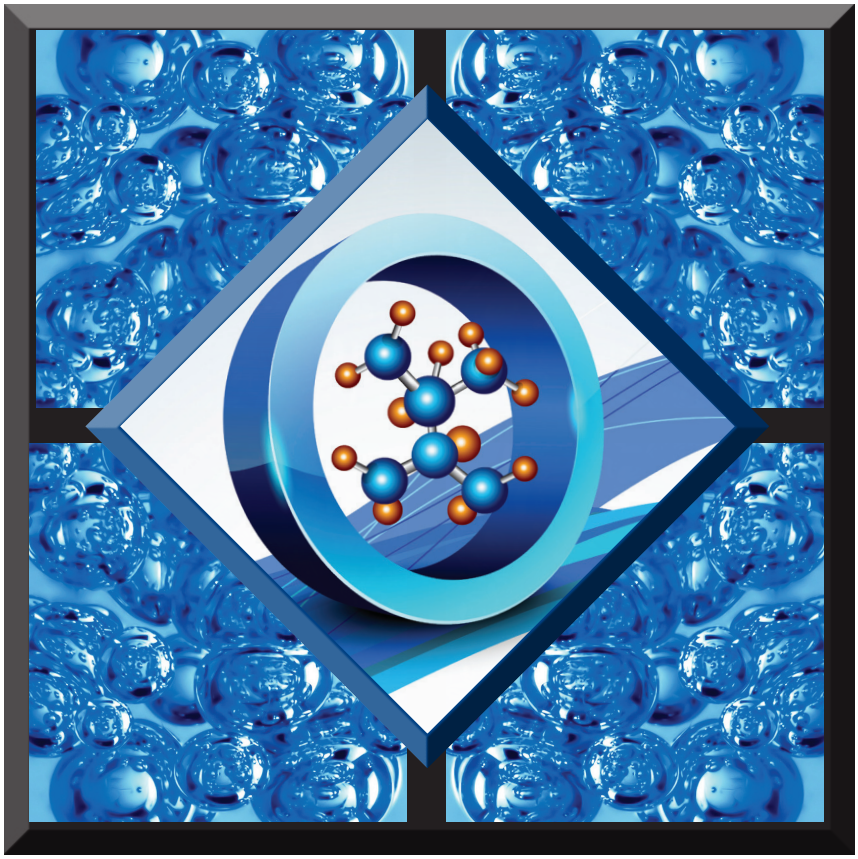

Extractables and Leachables: Standardizing Approaches to Manage the Risk

by Angelo DePalma

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Extractables and Leachables

Standardizing Approaches to Manage the Risk

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Extractables and leachables (E/L) originate from the same sources, arise through similar physical phenomena, and often are the very same substances — making them an "and/or" concept rather than an "either/or" issue. However, the terms have specific meanings for biopharmaceutical purposes. The draft version of USP <1663> contains one official definition of E/L. It follows below, with my bold italics added to reflect the current use of plastic components in single-use bioprocessing (**1**):

> Extractables are organic and inorganic chemical entities that can be released from a pharmaceutical packaging/delivery system, packaging component, ***equipment employed in drug manufacturing***, or packaging material of construction under laboratory conditions. Depending on the specific purpose of the extraction study (discussed below), these laboratory conditions (e.g., solvent, temperature, stoichiometry, etc.) may accelerate or exaggerate the normal conditions of storage and use for a packaged dosage form. Extractables themselves, or substances derived from extractables, have the potential to leach into a drug product under normal conditions of storage and use.
>
> Leachables are organic and inorganic chemical entities that migrate from a packaging/delivery system, packaging component, ***component or equipment employed in drug manufacturing***, or packaging material of construction into an associated drug product under normal conditions of storage and use or during accelerated drug product stability studies. Leachables are typically a subset of extractables or are derived from extractables. Note that chemical entities can also leach from packaging/delivery systems to patients via direct contact.

