measured concentrations, in full consideration of how the pharmaceutical product is used.

6. **Auxiliary Information:** Provisions in the Guidance and Guidelines are made for the petitioner to provide additional information (e.g., biological toxicological assessments) that may support or augment the chemical toxicological assessment.

**MOVING FORWARD**

While the basic outline of a safety assessment may be clear as noted above [(1) the construct will be extracted by some means, (2) the extract will be chemically (and/or biologically) characterized, and (3) the results of the chemical (and/or biological) characterization will be interpreted in the context of safety (hazard risk)], the details of such assessments are not. That is, there are no universally accepted processes, procedures, specifications, or acceptance criteria for assessing the safety impact of construct–substance interactions. Given the great diversity in therapeutic substances (e.g., finished drug products) and constructs and the splintered nature of the global pharmaceutical marketplace, this is an unfortunate but not altogether surprising situation. While one potential outcome of such a situation is chaos, this need not be the case in the arena of safety assessment for construct–substance
contact. This statement is true because the pharmaceutical industry has amassed a wealth of experience in terms of the strategy and tactics of properly, efficiently, and effectively performed safety assessments.

Collaborators from industry, academia, and regulators agencies have mined this experience to effectively reconcile the seemingly conflicting objectives of expeditiously bringing safe products to the market. The remaining chapters consider the strategies and tactics for performing safety assessments and establish the means for interpreting the results obtained from such assessments.

As was previously noted, the safety assessment process is an indirect one, unless it is based on the collection of considerable data in the clinical setting. Thus, safety assessment, based on extractables and leachables data and the interpretation thereof, is an exercise in risk management. In such an exercise, there is no such thing as an extractables and leachables strategy that reduces risk to zero (where the risk being considered is that the construct and the product interact in such a way that the product’s safety and/or efficacy is adversely impacted). Rather, the degree of risk is minimized via the aggressive, systematic, extensive, and judicious utilization of “good” theoretical and practical science. Because the degree of acceptable risk may vary from situation to situation, extractables–leachables strategies that are wholly acceptable and accepted for one situation may be either hopelessly inadequate or grossly excessive in another situation. Thus, this book does not deal in absolutes and cannot (and does not) prescribe a strategy (or even tactics in many cases) that is universally applicable or “guaranteed to generate a safe and effective product each and every time or your money back”. Rather, this book takes a shopping cart approach, essentially identifying the many possible components of leachables–extractables assessments, identifying and discussing the risk management aspects associated with each component and providing concept clarity through the use of relevant case studies.

REFERENCES


