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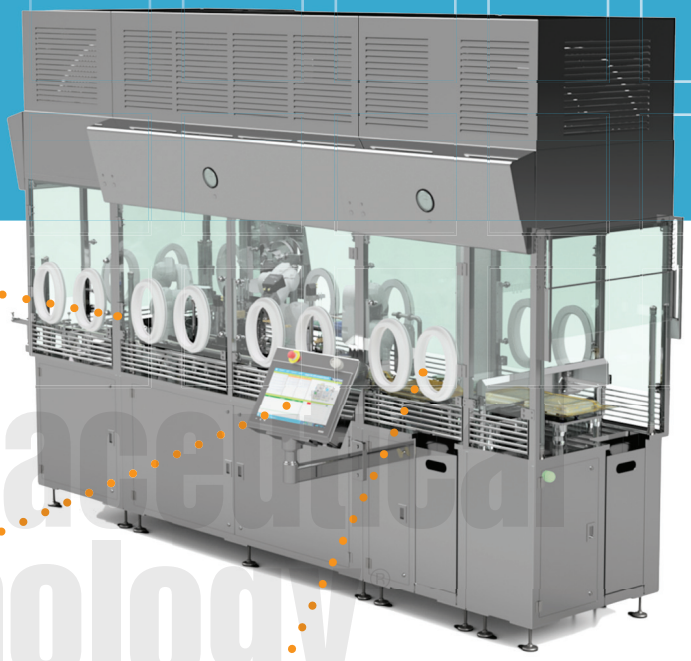

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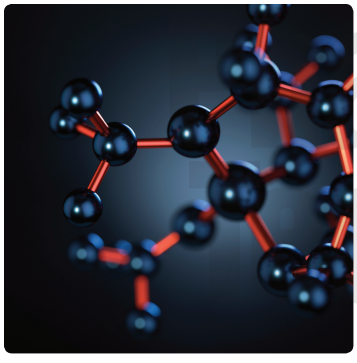
Proactive Evaluation of Possible Genotoxic Impurities During the Early Stages of Drug Development

Aloka Srinivasan



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The author provides a direction for identifying genotoxic impurities early in the drug development process, regulating genotoxic impurities at acceptable levels in the API or drug product, and avoiding negative product regulation late in the development and/or marketing process, including expensive recalls.

Control of mutagenic and/or genotoxic impurities in an API has been the topic of deficiencies cited by FDA and other regulatory agencies all over the world for the past few years (1–3). Before delving into what may be the source of these deficiencies and identifying any proactive steps to avoid them, it is important to understand the relationship between mutagenic and genotoxic impurities. For a long time, these two terms have been used interchangeably by regulatory agencies and the pharmaceutical industry. However, International Council for Harmonisation (ICH) M7(R1) (4) specifically mentions "mutagenic" impurities in its title as well as content rather than the general team, "genotoxic". Hence, a few words related to the relationship between the mutagenic and genotoxic impurities may be useful prior to commencing discussion on this topic. Based on the definitions in ICH M7(R1), genotoxicity is "a broad term that refers to any deleterious change in the genetic material regardless of the mechanism by which the change is induced" (4). Also, the *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)*, Fifth Revised Edition, United Nations, Chapter 3 has the following definitions of mutagenic and genotoxic materials (5):

"3.5.1.3 The term mutation applies both to heritable genetic changes that may be manifested at the phenotypic level and to the underlying DNA modifications when known (including for example, specific base pair changes and chromosomal translocations). The term mutagenic and mutagen will be used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms."

"3.5.1.4 The more general terms genotoxic and genotoxicity apply to agents or processes which alter the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner (temporarily) alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects."

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Thus, mutagenicity implies induction of permanent transmissible changes in the amount or structure of the genetic material of cells or organisms, while all genotoxic effects are not necessarily associated with mutations. Hence, all mutagens are genotoxic, but, not all genotoxic substances are mutagenic. When genotoxic impurities are mentioned in publications and deficiencies cited by FDA and other regulatory agencies, they include mutagens and also other impurities that can cause DNA damage though different pathways. In this paper, the term genotoxic impurities will be used to refer to mutagenic as well as other genotoxic impurities, unless there is specific need to refer to a material as mutagenic.

The purpose of this article is to provide a direction for identifying genotoxic impurities early in the drug development process, regulating genotoxic impurities at acceptable levels in the API or drug product, and avoiding negative product regulation late in the development and/or marketing process, including expensive recalls. The focus of this discussion are the dossiers submitted to FDA, especially for generic drugs (e.g., 505(j), abbreviated new drug applications [ANDAs], and 505(b)(2) new drug applications [NDAs], which use APIs that are already approved by FDA). However, most of the principles also apply to new chemical entities and also other regions of the world that follow ICH guidelines.

The current resurfacing of nitrosamines in the pharmaceutical world due to FDA and other international agencies finding traces of these compounds in the angiotensin II receptor blockers (ARBs), commonly known as the "sartans," has led to recalls of several drugs of this class (6). As of now, valsartan and losartan are the worst affected, and several lots of these products have been recalled (7). Currently, we have also been informed by FDA about the presence of nitrosodimethylamine, NDMA, in ranitidine hydrochloride (8). While the pharmaceutical industry has been diligently working to address the nitrosamines in ARBs, questions have also arisen as to how a situation of this kind could be anticipated and possibly avoided in the future, not just for nitrosamines but other genotoxic impurities as well.

Discussion

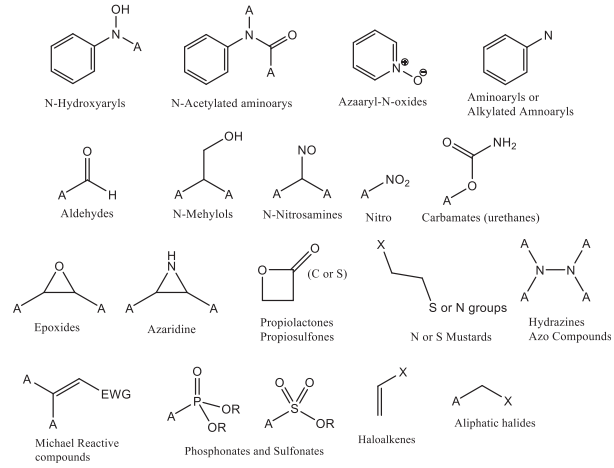
Genotoxic impurities can occur in drug products based on the manufacturing of the API, degradation of the API, or in some cases, from the excipients (9). The source of genotoxic impurities in the API and drug product generally is the API manufacturing process, including starting materials and reagents. Reagents used in API synthesis are often highly reactive, and genotoxic impurities can result from leftover reagents carried through the manufacturing process, by-products of the chemical transformations, or the subsequent degradation/interactions of the API (9,10). Although rare, genotoxic impurities occasionally form in the drug product as a result of interaction of the API with excipients. This article, however, focuses on the possible genotoxic impurities rising from the manufacture of the API.

Inability to apprehend the possibility of formation of impurities with genotoxic potential can significantly impact the approval of an NDA or ANDA. Usually, with new chemical entities related to 505(b)(1) applications, the sponsors perform evaluation of the synthetic pathways and address possible and plausible impurities, including impurities with genotoxic potential early in the investigational new drug (IND) process. In the best-case scenario, the control strategies are shared with, and agreed upon, by FDA prior to submission of the NDA. However, with the 505(j) and some 505(b)(2) applications, where an API used is already present in an FDA-approved drug, the detailed understanding of the risk related to the API manufacturing process often takes a back seat. Irrespective of the fact that the API is present in an FDA-approved product, there can be risk related to genotoxic impurities based on a new synthetic route, origin of the starting materials, sources of reagents, and solvents used. This can also be an issue during the lifecycle management of a 505(b)(1) NDA. It is essential that the manufacturing process of the API is appropriately evaluated and also that the origin and controls of the starting material and reagents are appropriately scrutinized to ensure that there are no surprises in the impurity profile during the FDA's review or lifecycle management.

The question often comes up as to where to start the process of identifying plausible genotoxic impurities in an API manufacturing process. The best place to start is by being cognizant of the structural alerts related to genotoxicity as provided in **Figure 1** (11).

For an API manufacturer to increase the chances of avoiding deficiencies related to controls of genotoxic impurities, several aspects of the manufacturing process and controls should be evaluated. If any starting material, reagent, intermediate, or possible side product has one of the structures in **Figure 1**, an evaluation should be initiated immediately, and a control strategy put in place. In addition, the following are some other angles from which the possible presence of genotoxic impurities may be addressed.

Figure 1. Structural alerts for genotoxicity.



Selection of the manufacturing process. This is a good place to start to reduce risk related to genotoxic impurities. A manufacturing option with more steps is favored if it involves lesser use of potentially genotoxic reagents or generation of potentially genotoxic intermediates or side products.

Starting material. The selection of starting materials in the synthesis of API is crucial for many reasons, one of them being its impact on the impurity profile of the API. The starting material should not be defined significantly downstream in the process, as this may make it difficult to purge impurities arising from the starting material. Also, there needs to be knowledge related to the manufacturing process of the starting material and a good understanding regarding any of the reagents or intermediates or by-products of the process being a structural alert for genotoxic impurities. If there are potential genotoxic impurities in a late-stage intermediate that is being defined as a regulatory starting material (RSM), the API manufacturer may have an uphill task of adding significant controls to the RSM and final API or convincing FDA that these impurities are purged efficiently by the process and do not pose a risk to the API or drug product. Both options are expensive and time consuming and could be the cause of delay in approval.

By-products of reaction. If any of the by-products of side reactions in the manufacturing process are structural alerts for genotoxicity, it needs to be evaluated to determine whether they are completely consumed in subsequent reactions or persist throughout the manufacturing process. If needed, control for these by-products should be included at appropriate steps. The best place to control an impurity is close to its origin. However, if the by-product persists in the final API, controls may need to be added at the point of origin as well as the API.