Leachables are typically a SUBSET of extractables or are derived from extractables.

Concern over E/L rose years ago with primary drug packaging, particularly for liquid formulations. The advent of single-use bioprocessing increased concerns regarding the potential for chemicals from plastics to enter drugs (and through them, to humans). Many terms and ideas that apply to packaging have parallel significance for single-use bioprocess equipment in all its embodiments.

Testing Parameters and Criteria

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Extractables are determined experimentally by subjecting materials to extraction protocols using varying (often exaggerated) conditions of solvent, exposure time, and temperature. Physical disruption and heating also may be applied to enhance extraction).

"Extraction studies give you an idea of what to expect in your leachables, but leachables are where regulators get involved," says Desmond Hunt, principal scientific liaison at the US Pharmacopeial Convention, Inc. (Rockville, MD). "Searching for leachables without a prior extractables study is like looking for a needle in a haystack."

That's because leachables are the compounds, uncovered during extraction studies, that survive downstream purification steps in normal conditions. Unless they are specifically dealt with, patients will be exposed to those leachables that remain in final formulations. Leachables also can interact with biological drug products to initiate particle formation, complexation, inactivation, and other undesirable interactions with excipients or drug substance.

Leaching is a function of the same physicochemical factors that affect extraction and diffusion, namely temperature, contact time, and chemical composition. Long contact times, large surface-contact areas, and high temperatures influence leachables profiles, and chemical compatibility (as in "like dissolves like") also plays a role. Assessment of patient risk incorporates those parameters along with toxicology, primarily the inherent leachate toxicity and exposure parameters when they are known.

Biologics are particularly vulnerable because their complex chemistries afford multiple avenues for negative interactions with leachables. Hydrophobic and hydrophilic regions on proteins, for example, provide mechanisms with leachables of compatible chemistry. Interactions with leachables can induce oxidation, unfolding, aggregation, particulates, adducts, undesirable posttranslational events, and during expression even altered protein translation (**2**).

Contact time cannot be overstressed as an independent E/L risk factor. Interaction between process fluids and manufacturing materials is short during drug-substance downstream processing, but it may go on for weeks during cell culture or years of drug-product storage. Physical state matters too: Long-term storage of liquid dosage forms is riskier than it is for frozen or lyophilized products.

Downstream purification steps such as ultrafiltration/diafiltration (UF/DF) can remove some leachables introduced upstream, but their efficiency depends on both purification modality and leachable chemistry, mainly polarity. Polar compounds tend to clear out more efficiently than apolar materials. Clearance of leachables may be possible during drug-substance processes but not, beyond dilution, during manufacture of drug products.

"This is why depth-filtration directly after fermentation is of lower risk than sterile filtration during drug-product manufacturing," says Michael Jahn, group head of forensic chemistry at Lonza (Basel, Switzerland). Over the years, E/L concerns has had the effect of inducing suppliers to improve processing and materials for container–closure systems. Surface treatments evolved for packaging: e.g., fluoropolymer coatings on rubber stoppers for vials and syringes prevent chemicals present in those stoppers from leaching into drug-product formulations.

Ultimately, the interaction of drug products with patients becomes a critical factor in assessing the effect of leachables on product safety. Inhaled and injected administrations are considered the riskiest; solid, oral dosing (e.g., for small molecules) presents lower risk. "For orally inhaled and nasal drug products," Jahn explains, "the safety thresholds are established more conservatively compared to parenterals because these drugs are applied directly to the affected organ, which is not the case with parenteral delivery."

When extractables studies are conducted thoroughly, leachables will be a subset of the materials they identify. Therefore, whereas extractables are a "maybe," leachables are a certainty. Jahn states outright that leaching is inevitable: "Our industry is married to it. Whenever you have contact between two materials, you have chemical migration from one into another. Leaching can be controlled, but not eliminated."

Single-use containers can be a source of E/L contaminants. (WWW.LONZA.COM)

Organizations

E/L testing and risk mitigation always were complex scientifically. But by 2017, they have become a mega-issue for biopharmaceutical developers. The subject occupies an alphabet soup of organizations and committees attempting to set standards, make recommendations, and issue guidances. From these activities has sprouted a significant and growing follow-on industry of regulatory consultants, analytical laboratories, conferences, reports, and independent pundits. From that apparent chaos, a consensus is slowly emerging.

Among organizations claiming to speak for science and safety are the American Association for Pharmaceutical Science (AAPS), the BioProcess Systems Alliance (BPSA), the BioPhorum Operations Group (BPOG), the Extractables and Leachables Safety Information Exchange (ELSIE), the International Pharmaceutical Aerosol Consortium on Regulation and Science, the Inhalation Technology Focus Group of AAPS, the Polymer Forum, the National Institute of Standards and Technology (NIST), and the Product Quality Research Institute (PQRI).

Thanks to those groups — and the industry's cautious embrace of regulators' forward-looking position on risk — biopharmaceutical developers are beginning to understand that more testing does not necessarily guarantee higher quality or safety. And polymer suppliers recognize that drug containers are very different from car seats. All stakeholders know that reaching a consensus on how to deal with E/L will require borrowing the best ideas from multiple expert sources.

Searching for Standards

E/L testing for single-use bioprocess equipment has its historical origins in the medical device industry. The normative framework is ISO 10993: *Biological Evaluation of Medical Devices.* It offers biocompatibility standards and includes sections on chemical characterization, genotoxicity, toxicokinetics of degradation products, and other relevant topics. In 2016, the US Food and Drug Administration issued its own final guidance on implementing ISO 10993-1: *Evaluation and Testing in the Risk Management Process.* The final draft was nearly 20 years in the making (**3**).

Regulators and drug-makers increasingly recognized that biomanufacturing in single-use equipment entails additional challenges and risks from leachables. Of concern are maintaining quality and safety levels within the diverse matrix of plastics, structures, drugs, formulations, contact surfaces, and conditions. Thus, independent of the 10993-1 normative framework for medical devices, standards working groups have contributed additional ideas for testing and safety evaluation of single-use bioprocess systems.

The modern era of E/L began in 2006 with publication of a paper from the PQRI's Leachables and Extractables Working Group (**4**). PQRI took a multidisciplinary (toxicology, materials science, and analytical chemistry) approach that became today's model for E/L investigation, which carried forward into USP chapters <1663> "Assessment of Extractables Associated with Pharmaceutical Packaging/

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Regulators and drug-makers have increasingly recognized that biomanufacturing in SINGLE-USE equipment entails additional challenges and risks from leachables.

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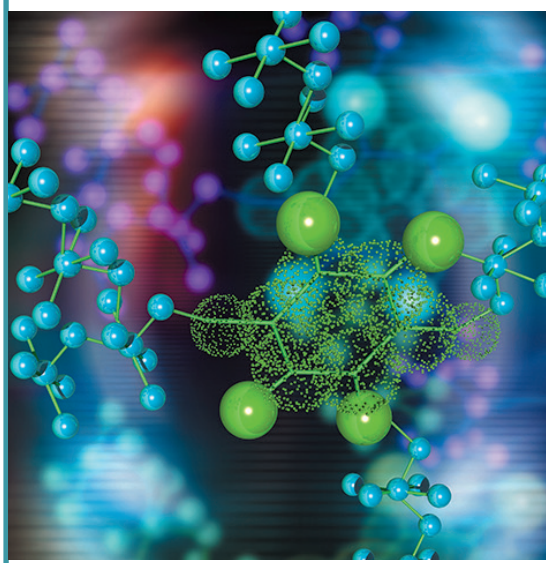
Delivery Systems" and <1664> "Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems." The same approach also has demonstrated utility in some revised earlier chapters, particularly <661.1> (raw materials), <661.2> (packaging systems), and the upcoming <661.3> (single-use manufacturing systems), which is likely to become a separate chapter of its own.