Reagents and solvents. Many of the reagents are structural alerts for genotoxicity or may generate structural alerts downstream based on the reaction with intermediates or other reagents. Many of the surprises related to genotoxic impurities come from a lack of understanding of the reagents and solvents or their impurity profiles, as we have seen in the case of nitrosamines. The behavior of the solvents used during the manufacturing process should also be understood in the perspective of the synthetic steps. Some solvents are considered reactive and can do more than provide a medium for the reaction to happen. A classic example is acetone, which can undergo aldol condensation followed by dehydration under acidic conditions to product a genotoxic impurity, mesityl oxide (12). The nitrosamines in the "sartans" are believed to have originated from impurities like dimethylamine and diethylamine in upstream solvents like dimethylformamide and diethyl acetamide, reacting with the downstream reagent, sodium nitrite (13).

Degradant. If the potentially genotoxic or impurity is a degradant of the API in addition to being generated by the manufacturing process, a control of the impurity will be needed in the API and also in the finished dosage form keeping the maximum daily dose (MDD) of the drug product in mind.

Control strategy. Once the possible and plausible genotoxic impurities are identified in the API manufacturing process, a strategy is needed related to controlling them. This strategy can start with understanding the acceptable intake of the impurity based on the MDD as well as duration of the treatment as provided in Table 2 of ICH M7(R1) (4). There may be significant difference in acceptable intake based on whether the drug is for chronic use or a short-term use. For drugs with variable MDD based on indications, the most conservative MDD should be used to determine the threshold of toxicological concern (TTC). This determination should be followed by developing analytical method(s) that are sensitive enough to detect and quantitate the potential genotoxic impurities at the proposed levels. For potential genotoxic impurities that are generated upstream, spike and purge studies may be performed to ensure that these impurities are present at lower than 30% of the TTC level in the final API. The control strategy may also be based on the scientific understanding of the nature of the impurity and the measured or predicted purge factor (4,14).

In cases where the impurity is produced downstream in the API manufacturing process and persists in the API based on spike and purge or purge factor studies and/or is a known degradant, the impurity should be controlled in the drug substance and possibly in the drug product. The limit of the genotoxic impurities to be controlled in the intermediate or the final API can be justified by the TTC and also the spike and purge studies. The ICH M7(R1) guidance provides an approach for both classifying genotoxic impurities as well as determining safe levels. Other guidance, such as ICH S2(R1) (15) on genotoxicity testing, identifies bacterial and mammalian *in-vitro* and *in-vivo* testing options if a genotoxic impurity is identified based on quantitative structure activity relationships (15). The exception being if the compound of interest has the same structural alert as the API itself. In that case, it can be treated as a non-mutagenic impurity and controlled based on ICH Q3A(R2) qualification or identification threshold (4).

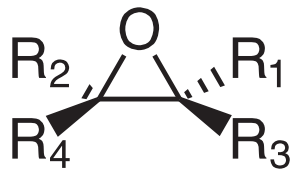
A few common genotoxic impurities and some examples of drugs where they can occur are summarized in the following sections. This is not intended to be a comprehensive list but covers some well-known genotoxic impurities, which may originate from the reagents used or even be present as impurities in reagents.

Examples of common genotoxic impurities

Epoxides. Epoxides (shown in **Figure 2**; where R1–4=alkyl, aryl or H) are highly reactive compounds that can interact with the DNA and are considered structural alert for genotoxicity (10,16). Epoxides can be formed as intermediates in reactions and can also when the synthetic route involves generation or use of alkenes and along with oxidants, such as peroxy acids. Epoxides usually undergo reaction in presence of strong acids and alcohols to produce non-genotoxic glycols.

Some of the examples of drugs that may have epoxide impurities include the following: acebutolol, atenolol, atorv-

Figure 2. Typical epoxide.



astatin calcium, betamethasone, bicalutamide, fluocinolone acetonide, loteprednol etabonate, mometazone furoate, mupirocin, nadolol, stavudine, and vincristine.

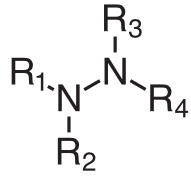
Alkyl halides. Alkyl halides (shown in **Figure 3**; where R=alkyl, aryl group, or H and X=iodine, fluoride, chlorine, or bromide and other good leaving groups) are used extensively as alkylating agents in the synthesis of APIs (17,18). Alkyl halides are mostly left as residues at the end of alkylating reactions as they are used as excess. Alkyl halides are ubiquitous and are commonly used in numerous API manufacturing processes. The examples below are a few drugs where these impurities have been definitely identified. They are mostly highly reactive (e.g., alkylating agents) and are known genotoxic and carcinogenic compounds.

Figure 3. Typical alkyl halide.

Some examples of drug products that may have alkyl halide impurities are the following: fexofenadine, anastrozole, aripiprazole, latanoprost, capecitabin, sitagliptin, sunitinib maleate, pazopanib, conivaptan hydrochloride, linezolid, and linagliptin.

Hydrazines. Hydrazine (shown in **Figure 4**; where R1–R4 are alkyl, aryl group, or a hydrogen), hydrazides (shown in **Figure 4**, where R1 = O, R2, R3, R4 = H, alkyl or aryl groups), and hydrazones (shown in **Figure 4**, where R1, R2 = alkyl or aryl groups, R3 = NH2) are common reagents used in the synthesis of APIs. Hydrazine itself is a well-known base and reducing agent (10,18,19). They are also known genotoxic and carcinogenic compounds. Hydrazines, being strong bases, can be washed out if there are steps downstream which involve strong acids.

Figure 4. Typical hydrazine, hydrazide, and hydrazine.



Some examples of drugs that may have hydrazine, hydrazide or hydrazone impurities are the following: allopurinol, carbidopa, celecoxib, dihydralazine, hydralazine sulfate, isoniazid, mildronate, rifampicin, rizatriptan benzoate, sunitinib maleate, sildenafil citrate, saquinavir mesylate, and ziprasidone.

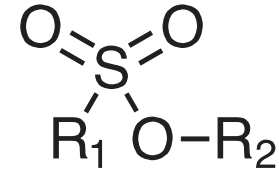
Figure 5. Typical nitrosamine.

Nitrosamines. Nitrosamines (shown in **Figure 5**; where R1–2 are alkyl or aryl groups) are well-known genotoxic and carcinogenic chemicals that are widely found in the environment and the food chain (20,21). Nitrosamines usually form in the API or drug product when a secondary amine (either part of the API structure or reagents in the manufacturing process) is exposed to a nitrosating agent such as sodium nitrite in a low pH environment. Nitrosamines can also form when there are secondary amine impurities in reagents and solvents. Thus, if an organic or inorganic nitrite is used in manufacturing of the API, the sponsors should evaluate the possibility of nitrosamines based on amines or amides that can be used or formed during the process.

Some examples of drug products which may have nitrosamine impurities: valsartan, olmesartan, irbesartan, losartan potassium and other "sartans", chlorhexidine gluconate, propranolol, metoprolol, piperazine, ethambutol, ephedrine, indomethacin, phenytoin, and ranitidine.

Sulfonate esters. Sulfonate esters (**Figure 6**; where R1=alkyl or aryl group; where R2=alkyl groups) (10). Sulfonate esters are one of the most common and well-known genotoxic impurities formed during the API manufacturing process. The reason behind this is that the precursors to alkyl sulfonate es-

Figure 6. Typical sulfonate ester.



ters, alkyl sulfonic acids, and alcohol or also alkyl halides are some of the most widely used in organic reactions. Many APIs are salts of alkyl sulfonic acids like mesylates, tosylates, besylates, and triflates, which lead to the presence of a conjugate base of alkyl sulfonic acids in stochiometric proportions in the API. Also, the alkyl sulfonic acids are used in protection and deprotection of functional groups and also as acid catalysts in several reactions. Alcohols like methanol, ethanol, and isopropanol are common solvents used in API manufacturing process. Also, alkyl halides, which can react with alkyl sulfonic acid to generate potentially genotoxic sulfonate esters, are themselves considered structural alerts for genotoxicity and also commonly used reagents in API manufacturing. Sulfonate ester formation can be controlled based on the levels of water or free base present during the reactions (22).

Some examples of drug products that may have sulfonate ester impurities: nelfinavir mesylate and other drugs which are mesylate salts, glycopyrronium tosylate and other drugs with tosylate salts, clobetasol propionate, halobetasol propionate, mometasone furoate, oseltamivir phosphate, fosinopril sodium, esomeprazole sodium, orlistat, and tolterodine tartrate.

Conclusion

Genotoxic impurities need to be anticipated and identified early in the drug development process. Late identification of potential genotoxic impurities in API manufacturing can result in delays in submission of dossiers due to disruption in the manufacturing process. Request for evaluation of potential genotoxic impurities during the review process by agencies can lead to delays in agency approvals and loss of market share. Should identification occur post-marketing, this could result in disruption in supply of the drug product and, in some cases, drug shortage. Identification of any structural alerts in the API manufacturing process, along with quantitative structure activity relationship (QSAR) model positive confirmation (23), indicates the need for running a bacterial reverse mutation assay for confirmation and/or creating control strategies as per ICH M7(R1) (4). A sponsor's awareness regarding the potential genotoxic structural alerts that may result from the chosen manufacturing process of an API, and early planning regarding how the potential genotoxic impurities may be controlled, would be a giant step toward reducing review cycles which in turn may be the pathway to quick approval. After all, as Benjamin Franklin once said, "An ounce of prevention is worth a pound of cure."

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Perspectives on Quality Attributes of Drug Products Containing Nanomaterials

Anthony Hickey, Emmanuel Akala, Lawrence Block, John Hammond, Munir Hussain, Brent Kleintop, Nancy Lewen, June Liang, Jolyon Mitchell, Norbert Maurer, Myke Scoggins, Timothy Shelbourn,Thomas Tice, Katherine Tyner, Eloise Welfare, and Kahkashan Zaidi

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In this article, the contents of a stimulus article produced by the joint subcommittee of the *USP* Expert Committees on Dosage Forms, Physical Analysis, and Excipients and relevant comments from a workshop session are summarized.