USP <661> provides standards and test methods for relevant plastics and has been used to designate certain packaging materials as "medical grade." Subsequently, the chapter received an overhaul that aligned it more closely with its actual use: conducting E/L programs for safety risk assessments. This is the model accepted today by biopharmaceutical companies and their regulators.

USP's interest in developing a standard for single-use bioprocessing components began about three years ago. Stakeholders had queried the organization about which compendial standards to apply in selecting components or systems. "That got us thinking and led to the development of the new standard," says Hunt. One goal was to help the industry move away from routine testing by incorporating a risk-based mindset into the new standard. For example, processes that involve no liquid process streams involve lower risk and should require less testing. "We want the data generated through the standard [method] to add value in selection of a component or system while eliminating unnecessary testing." Based on that thinking, USP incorporated a risk-evaluation matrix into the standard.



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Choice of extraction solvents is a perennial issue for such standard approaches. USP wanted a standard that applied to both biologics and small-molecule drug-product manufacturers. "With a baseline standard, more testing might be necessary in some situations," Hunt says. But the baseline is a fair starting point for the standard's intended purpose, which is to assist in component selection, not qualification.

USP general chapter <661.3> "Plastic Components and Systems Used in Pharmaceutical Manufacturing," appeared in *Pharmacopeial Forum's* May 2016 issue. The chapter since has been revised based on stakeholder feedback and will be republished for public comment in May 2017 of the same journal as <665> "Polymeric Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products."The proposed document has generated numerous comments from bioprocessors, academia, and industry groups.

By contrast, the seven-solvent BPOG extractables protocol (USP lists only three solvents) is designed to generate "a comprehensive extraction profile" and "to ensure [that] extractables are not missed" (5). Although it is possible to take this view to the extreme, the balance between risk and comprehensiveness is not easy to achieve. In a presentation at a 2015 conference, Seamus O'Connor of Regeneron noted that this method uncovered at least one extractable in each solvent that was not found with any other solvent. Many extractables were found after only seven days of storage.

That illustrates BPOG's reputation for thoroughness — or over-thoroughness, depending on who you talk to. "They aim to cover 80% of potential situations, whereas USP protocols aim at a middle ground,"

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comments Jeff Carter, strategic project leader at GE Healthcare (Marlborough, MA). "You could argue that BPOG provides a wider view of possible extractables, but all extractables data and testing are a means to an end. The real goal is to assure that drugs are safe for administration. The extractables tests are merely steps along the way."

Toxicologic E/L assessments also involve uncertainty and a lack of standardization. Before single-use systems became commonplace, when packaging and closures were the primary focus for E/L, biomanufacturers used simple cell-based assays and rodent or rabbit tests for biological reactivity as a means to understand the risk of a material's extraction profile. The Plastic Class VI test is the most comprehensive testing level in USP <88> "Biological Reactivity Tests, In Vivo," which uses four extraction agents: saline, vegetable oil, ethanol in saline, and polyethylene glycol. Those solvents fairly represent the spectrum of chemical solubility but lacked relevance to bioprocessing.

"Today toxicologists generally ignore those data as essentially meaningless for assessing patient safety risk," says John Iannone, director of extractables/leachables and impurities at Albany Molecular Research, Inc. (AMRI in New York).

Before single-use systems became commonplace, when packaging and closures were the primary focus for E/L, biomanufacturers used simple BIOLOGICAL REACTIVITY TESTS to understand the risk of a material's extraction profile.

Materials of Construction

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The quality issue bioprocessors and drug packagers face is illustrated by a few facts from the world of plastics. About 300 million tons of polymers are produced worldwide each year. The automotive industry uses 15 million tons of plastics per year, but its quality standards fall far short of what the biopharmaceutical industry must demand (**6**). Suffice it to say that no quality attribute exists for biopharmaceuticals that is analogous to the highly valued "new car smell," a result of automobile interiors releasing volatile organic compounds (VOCs) into the air.

The demand differential represents an intractable reality, says Andreas Nixdorf, E/L business development manager at testing-services company SGS Intitut Fresenius (Wiesbaden, Germany). "Pharmaceutical equipment vendors buy only hundreds or thousands of kilograms from polymer suppliers but demand very high quality. The polymer industry tells them to 'take it or leave it.' Fabricators therefore lack control over their suppliers' materials. Unintentionally added chemical substances become uncontrolled impurities that could end up in finished pharmaceutical drug products through leaching."

Some impurities discovered in pharmaceutical packaging and single-use components boggle the mind: uranium-232 and 2,4-dichlorobenzoic acid in cured silicone. Impurities can arise from polymer processing or ingredient-related factors, from faulty cleaning between polymer processing batches, and from myriad other sources and situations.

Supply and Responsibility

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Characterizing extractables and tracking them from early in the supply chain could offer a useful first step in managing E/L risk. Perfect control is impossible given the proprietary ingredients, catalysts, and processes for generating virgin plastics, as well as the quality of monomers. Moreover, suppliers would have to be on board with a

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consensus extraction protocol that could be streamlined at the fabricator level. End users then might follow a risk-based leachables testing protocol to meet their individual needs.

Extractables data from suppliers are useful but not always sufficient to satisfy regulators and good scientific practice. "The challenge is how closely extractables testing mimics real-life application," Carter explains. "Potential differences might not matter so much in phase 1, but in phase 3 developers rightfully become more risk averse."

And that is where the biopharmaceutical industry and its suppliers struggle, he says. "Industry has not yet converged on common ways of viewing risk to the point where companies can take advantage of existing data and need not generate their own." Most biopharmaceutical manufacturers accept a supplier's extractables data for buffer bags, but looking downstream at bulk drug substance or product holding containers, they'll want to generate their own data.

Assigning or "owning" E/L supply chain responsibility involves many considerations. "A gap exists for upstream suppliers, molders who convert the raw materials to structures, processors and extruders of resin beads, and upstream from that the suppliers of virgin materials," says James McLean, scientific manager of extractables and leachables for development, manufacturing, and analytical services partner Catalent (Somerset, NJ). "It's up to users to understand the entire chain of materials and product manufacturing," he cautions, "and to evaluate patient risk from leachables." Ideally that understanding correlates leachables found in a given drug product to extractables known to exist in the materials of construction as well as fabricated devices.

But end users generally do expect some level of qualification for single-use systems. "Our industry uses what is commonly referred to as 'medical grade' plastic, a term without requirements or specified expectations," says Iannone of AMRI. "It's a marketing term without regulatory or quality implications. Some suppliers of materials or components label materials as 'FDA-approved,' which is a bogus designation because the FDA does not approve materials. So there can be a great deal of inconsistency as to what level of material qualification that single-use system fabricators are receiving as part of their qualification binder. Some end users recognize those discrepancies; others don't." The situation persists despite the growing interest of end users in those producers' validation binders.

Changes in materials or raw ingredients are a major issue: "Historically, the upstream suppliers are driven by volume and cost, which necessitates continuously pushing for process efficiencies to remain competitive," McLean continues. "In the absence of a binding service-level agreement, raw material suppliers are under no obligation to notify pharmaceutical industry end users of these changes".

"In the end, the ultimate legal responsibility lies with drug owners. But in practice, assuring an acceptable E/L profile must involve the suppliers up to the earliest ones in the supply chain," says Nixdorf. He mentions ISO 13485 (*Quality Management for the Design and Manufacture of Medical Devices*) as a possible guide to parallel thinking for single-use equipment (**7**).

Extractables data from suppliers are useful but NOT always sufficient to satisfy regulators and good scientific practice.