Anthony Hickey, Emmanuel Akala, Lawrence Block, John Hammond, Munir Hussain, Brent Kleintop, Nancy Lewen, June Liang, Jolyon Mitchell, Norbert Maurer, Myke Scoggins, Timothy Shelbourn, Thomas Tice, Katherine Tyner, Eloise Welfare, all members of the Joint Subcommittee of the *United States Pharmacopeia* Expert Committees on Dosage Forms, Chemical Analysis, Physical Analysis, and Excipients; and **Kahkashan Zaidi**, *United States Pharmacopeia**, kxz@usp.org

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The current interest in nanotechnology and its application to the medical field has historical precedent. Initial products employed general physical chemistry of colloids to produce stable drug suspensions and improve bioavailability. The later introduction of liposomes began the evolution to today's more sophisticated, and potentially revolutionary, new technologies accompanying the rapid growth in biotechnology product opportunities, notably including targeted drug delivery products.

The term 'nanomaterials' describes materials that have features or structures that exist on the nanoscale in any of the three spatial dimensions. The large numbers of formulations containing nanomaterials that are currently under development, under review, or have already received approval from FDA emphasizes the need to identify important properties of these formulations and methods of measurement of their properties to ensure quality and performance. FDA has offered guidance to nanomaterials (1). The document emphasizes the need to evaluate materials with any dimension in the nanoscale (1–100 nm) as well as products showing size-dependent properties with dimensions up to 1000 nm.

Nanomaterials may be added to the dosage form to confer a desired physicochemical or mechanical properties; for example, colloidal silicon dioxide (i.e., fumed silica), which acts as a glidant in tablet manufacture. Despite achieving the desirable properties, undesirable effects of excipients should also be considered. A guidance for industry from FDA addresses the needs of this class of nanomaterials (2).

Structure of nanomaterial

When considering the composition of specific nanomaterial formulations a variety of structures can be considered including: carbon nanotubes (3,4); dendrimers (5); drug (6) and inorganic (7) nanoparticles; liposomes (8), micelles

(9,10), nanobubbles (11); nanoemulsions (12), nanofibres (13–15), polymeric (16,17) (natural and synthetic); and solid-lipid nanoparticles (18). Characterization of nanomaterial is presented below.

Products may initially contain nanomaterials, or this state of matter might result from post-market changes to existing products through processes to create nanostructures. Over a period of 10 years, spanning the turn of the Millennium, products for cancer (doxorubicin and paclitaxel), anaemia (sodium ferric gluconate complex), macular degeneration (pegaptanib sodium), tear production (cyclosporine), aspergillosis (amphotericin B), acromegaly (lanreotide acetate), and hypercholesterolaemia (fenofibrate) as liposomes, inorganic, and polymeric (natural and synthetic), nanotubes, nanocrystal emulsions, and micelles (19) were prepared. Many of the aforementioned formulations have yet to be translated to commercialized products. However, it should be anticipated that many will find their way onto the market.

Applications of nanomaterials

Nanotechnology can be employed to modify the biopharmaceutical disposition, bioavailability, and biodistribution, of a drug substance. Desired characteristics such as solubility and the route of administration of the drug substance dictate how critical the size and structure of nanomaterials are to their function.

Rapidly degrading/dissolving nanoparticles exhibit near instantaneous loss of morphology and release drug substance for absorption and distribution, whereas nanoparticles that remain intact for extended time periods may play a role in the pharmacological effect of the drug in the central compartment due to their size and/or structure. Following oral administration, a rapidly dissolving, readily bioavailable nanocrystal drug substance/formulation is known to exhibit different pharmacokinetics compared to that exhibited by a formulation containing the drug substance of larger particle size. Similarly, differences in integrity of nanoparticles, rapid or slow dissolution, will influence systems administered by the parenteral route. Hydrophobic systems are routinely used for intravenous injection and inhalation. Synthetic and natural polymeric nanoparticles forming rigid structures have been used primarily for intramuscular depot delivery. Nanocrystals have been delivered in oral solid dosage forms for gastrointestinal (GI) absorption.

Generalizing critical quality attributes from one product to the next to accommodate the needs of quality by design is difficult (19). Nevertheless, key variables should be identified, and their impact characterized and controlled to support quality metrics. Considerations with respect to products containing nanomaterials have been reviewed (20) and risk has been characterized (21).

General texts on the safety of nanomaterials exist (22). Specific considerations for drug products containing nanomaterials relate to the kinetics of dissolution and disposition following administration and the fate of components of the materials. Safety considerations for pharmaceutical nanomaterials in a regulatory context have been described (13,16,20,22).

The risk associated with the drug alone exposure is a baseline consideration for a nanoparticle formulation. It can be assumed that rapidly dissolving nanoparticles carry the same risk as molecular drug presentation, because the existence of the nanomaterial is transient. Long residence-time nanoparticles potentially modulate the risk. Limiting the release rate of the drug may reduce the risk of adverse effects. In contrast, the risk may be elevated beyond that of the drug and components alone if accumulation or concentration in specific physiological compartments occurs. Parenterally administered inorganic particles (e.g., gold and silver), micelles, and liposomes are among the drug nanomaterial combinations that might present an elevated risk. Oral administration of nanoparticles may affect the residence time of nanoparticles in the GI tract as a desirable drug delivery function but may also raise the potential for elevated risk.

Every drug product requires the assessment of quality parameters to grant safety and efficacy to be released for human and veterinary use.

Evaluation of nanomaterials

Every drug product requires the assessment of quality parameters to grant safety and efficacy to be released for human and veterinary use. Yet, nanomaterials add an additional layer of complexity to the formulation steps. For example, the processes of mixing/blending, filling (solid and liquid), compression, and lypophilization require consideration of the nanomaterial state and its preservation throughout manufacturing. Performance quality tests follow the dosage form characterization and route of administration considerations set forth in the *United States Pharmacopeia* (*USP*) and regulatory guidance. If the nanomaterial is essential to the function of the dosage form, additional specific tests may be requested.

A comprehensive approach to the measurement of physicochemical characteristics includes the following:

- Aerodynamic particle size distribution using *USP* <601> for micro-aggregated nanoparticles and <1601> nebulized particles or low-pressure impactor for nanoparticle aerosols (23)
- Composition and structure using atomic absorption spectroscopy and photon-correlation spectroscopy

- Dissolution and *in-vitro* release using microdialysis (24), fiber optic probe (25), infrared (26) and Raman (27) spectroscopy
- Encapsulation efficiency
- Particle size using scanning and transmission electron microscopy (SEM and TEM) and atomic force microscopy (AFM)
- Particle distribution using photon correlation spectroscopy, small angle X-ray and neutron scattering (SAXS and SANS);
- Purity, shape using SEM, TEM, AFM, SAXS and SANS, and solubility
- Surface area using gas adsorption, surface properties using X-ray photoelectron spectroscopy, secondary ion mass spectroscopy, zeta potential, and freeze fracture SEM
- Physical stability.

Critical quality attributes (CQA) and regulatory considerations. It should be noted that FDA and the European Medicines Agency (EMA) do not formally use the term 'nanomedicines' and EMA has only recently acknowledged it.

Nanomedicines in combination products are subject to the overarching FDA guidance and then assessed on a case-by-case basis. There are no combinations in the EMA lexicon so it is important to meet with the regulatory agency early to address requirements.

FDA has guidance that is overarching, class-specific, and product-specific. The International Pharmaceutical Regulators Forum is developing a map of relevant guidance and regulations.

Methods and specific product considerations. An example of specific consideration is the use of an oral formulation with and without nanomaterial. In this case, FDA would conduct a risk assessment and track this information over time as it would for products not containing nanomaterials. Each product would be managed on a case-by-case basis, and the complete package would be evaluated regarding the materials and their physicochemical properties, and how they impact quality. This approach ensures that methods are appropriate to the way the product is characterized. This approach necessitates that CQAs are defined and have adequate characterization methods, stability testing, and a risk management plan.

As bioequivalence implies drug bioavailability from the drug product, the extent to which the unique contribution of nanomaterials as a subcomponent should be evaluated depends on the dosage form. For example, drug release information from drug products containing nanomaterials may be required by FDA. Consequently, dissolution testing may be a tool that can be used for evaluation. The analysis of dimers (or other polymers) may require a different method and gel electrophoresis has been considered.

There may be subtle differences in the way in which dynamic light scattering (DLS) measures particles based on their material properties, hard versus soft, for example. FDA is also working with the International Organization for Standardization (ISO), American Society for Testing and Materials (ASTM) International, and *USP* to develop and disseminate DLS standards. It is important to recognize which materials DLS would appropriately characterize. Complementary methods to DLS seem to focus on microscopy.

The most frequently measured characteristic—particle size distribution—and the DLS and high-resolution imaging techniques employed, will be the initial focus of the *USP* in preparing general chapters to address these topics.

Data collection and collation. An informatics strategy for the collection and collation of data is required to characterize CQAs of the nanomaterial in the product. It is difficult to identify biological endpoints attributable to the nanomaterial. Measures of efficacy and safety should be derived from the studies of the drug product.

Conclusion

The most prominent drug formulations comprising nanoparticles are liposomes, drug nanocrystals, and iron colloids as illustrated by the earlier mentioned extensive description. The most frequently measured characteristic—particle size distribution—and the DLS and high-resolution imaging techniques employed will be the initial focus of the *USP* in preparing general chapters to address these topics.

A strategy will then be adopted to continue to introduce general chapters as new delivery systems come to market and to increase the compendium of important physicochemical properties measured. In this regard zeta-potential measurement has been identified as an important method for which a general chapter should be developed. In addition, the expert committee with the most relevant expertise to prepare these chapters

will be alerted to the need and tasked with generating the document (e.g., physical analysis, dosage forms or excipients).