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If suppliers are left to their own devices, however, some of their extraction conditions may generate many more extractables than typical users ever will see in packaging or bioprocessing equipment, components, and containers. The industry needs extraction protocols and qualified analytical methods to generate chemical profiles that will be comparable for materials derived from different suppliers but for the same function. That way, end users could make informed decisions on each material's suitability. Nixdorf therefore suggests adopting an extraction protocol that is somewhat exaggerated — but not to the degree that it triggers unnecessary testing.

That raises the point of the trustworthiness of vendor documentation for their customers' subsequent evaluatations of E/L. "Some vendors' validation guides combine science and marketing," Nixdorf warns. "Suppliers don't tell you everything they know. When extraction conditions are too harsh, they often list only extractables that they have identified, without including those that must be flagged as unknowns."

Although supplier documentation is not quite where it needs to be, most vendors now provide certificates confirming baseline material compatibility and some level of safety testing if their materials will be used for pharmaceuticals or foods. Common contaminants studied include heavy metals, nitrosoamines, polyaromatic hydrocarbons, and bisphenol A. Suppliers are in some ways stuck, however, because they are not privy to the precise end use of their materials. "So they test according to the 80/20 rule," McLean says, "in which they cover in some fashion 80% of the formulations their materials might encounter."

It is up to end users to conduct a gap analysis, examining compatibility and safety data from material suppliers and asking whether their test criteria suffice for the intended use, given their own product, solvents, fluids, excipients, and processes. Does potential exist for adverse physical or chemical interactions, for product adulteration? "That is when users will decide to conduct additional tests to demonstrate safety and compatibility," McLean explains, citing controlled extraction studies for plasticizers, low–molecular-weight polymers, metals, or "anything else that may be suspected of interacting with large bioactive molecules."

He believes that gaps in knowledge and understanding may be bridged through simple communication. "Suppliers are beginning to form boutique or niche business units that serve the pharmaceutical industry, and they are taking on expertise to prepare for greater regulatory compliance and testing for drug-manufacturing markets." Service-based agreements are emerging through which suppliers will notify end users if they change how they make single-use and packaging products. Raw material vendors, fabricators, and component-production facilities are beginning to align with pharmaceutical industry needs.

"Sometimes what a [plastics] manufacturer considers to be an insignificant change for bulk polymer markets could be significant for biopharmaceutical manufacturing and packaging," says McLean. For example, changing a polymerization catalyst might produce a functionally identical resin that has a different leachables profile and could substantially affect product quality or safety.

E/L Analytical Methods

Fourier-Transform Infrared Spectroscopy (FTIR) can supply functional-group information and is useful for identification of unknowns. This technique is most valuable for relatively pure compounds.

Gas Chromatography (GC) separates individual sample components based on intrinsic chemical properties such as molecular weight, polarity, and vapor pressure. GC can detect most compounds as long as they are volatile or semivolatile.

High-Performance Liquid Chromatography (HPLC) separates sample components based on chemical properties such as molecular weight, polarity, and electrical charge. They are detected by, e.g., UV-vis (ultraviolet–visible light), mass spectrometry (MS), and fluorescence. HPLC separates compounds regardless of their volatility, but no single detector can catch all molecules.

Inductively Coupled Plasma (ICP) and ICP-MS uses light wavelength detection and is amenable to all analytes (most commonly used to identify and quantitate metals).

Mass Spectrometry (MS) electrically breaks target compounds into ion fragments and separates them based on mass and charge. MS can be used as a detector for HPLC (LC-MS) or GC (GC-MS), and an analysis of fragment patterns can help to identify compounds.

Nonvolatile Residue (NVR) Analysis measures nonvolatile extractables and many semivolatile extractables. It will not capture volatile and certain semivolatile extractables, depending on the relative vapor pressure difference of the extractables and extraction media. The technique is used with extraction media that do not contain significant nonvolatile compounds.