There is a need for clarity on CQAs, their measurement and impact on product quality, safety, and efficacy.

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Additives and Processing Aids in Pharmaceutical Excipients

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This article seeks to encourage continued dialogue among stakeholders to achieve consensus regarding excipient additives and processing aids.

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Advances in analytical methodology and increased sensitivity have facilitated detection by pharmaceutical manufacturers of low levels of previously undetected components in well-established, widely used excipients. Unfortunately, this increased awareness has led to potential concerns that excipients and pharmaceutical products containing these excipients with previously undeclared additives, processing aids, and/or concomitant components could now be considered adulterated and/or misbranded. This is, in part, due to these new identified components being considered erroneously by some as impurities in excipients. In addition, compendial excipients having *United States Pharmacopeia–National Formulary* (*USP–NF*) monographs could face further issues because *USP* General Notices 5.20 (1) specifically prohibits the presence of such non-disclosed components.

Many additives, processing aids, and concomitant components have always been present and have had a long precedence of acceptable use in excipients. In addition, excipients containing these additives and processing aids have been safely used in pharmaceutical products for many years (sometimes decades) without incident. However, the identity of these additives and processing aids, as well as their presence, was often not disclosed in excipient composition profiles. In certain cases, excipient manufacturers have not been willing to disclose the identity of such components due to the proprietary nature of their use. As a result, there are a large number of excipients in approved medicines that contain undeclared additives, processing aids, and/or concomitant components.

There is typically a justifiable technical need for additive and processing aid inclusion in excipients. Additives and processing aids should not be reduced or eliminated, or considered as impurities, nor should excipients containing additives or processing aids be avoided without understanding the impact to pharmaceutical product safety or efficacy.

This article expands on a previous publication (2) and a US Pharmacopeial Convention (USP) stimuli article (3) and addresses:

- History and use of additives and processing aids in excipients
- Current regulatory position including acceptance of concomitant components as part of excipient composition
- Recommendations to ensure pharmaceutical products are not being deemed adulterated and/or misbranded.

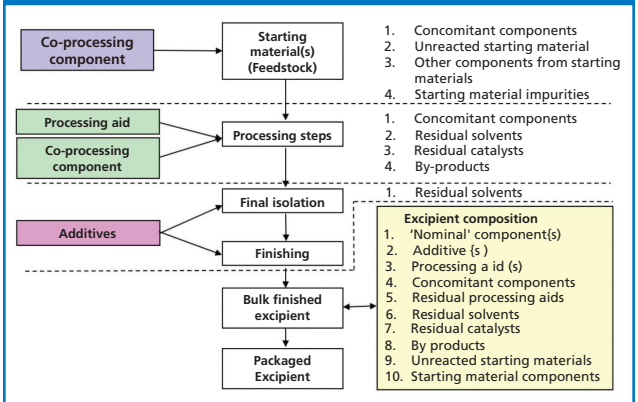
This article focuses on the use of additives and processing aids in excipients with established safety profiles and precedence of use and the concerns with compliance to FDA labeling and *USP* General Notices requirements. The presence of additives, processing aids, and concomitant components has not been well understood by regulators and pharmaceutical manufacturers. A follow up article will address concomitant components which, based on USP's stimuli article (3), are now recognized as a natural part of excipient composition and not as impurities. **Table I** provides the International Pharmaceutical Excipients Council (IPEC) definitions of common terms (4).

Table I: International Pharmaceutical Excipients Council (IPEC) definitions.

Term	Definition
Additive	A substance added to the excipient to improve or maintain a characteristic such as a preservative, flow agent, antimicrobial, etc.
Processing aid	Materials, excluding solvents, used to aid in the manufacture of an excipient, intermediate, or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc.).
Concomitant component	A substance found in an excipient that is not the intended chemical entity, may be necessary for assuring the proper performance of the excipient in its intended use, and is not an impurity or a foreign substance. (Formerly referred to as minor component, e.g., the main component in polysorbate 80 is oleic acid [~58%] and minor components include other fatty acids [~42%]).
Impurity	An undesirable material found in an excipient as a consequence of the raw materials, excipient manufacturing process, or excipient degradation.

Source: IPEC, "General Glossary of Terms and Acronyms" (Arlington, VA, 2014).

Figure 1: Examples of excipient components.



IPEC Excipient Composition Guide/ 2009

Excipient composition

Most excipients are not pure substances, but rather, multicomponent ingredients that likely would not perform the same if any of the components were removed. Inherent residual and trace components present in excipients are important and can impact key excipient functional characteristics when used in pharmaceutical formulations. These components in excipients are not considered impurities by excipient manufacturers and could vary from supplier to supplier due to different raw materials and manufacturing processes. Although for APIs high purity is deemed a superior product, for excipients high purity is not necessarily better and may lead to decreased functional performance. Examples of excipient components can be found in **Figure 1**.

Additives and processing aids in excipients

Additives are important components commonly used at low concentrations in excipients. Additives provide certain functions such as enhancing stability, modifying pH, preventing microbial growth, etc. For many excipients currently containing additives, the absence of additives could adversely impact excipient performance and/or stability.

Processing aids are used by excipient manufacturers to support excipient manufacturing processes. Examples of processing aid functions might include reducing excipient adherence to manufacturing equipment, increasing powder flow through piping and hoppers/bins, and decreasing viscosity to facilitate pumping.

The benefits from process aid inclusion in excipient composition realized by excipient manufacturers might also be advantageous to pharmaceutical manufacturers. Often, the relationship between excipient composition, physical form, and performance is not fully understood. Removal of undeclared additives and/or residual processing aids could have unintended negative consequences, and the impact of the removal would have to be evaluated in all pharmaceutical products containing excipients with additives and/or process-

ing aids. For example, switching from butylated hydroxytoluene (BHT) stabilized polyethylene glycol (PEG) to an additive-free PEG could compromise pharmaceutical product stability if the pharmaceutical product is unknowingly stabilized by the undeclared antioxidant contained in the excipient. Fully understanding excipient composition profiles, including potential undeclared additives or residual processing aids, via early dialog with excipient manufacturer, would avoid such problems. Additionally, having this information could help to avoid similar future problems should a new excipient and/or supplier be qualified where the substituted excipient comprises different additive or processing aid types or levels or is free of additives or processing aids altogether.

Many pharmaceutical excipients are also manufactured for non-pharmaceutical applications. These applications do not always require identification of additives and/or processing aids. Due to the multitude of industries that excipient manufacturers support, historically, they may not have understood how important it is for pharmaceutical manufacturers to know if additives and processing aids exist in their ingredients. In addition, intellectual property confidentiality concerns may be a factor in non-disclosure of these components. As a result, unlike APIs, which are typically single entities, excipients are often complex substances that may contain components not appearing on labeling or in monographs. Differences in additives and/or processing aids due to raw material sourcing or manufacturing processes can result in different excipient composition profiles for seemingly identical excipients that meet the same pharmacopeial specifications. For pharmaceutical products, excipient substitutions from one supplier to another supplier could have an adverse impact on product performance and could pose potential risks by compromising safety, stability, or efficacy.

Additives and processing aids can serve a variety of functions. These include, but are not limited to:

- **Anti-adherent agents.** Additives such as silica or talc may be used as anti-caking agents.
- **Antioxidants.** Antioxidants are agents that prevent the oxidation process, thus avoiding its deterioration. Potential antioxidants found in excipients might include ascorbic acid, butylated hydroxyanisole (BHA), and BHT.
- **Buffering agents.** Designed to control the pH drift. Examples of buffering agents might include sodium bicarbonate and calcium biphosphate.
- **Diluents/fillers.** Some excipients may contain diluents or fillers such as calcium carbonate and lactose.
- **Emulsifying agents.** Emulsifying agents might be added to an excipient (e.g., simethicone emulsion) to enhance the emulsion stability, thus avoiding separation between two phases. Examples include sodium lauryl sulfate and polysorbate 60.
- **Glidants.** Glidants may be added to powders or granules to enhance their flowability. Examples of glidants might include silica and/or silica derivatives.
- **Preservatives.** Preservatives may be added to excipients in order to prolong their shelf life by protecting them from micro-organism deterioration. Examples of preservatives might include benzoic acid and butylparaben.

Based on excipient good manufacturing practices (GMPs) (5), IPEC-Americas believes that additive and processing aid use should be controlled. The USP stimuli article (3) supports IPEC-Americas' position, as stated in their conclusion: "A distinction must be made between excipient impurities that detract from the quality of the excipient (including safety), and those components which can be present, have always been present, and which may need to be present to achieve the necessary performance in the application."

Therefore, it should be clearly understood that additives and processing aids are not impurities.

The pharmaceutical industry is currently facing a dilemma where FDA and USP expect more detailed composition information in monographs and labeling.

Current regulatory situation

Due to excipient sourcing globalization and increased need to detect and prevent supply of adulterated ingredients, many new and modernized test methods are now finding previously undetected components in excipients. Historically, excipient manufacturers have used common techniques that measure single-variable characteristics, like solution pH, to confirm desired endpoints. These techniques do not detect the presence of multiple components of a product. With the concern for adulterated ingredients, more sophisticated methods, such as high-performance liquid chromatography (HPLC), are employed and can detect the presence of multiple components within a given sample. Although they are now being detected, these components have always been present but undetectable by older, less sophisticated methods.

Further, preclinical toxicology studies conducted on excipients containing additives and processing aids have not exposed any health or safety issues or any other adverse impact due to the presence of these excipient components.

FDA expects pharmaceutical manufacturers to have a thorough understanding of composition and impurities in pharmaceutical products. As a result, because these components had not been disclosed in the past, and because pharmaceutical manufacturers are analyzing for and finding these components due to advances in analytical techniques, it is not well understood if these components have been added intentionally or in the case of concomitant components, are inherent to excipient composition and are not impurities.

IPEC-Americas survey. IPEC-Americas is concerned that discovery of additives or processing aids present in excipients could result in undue alarm and potentially trigger consequences that could negatively impact availability of pharmaceutical products when there is no safety concern. As a result, IPEC-Americas completed a survey to identify additives and/or processing aids that are integral to excipient composition. The survey identified a list of more than 70 additives currently undeclared in commonly used excipients with all but five of the additives currently listed as excipients in the FDA Inactive Ingredient Database

(IID). Examples include, but are not limited to, silica, BHT, and propyl gallate.

Based on the survey results, IPEC-Americas developed a backgrounder document (6) that includes a list of additives and processing aids used in excipients, submitted a formal request to FDA in July 2017 (7) for a meeting to develop a strategy for handling undeclared additives and processing aids in excipients, and continues to look forward to dialoging with them.

Concerns with current USP policy. The excipient manufacturers have concerns about *USP* General Notices 5.60, which states, "the presence of an unlabelled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater" (8). This is further complicated by *USP* General Notices 5.20 requirements that state, "Official substances may contain only the specific added substances that are permitted by the individual monograph. Such added substances shall not exceed the quantity required for providing their intended effect. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s)" (1).

Therefore, based on *USP* General Notices 5.60 and 5.20, presence of undeclared additives or processing aids, at or above 0.1%, is not allowed. This is a major concern to excipient manufacturers because undeclared additives or processing aids are present in many *USP*- or *NF*-grade excipients currently used in pharmaceutical products and typically this has been the case for many years.

Ensuring drugs are not being deemed adulterated and/or misbranded

The pharmaceutical industry is currently facing a dilemma where FDA and USP expect more detailed composition information in monographs and labeling. In addition, pharmaceutical manufacturers need a better understanding of excipient composition. However, excipient manufacturers may need to keep certain additive and processing aid information confidential for intellectual property or trade secret reasons. Resolving this issue will require collaboration by all impacted stakeholders.

Historically, there has not been a consistent approach to disclosure of additives and processing aids in excipients, even though they have been used for many years without adversely impacting product safety. Given the large number of excipients currently in approved medicines containing undeclared additives or processing aids, and the much greater number of pharmaceutical products potentially affected, there is an urgent need for the pharmaceutical and excipient industries, FDA, and USP to collaborate in developing a strategy for addressing additives and processing aids in excipients. This approach should allow excipient suppliers to share confidential information with FDA without direct disclosure of the identity and level of additives and/or processing aids to pharmaceutical manufacturers.

Specific recommendations from IPEC–Americas include:

1. To avoid restricting current, safe excipient use, FDA should review and acknowledge additives and processing aids not listed in the IID, but which have historically been present in and demonstrated to be safely used in excipients.

2. FDA should exercise enforcement discretion to allow additives and processing aids, listed in the IID and present in excipients, as well as individually in pharmaceutical product formulations to exceed IID maximum potency limits in final pharmaceutical products, if it can be shown that there is a precedence of use in excipients having been used in the route of administration being reviewed.

3. FDA, USP, and industry stakeholders should collaborate to develop a strategy that addresses how intellectual property and labeling issues related to additives and processing aids might be handled. One such approach could include a bridging justification, reference to use in food, or generally recognized as safe (GRAS) position to justify the safety.

4. USP should include identified excipient additives and processing aids in the exclusion list for compliance with *USP* General Notices 5.60.10 impurity labeling requirements. Current list of exclusions includes:

- Fermentation products and semi-synthetics derived therefrom
- Radiopharmaceuticals
- Biologics
- Biotechnology-derived products
- Peptides
- Herbals
- Crude products of animal or plant origin.

5. USP should create a new General Notice section 5.20.15 that exempts excipients from declaring specific additive and processing aid types and levels on labeling unless the excipient manufacturer desires to do so. This information, when considered confidential by the excipient manufacturer, can be shared with FDA using a Type IV drug master file (DMF) and referenced in drug applications using a letter of authorization. The excipient manufacturer, however, would need to identify that an additive or processing aid was present.

Conclusion

Many excipients contain additives and/or processing aids to enhance performance or facilitate manufacture. While additives can be used for such purposes as pH buffering, controlling microbial contamination, preservation, etc., processing aids are used to improve manufacturing processing and efficiency. Many additives and processing aids contained in excipients may not be found on labeling or in monographs, and additive and processing aid concentrations and types may differ among excipient manufacturers. Generally, additives and processing aids are themselves excipients or food additives and have been used safely in pharmaceutical products for years and sometimes decades. As a result, their presence in pharmaceutical products poses no risk to patient safety. However, while additive and processing aid use pose no safety risk, absence of these components could compromise pharmaceutical product stability and efficacy.

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Advancements in Encapsulation Technology

Nicolas Madit and Matt Richardson

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Technological advancements can address the formulation and dissolution challenges of HPMC polymers.

With an ever-increasing range of hard capsule polymers to choose from, optimizing performance and efficacy is a priority in the drug development process. As many new chemical entities (NCEs) are moisture-sensitive, formulators must look to technologies and alternative processes to stabilize these formulations and improve drug performance. In particular, capsules that utilize the excipient polymer hydroxypropyl methyl cellulose (HPMC) have seen increasing global use for their stability against challenges that typically afflict gelatine capsules.

HPMC has been well-vetted in the market as a pharmaceutical excipient long before its use as a capsule polymer. To that end, it has attained regulatory approval in all major pharmaceutical markets. HPMC-based capsules, in general, are the preferred polymer for formulators as a result of lower moisture content compared to gelatine capsules, which makes them ideal to encapsulate moisture-sensitive and hygroscopic APIs.

While first-generation HPMC capsules presented formulators the challenge of differing *in-vitro* dissolution profiles, an innovation in the manufacturing process of HPMC capsules has provided reproducible, pH-independent *in-vitro* dissolution performance comparable to gelatine capsules on the market. Today, HPMC capsules are the preferred alternative dosage form to gelatine capsules as both a valuable and effective development tool, providing formulators the flexibility to encapsulate a broader range of drug products and formulations.

Formulation challenges caused by moisture

In formulation, careful attention must be paid to moisture and its impact on the overall final dosage form. Moisture, usually derived from the environment and atmosphere, can be detrimental to the physical stability of the capsule and/or chemical stability of the API.

Many APIs and excipients are either moisture-sensitive or hygroscopic. By absorbing water from the capsule or environment, compounds may chemically degrade or change morphology or physical characteristics. As such, the capsule selection offering a lower moisture content to maintain robustness and protect the API would be greatly beneficial.

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Gelatine capsules contain an average moisture content of 13–16%, whereas HPMC capsules have a lower average moisture content of 5–8%.

When hygroscopic compounds interact with gelatine capsules, the loss of moisture can lead to brittleness of the capsule shell. Gelatine relies on water for plasticity, while HPMC capsules do not. Therefore, HPMC capsules can sustain mechanical stability at a lower percent relative humidity (% RH) range (**Figure 1**) and are better suited for moisture-sensitive and hygroscopic APIs (1).

As a basic requirement to ensure the efficacy of a drug and patient safety, the API must remain stable in the finished dosage form until the end of its shelf life. The stability of gelatine capsules relies on an environment maintained at 35–65% RH and 15–25 °C. Some formulations cannot remain stable in these conditions, which can lead to degradation of the drug or changes in the formulation over time. In a study of moisture diffusion of hard gelatine capsules and HPMC capsules, the moisture uptake of gelatine capsules was higher at all levels of % RH (2). The study found that HPMC would appear to be a better choice in protecting hygroscopic capsule contents from moisture-induced deterioration even when both types of capsules are stored properly.

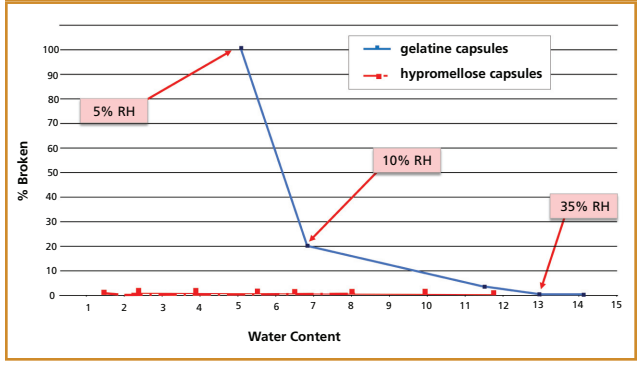
With the ability to protect encapsulated APIs against moisture, HPMC capsules are an ideal formulation tool when gelatine capsules are incompatible.

Another study observed HPMC and gelatine shells, filled with a moisture-sensitive API, in inductively sealed bottles such that the primary source of moisture is the capsule shells. The API filled in HPMC capsules only showed 2% degradation versus 8% in gelatine over 18 months. HPMC shells demonstrated less hydrolysis caused from the moisture content contained in the capsule shells, meaning increased shelf life of moisture-sensitive compounds encapsulated in HPMC capsules and continued safety and efficacy of the drug.

Diving into dissolution

Efficacy generally refers to the product's stability in dissolution performance once it is ingested. There are various types of commercial two-piece HPMC capsules developed using both different formulations and manufacturing processes, providing distinct *in-vitro* and *in-vivo* characteristics. HPMC capsules were first developed with the use of a gelling system to create a two-piece hard capsule. Those first-generation

Figure 1: Effect of moisture content on capsule shell brittleness for gelatine and hypromellose capsules. RH is relative humidity.



HPMC capsules relied on secondary gelling agents (e.g., carrageenan, gellan gum) and ionic gel promoters (e.g., potassium acetate, potassium chloride) that cause variability in dissolution rates depending on the pH and ionic strengths of the dissolution media. Traditional HPMC capsules did not dissolve consistently, and as expected, the encapsulated compound would be released inconsistently or belatedly.