Total Organic Carbon (TOC) Analysis oxidizes organic carbon in extraction media to form carbon dioxide, which is then measured using an IR detector. TOC accurately measures organic extractables with test media that do not contain significant amounts of carbon.

Source: BPSA Extractables and Leachables Subcommittee. Recommendations for Extractables and Leachables Testing. BioProcess Int. *6(5) 2008: S28–S38; www.bioprocessintl.com/2008/recommendations-for-extractables-and-leachables-testing-183979.*

Reference Compounds and Methods

The myriad techniques for generating, collecting, and characterizing both extractables and leachables range from high-end to simple (see the "Analytical Methods" box on page 11). Most E/L testing incorporates gas or liquid chromatography with mass spectrometry. But less sophisticated, more common laboratory techniques also come into play. For example, Gerstel (Linthicum, MD) has introduced a stir bar absorptive extractor that captures extractables from common buffers efficiently enough to enable analysis down to the parts-per-quadrillion range. The company also has introduced a thermal desorption method for driving low–molecular-weight components out from polymeric materials of construction. Gerstel has collaborated with Agilent on the analysis of leachables, demonstrating that its Twister stir-bar product is comparable to more conventional alternatives.

Such levels of detection raise issues regarding how many identified extractable compounds would be too many and what concentrations would be too low to deserve attention. A thermal-desorption study reveals potential E/L molecules under conditions that are far more extreme than would be encountered by packaged or processed biopharmaceuticals. It is possible to construct libraries of possible extractables based on thermal and standard extraction methods (see ELSIE box, right).

Many drug developers maintain their own lists of "compounds of concern" that extract from their particular packaging and process equipment. They screen for those after reviewing extractables data and do so again at the drug-product stage. Then they can apply factors that account for dosing, toxicologic threshold levels, and delivery site/mechanism. Yet even with so much data "in the bank," risk assessment remains an individualized exercise.

But Edward Pfannkoch, director of technology development at Gerstel, doesn't think E/L libraries are of much use. "They can be a starting point, but you never know what changes may have occurred during polymer processing. The fabricator may have treated surfaces with a corona discharge, which might generate something new. I would never trust a list; I would test the material multiple times."

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The ELSIE Database

If a safety issue related to extractables or leachables is not detected until late in product development, a sponsor could face substantial delays in regulatory review and market introduction. They can cost millions of dollars in additional work, lost market revenue, and shortened patent exclusivity, as well as depriving patients of needed medicine. ELSIE seeks to help the industry address these concerns and advance the principles of quality by design (QbD) by gathering together information on 421 extractable compounds (so far) to "support member companies' regulatory filings, reduce duplication of effort and minimize testing, and decrease the risk of substantial, unanticipated delays and associated costs." With a container–closure focus, this organization provides chemical information on each entry with toxicity; mutagenicity/carcinogenicity; and absorption, distribution, metabolism, and excretion (ADME) data. Learn more about it online at www.elsiedata.org/elsie-database.

Test, Retest, Ad Infinitum

The study of E/L began with medical devices and packaging and has experienced renewed interest with the widespread use of single-use bioprocessing equipment. Standards for testing, applying risk-based methods, and assessing subsequent toxicologic effect of leachables are far from set in stone now — and not likely to emerge for years. The industry must accept that leachables exist throughout the biopharmaceutical value chain, and it must be willing to do what it takes to mitigate their potential adverse consequences.

"We're closer to solving the problem of extractables and leachables than ever before," Iannone says, "but to solve the problem, you have to understand it. Anything and everything in a drug formulation can influence extraction propensity." Different ingredients, whether in a

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formulation or a process stream, result in different extraction profiles from the same polymer material.

"It's great that companies innovate to meet patient needs," Iannone cautions, "but as that occurs, the possibility matrix grows and grows." In each instance, vendor companies produce materials of construction by their own proprietary methods, each tweaking that "special sauce" for its own reasons. "Every time we change that combination, we change the potential extraction profile, which requires reevaluation in terms of patient safety."

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