A common gelling system, kappa-carrageenan and potassium salts, used in first-generation HPMC capsules showed enhanced resistance to dissolution when in the presence of foods with potassium and calcium cations (3). The delays in dissolution time resulting from that interaction in the stomach were shown in an *in-vitro* study in which caffeine-filled traditional HPMC capsules were tested in a number of dissolution media.

At pH 1.2 *United States Pharmacopeia (USP),* the normal acidity level of the stomach, 90% of the caffeine dissolved within approximately 15 minutes (**Figure 2**). The addition of 2 g/L of potassium chloride (KCl) resulted in no dissolution after 15 minutes, and a caffeine dissolution between 70% and 80% took more than one hour. As KCl content increased, the dissolution was delayed further; KCl content of 9 g/L had a dissolution rate of 10% in 45 minutes. The study also tested HPMC capsules in an alternative environment of simulated milk fluid, in which results showed similar delays in release and low dissolution rates thereby suggesting a difference in fed- and fasted-state dissolution.

HPMC capsules also demonstrate stable dissolution performance at high temperatures for short periods of time (4). After being heated at several temperatures—the highest reaching 90 °C—for 24 hours, the disintegration performances of hard gelatine and hypromellose capsules were tested in three media: pH 1.2 *USP* buffer, demineralized water, and pH 6.8 *USP* buffer. In this test, hard gelatine capsules sustained expected dissolution performance until they were heated at and above 60 °C, at which point they became deformed, partly molten, and stuck together. In general, thermal stability up to 60 °C is not always the case for gelatine capsules, as there is dependence on humidity, and gelatine may demonstrate chemical instability within that temperature range. HPMC

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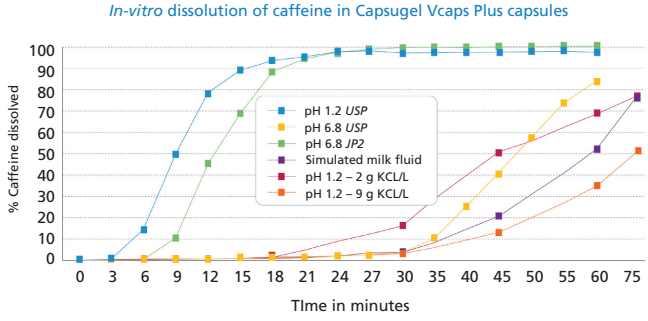
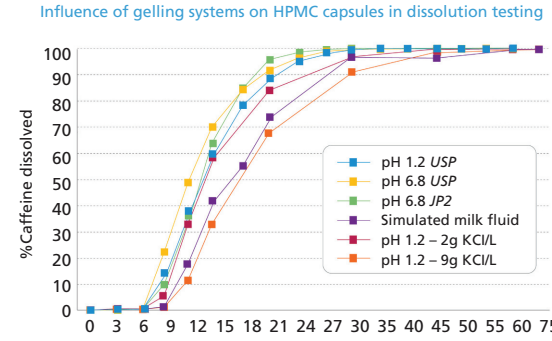
Figure 2: Caffeine *in-vitro* dissolution in hypromellose capsules produced with gelling systems vs. hypromellose capsules produced without gelling systems (Vcaps Plus capsules). Where *USP* stands for *United States Pharmacopeia*, *JP2* stands for *Japanese Pharmacopoeia—Disintegration Test Fluid No. 2.*



In-vitro dissolution of caffeine filled in hypromellose capsules produced with gelling systems

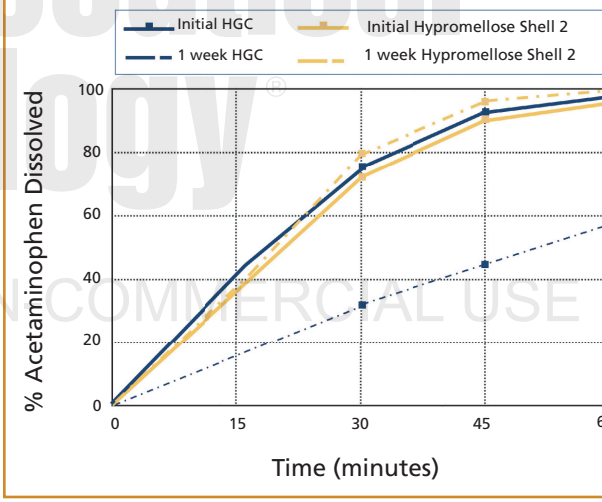


Caffeine *in-vitro* dissolution with various dissolution media exhibit pH independence with Capsugel Vcaps Plus Capsules

capsules remained functional and demonstrated no change in dissolution performance across all temperatures and media tested.

Another challenge that affects dissolution presented by gelatine is hard-gelatine cross-linking. Cross-linking can cause considerable changes within *in-vitro* dissolution profiles. The phenomenon often occurs when the capsule is exposed to chemicals incompatible with gelling agents or high temperatures. Dissolution studies have shown HPMC polymers are unaffected by cross-linking derived from either high heat and humidity or cross-linking chemical promoters like formaldehyde (**Figure 3**).

Figure 3: Dissolution of acetyl-para-aminophenol (APAP) in human chorionic gonadotropin (HGC) and hypromellose shell 2 after one-week exposure to lactose spiked with formaldehyde.



Thermo-gellation process enables next-generation HPMC hard capsules

Advancements in HPMC capsules have led to the widespread use of second-generation HPMC capsules—those without secondary gelling agents, making the risk of inconsistent dissolution avoidable. Due to the lack of a gelling agent, these advanced capsules provide improved and parallel dissolution performance compared to first-generation HPMC and gelatine capsules, respectively, and are able to mitigate issues of cross-linking, demonstrating enhanced stability when gelatine and other HPMC capsules may be less compatible.

Manufactured through a uniquely developed thermo-gellation process, Vcaps Plus capsules are made without a gelling system altogether, which is still commonly found in many marketed HPMC capsules. Dissolution studies have shown that performance variability is often noted when a gelling system is incorporated in the HPMC matrix, but a more consistent performance is afforded when the capsule is comprised of only HPMC and water as ingredients.

A human bioequivalence study of Vcaps Plus (Lonza Capsugel) capsules, with 24 patients, demonstrated equivalent performance to hard gelatin capsules with three BDCCS Class 1 biomarkers—acetaminophen, acetylsalicylic acid, and caffeine—further demonstrating its excellent performance while similar studies done on HPMC capsules which do contain a gelling system show greater intra-patient variability as well as a notable difference in onset time of drug absorption (T_{lag}) (4).

The study used Excedrin extra strength caplets to compare the dissolution rate of a fixed-dose combination compressed caplet containing three different rapidly-absorbed drugs over-encapsulated with either gelatine capsules or HPMC capsules using a thermo-gelation process. The *in-vitro* dissolution results confirmed that the APIs had slower release from the over-encapsulated product than from the unencapsulated caplets. As observed, an onset in the release of active of 5 minutes for the gelatine and 10 minutes for HPMC over-encapsulated dosage form versus the unencapsulated caplet. However, all three forms achieved a 95% release within 30 minutes.

Despite a short lag time generated by encapsulation, the use of either gelatine and HPMC capsules did not result in a significant difference in *in-vivo* pharmacokinetics in 24 human subjects. These results suggest that drug release and absorption from gelatine and HPMC capsules for the three model compounds are equivalent.

A study utilizing a Sotax disintegration test with an automated end point compared the disintegration times of Vcaps Plus capsules with gelatine capsules (5). Similarly, the test showed that the former capsules have no significant difference in disintegration time compared to gelatine capsules and will disintegrate in less than 15 minutes per requirements of major pharmacopoeia.

Further optimization of dissolution performance can be achieved with absolute pH and ionic media independence. Advanced HPMC capsules are effective for pharmaceutical manufacturers looking to optimize product performance. Given the gelatine-like appearance, dissolution, and machinability performance, formulators can begin development with HPMC capsules or more seamlessly switch from gelatine capsules to HPMC capsules with reduced costs and delay in repetitive stability testing.

Conclusion

With the ability to protect encapsulated APIs against moisture, HPMC capsules are an ideal formulation tool when gelatine capsules are incompatible. Moreover, HPMC capsules without gelling systems have been designed to overcome inconsistent dissolution performance presented by the interaction between gelling agents and the dissolution environment. Increased stability of the formulation and reproducible *in-vitro* dissolution help pharmaceutical manufacturers' drug product and encapsulated API remain effective and safe throughout shelf life, and the capsule acts as an optimal solution to consistently deliver the drug in the patient's body.

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Additives—*Contin. from page s19*

USP General Notices 5.20 and 5.60, in their current language, require additives and processing aids to be on labels and reported when used at levels >0.1% (based on International Council for Harmonization Q3B). Such a requirement(s) may present challenges for excipient manufacturers due to confidentiality concerns and for pharmaceutical manufacturers who may not understand the complete excipient composition profile. IPEC-Americas recommends changes to *USP* General Notices 5.20 and 5.60 regarding labeling requirements for additives and processing aids.

IPEC-Americas takes the position that excipient and pharmaceutical manufacturers should have open communication regarding the potential for the presence of additives and processing aids (9–11). This can include use of confidentiality disclosure agreements during excipient/supplier qualification. Details for accessing information regarding additive and processing aid use also may be via DMF, when appropriate. However, in other regions (e.g., Europe) where excipient DMFs are not applicable, the need for further discussion with regulators may be required.

Lastly, stakeholders, USP, and FDA, need to collaborate and develop a path forward that would affect the following:

- Ensure that identification of low levels of additives and processing aids in established excipients does not lead to pharmaceutical products being deemed adulterated and/or misbranded.
- Ensure that excipients containing additives and/or processing aids comply with revised USP requirements (as proposed).
- Create a means to share the above information in a manner that does not compromise excipient manufacturer's intellectual property.

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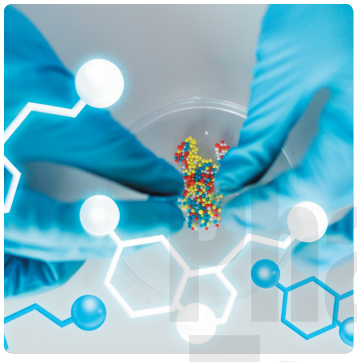
Uncovering Hidden Risks in Solid-State API Properties

Jonathan Loughrey



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An understanding—during early development—of the solid form landscape of an API can enhance product quality and manufacturing processes. By predicting polymorphism and hydrate formation developers can achieve better control over solid drug forms through scale up and development.

In the manufacture of small-molecule APIs, developers must be wary of the phenomenon of polymorphism, where an organic molecule can adopt a number of crystalline forms. Controlling the solid form of an API is a critical step in ensuring manufacturing control, as the uncontrolled occurrence of polymorphs can affect the filtration and drying characteristics during the synthesis, as well as the drug's formulation, long-term stability, and solubility properties. For example, the drug ritonavir had to be temporarily withdrawn from the market following launch, after a less-soluble polymorph that caused the drug to have much reduced therapeutic effect was discovered (1).

A number of strategies can be employed to control the polymorphic form during manufacturing. These strategies include seeding—where a small amount of the desired polymorphic form is introduced to promote crystallization of that form via nucleation—and screening for and choosing an appropriate solvent to perform the crystallization step. In another method, crystallization control, the crystallization is designed with the use of a quality-by-design (QbD) procedure and monitored using process analytical tools (PAT) to ensure it is robust and predictable during changes to temperature, solvent composition/anti-solvent addition, or agitation rates. The key step in delivering the desired solid form of an API is understanding and characterizing the polymorphic landscape to identify and predict phase transitions.

Hydrate formation and associated risks

Due to the ubiquitous nature of water vapor, hydrates are often very stable under ambient conditions. It is estimated that up to 75% of all pharmaceuticals are affected by hydrate formation (2), which has a direct effect on the physical properties of the API, and subsequently how a drug will eventually perform *in vivo*, in terms of stability, solubility, and bioavailability.

Hydrate formation can become apparent at any stage of development or manufacturing operations; specific steps can be taken to avoid this, but only once the hydrate has been understood. The risk of hydrate formation is increased upon formation of ionic species (salts) or a molecule hav-

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Table I: Analytical techniques for physical and structural analysis of polymorphs.

Technique(s)	Method(s)
Thermal analysis	Thermal gravimetric analysis (TGA) Differential scanning calorimetry (DSC) Variable temperature X-ray powder diffraction (VT-XRPD)
Hygroscopicity measurements	Dynamic vapor sorption (DVS) Variable humidity X-ray powder diffraction (VH-XRPD)
Critical water activity studies/maps	
Kinetic and thermodynamic solubility	Van 't Hoff Plots
Intrinsic dissolution rates (IDR)	High-performance liquid chromatography (HPLC)
In-situ characterization techniques	Infrared spectroscopy (IR) Near-infrared spectroscopy (NIR) Raman spectroscopy
Morphology	Polarized light microscopy (PLM) Scanning electron microscopy (SEM)
X-ray diffraction	Single crystal X-ray diffraction (SC-XRD) X-ray powder diffraction (XRPD)

ing polar functional groups such as carbonyl, hydroxyl, or amino functionalities.

Studies to predict polymorphism and hydrate formation are possible using computational methods and correlate well with experimental data (3–5). Standard techniques for characterization are shown in **Table I**.

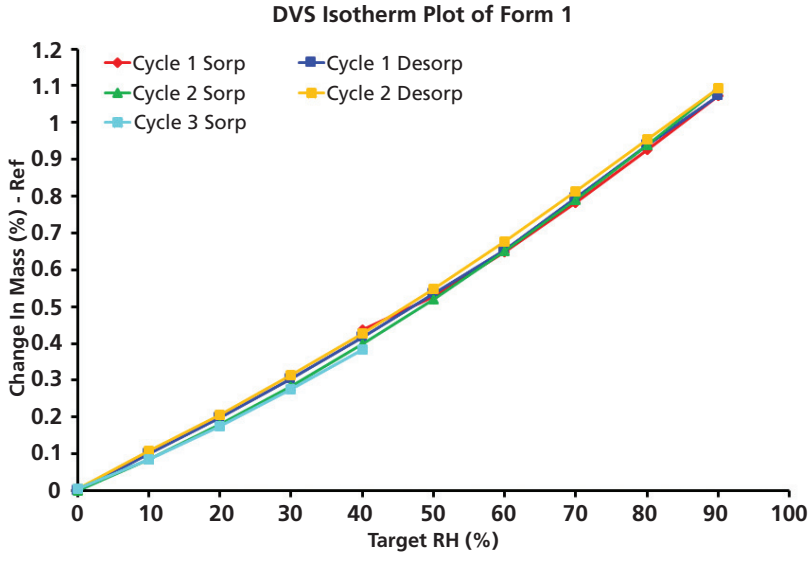
Once the studies are complete, the results offer crucial structural data on the solid forms, allowing crystallization development to be undertaken to enhance particle morphologies and give better control over the solid forms as the product progresses through scale up and development. Avoiding hydrate formation allows efficient large-scale manufacturing, yielding an API with good handling and processing properties, as well as being optimized for the formulation of patient-ready dose forms.

Locating and understanding hydrated forms of an API

As discussed, facile hydrate formation can drastically alter the processability, stability, and aqueous solubility of a given API; this example shows how an API was fully characterized to allow the development of a reliable method for synthesis, avoiding an undesirable hemi-hydrated form that was uncovered during a polymorph screening project.

Upon arrival, the single-crystal structure of the preferred polymorphic form, Form 1, was determined wherein the structure was found to be close-packed with normal density (1.3 g/cm^3) and no solvent/water accessible voids. Similarly, thermal gravimetric analysis (TGA) confirmed the anhydrous, non-solvated nature of the form, while analysis by dynamic vapor sorption (DVS) at 25 °C, showed minor hysteresis with a maximum mass uptake of 0.95 wt.% at 90% relative humidity (RH), confirming its status as a developable form (**Figure 1**).

Figure 1: Dynamic vapor sorption (DVS) isotherm plot of Form 1. RH is relative humidity.



During further screening, it became apparent that the changes in water activity could promote morphological changes in the API. As shown in **Figure 2**, when slurried in alcohol:water systems of varying water activity (Aw), the morphology changed from an irregular morphology at 0.1 Aw to a plate-like morphology at 0.3 Aw and finally, to a rod-like morphology at 0.9 Aw. It was noted that at 0.5 Aw, a mixed morphology was apparent, comprised of both plates and rods, which indicated that competing growth kinetics that could be exploited to maximize processability and filterability of the API at a later stage of the development program.

Investigation into the solid form recovered at high water activity (0.9 Aw) by X-ray powder diffraction (XRPD) showed that this

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was a novel form, herein denoted as Form 2, and found to be hemi-hydrated when characterized by TGA and Karl Fisher titration.

To properly de-risk the novel, hemi-hydrated Form 2, a suitable sample was characterized by DVS, which showed that the input Form 2 was stable between 10–90% RH, but dehydrated rapidly below 10% RH, forming a novel anhydrous species, Form 3 (**Figure 3**). When the relative humidity at 25 °C was cycled back to 40% RH, Form 3 prevailed, but rapidly rehydrated when cycled to 50% RH. These observations highlighted significant risk with development of the hemi-hydrated species for two reasons: the structure of the hemi-hydrated form collapsed on dehydration, forming a novel, anhydrous form; and upon rehydration, Form 3 collapsed and became amorphous prior to re-crystallizing to Form 2.

Variable humidity X-ray diffraction confirmed this observation. It was seen that within the window 30–70% RH, re-hydration of Form 3 to Form 2 was facile, and predictable, but proceeded via an increase in amorphous content (**Figure 4**), significantly heightening the risk associated with the development of either Forms 2 or 3. Based on the evidence, it was clear that the anhydrous Form 1 was the most desirable form for further development. However, to understand the conditions under which Form 1 would prevail, competitive slurry experiments were performed on Form 1 (anhydrous), Form 2 (hemi-hydrate) and Form 3 (anhydrous) in process relevant media. These experiments clearly

Figure 2: Light micrographs showing morphological control.

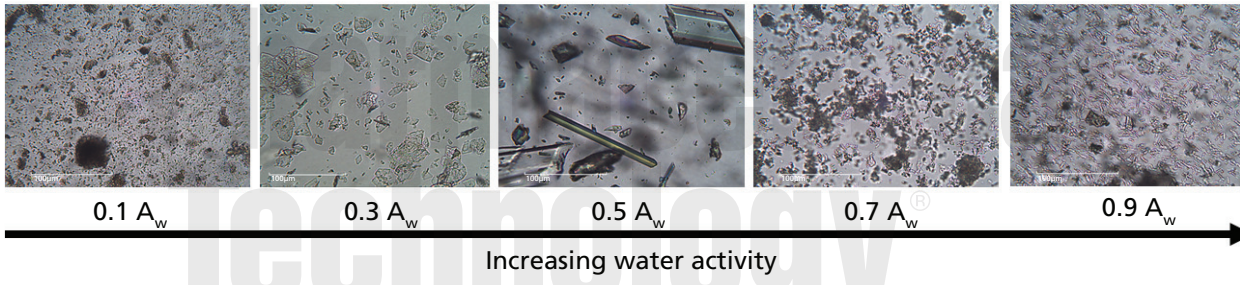


Figure 3: Dynamic vapor sorption DVS Isotherm Plot of Form 2. RH is relative humidity.

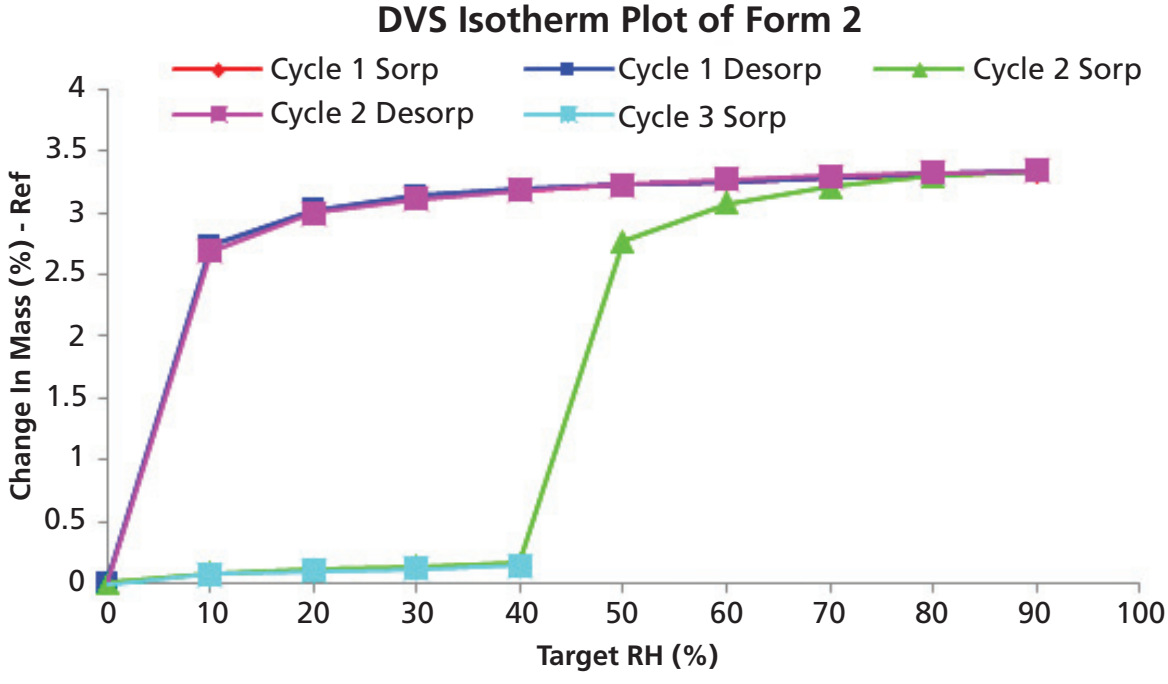


Figure 4: Variable humidity X-ray powder diffraction 2Θ diffractograms (Black: Form 3; Blue: Form 2). RH is relative humidity.

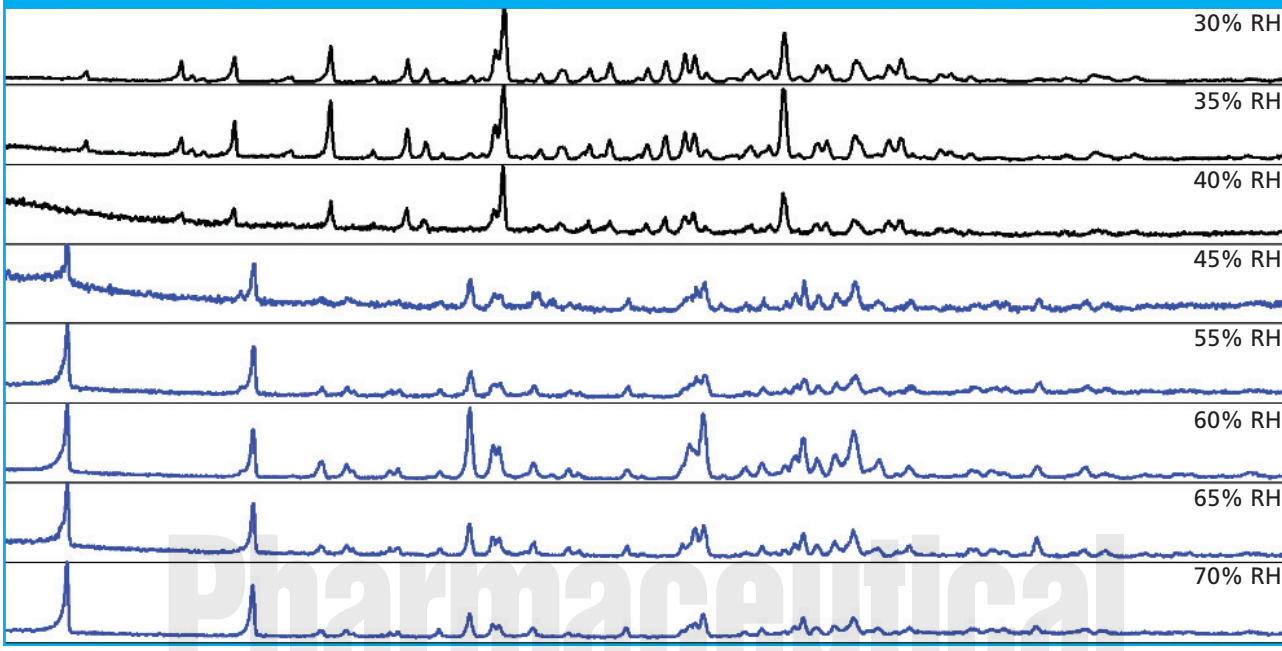
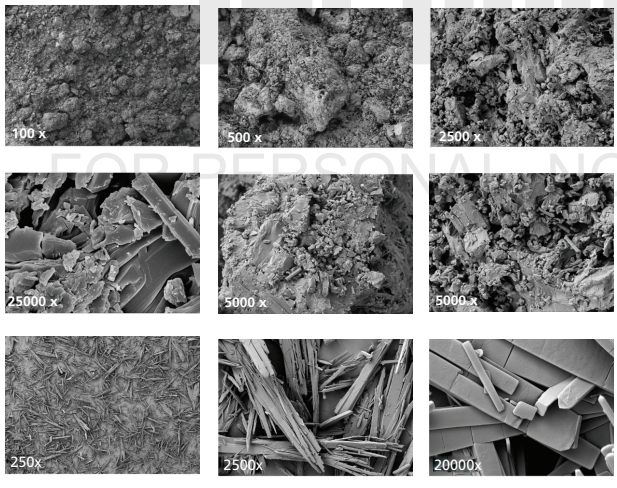


Figure 5: SEM images of Form 1 before (top 6 images) and after (bottom 3 images) morphology development.



showed Form 1 to be the preferred, thermodynamic form under anhydrous conditions for further development.

Despite being the thermo-dynamically preferred form, a key disadvantage for the development of Form 1 was found to be its poor particle morphology. During the screening studies, however, morphological differences were noticed due to competing crystal growth kinetics in systems containing varying water activity. Using the non-random two-liquid (NRTL) equation and measured water activity, a detailed hydration map was investigated across multiple organic solvents; it was found that the morphology of Form 1 was greatly improved using small volume aliquots of water in ICH class 3 solvents (e.g., 0.5 Aw = 95 % isopropanol : 5 % water, % v/v) to minimize the risk of hemi-hydrate formation. This vast improvement in particle morphology was exemplified by scanning electron microscopy (SEM) as shown in **Figure 5**.

The significant increase in particle size coincided with an increase in crystallinity and improvement in material handling properties, specifically with respect to flowability and bulk density. Once the preferred Form 1 was isolated with improved particle morphology, crystallization development was able to be undertaken to carry the compound forward by thoroughly investigating the metastable zone and understanding the critical process parameters of the isolation step directly from solution using a design of experiments approach.

De-risking the solid form landscape of an API early in development is of utmost importance to ensure success as a viable drug candidate. By controlling the solid-state properties of an API, downstream processing and manufacture will benefit from predictable stability, solubility, and bioavailability, minimizing development timelines and cost. This case study exemplified the risk that hidden hydrates may pose to process development, but when the solid form landscape is thoroughly investigated and stringently controlled, significant advantages in particle control may be realized.

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How Excipient Type Influences Self-Emulsifying Drug Delivery

Frank Romanski

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Lipid-based drug delivery systems are a well-established and effective technology for enhancing the bioavailability of poorly water-soluble APIs. High-throughput platforms can be used to develop tertiary phase diagrams, which can be leveraged to identify the most stable SEDDS formulations for lipid-based drug delivery systems.

Most published estimates state that greater than 70% of drugs in the small-molecule pipelines are considered poorly water soluble. Because the human body requires that a drug essentially be solubilized in an aqueous environment, this poor water solubility poses an enormous challenge to effective drug delivery. Drugs may be poorly water soluble for a number of reasons, such as molecules with strong crystal lattices and high melting points or, on the other end of the spectrum, drugs exhibiting extremely high hydrophobicity that simply do not interact physico-chemically with water. If these drugs are not solubilized, they cannot be absorbed and are thus not producing a therapeutic effect. As the "easy" molecules (i.e., those that are both water soluble and readily absorbed) become more rare in modern pharmaceutical pipelines, effective technological and formulation strategies need to be developed to effectively deliver the poorly water soluble molecules (i.e., APIs in BCS Class II and IV).

One key aspect for these formulations and technologies is that they need to be practical; formulations must be straightforward to manufacture, as well as pragmatic for the patient to consume. Thus, techniques such as amorphous solid dispersions (ASDs), which are made using hot melt extrusion and spray drying, and lipid-based drug delivery systems (LBDDS) are effectively used in the majority of the poorly water-soluble drugs brought to market. ASDs can be easily formulated into tablets, which are a widely accepted dosage form to be manufactured and ultimately consumed. LBDDS, with formulations that are often liquid or semi-solid, may be produced into hard or softgel capsules, which are also highly accepted from a patient compliance standpoint, and the knowledge base to manufacture these and scale them up exists within the industry. Despite the ease of manufacturing, however, the challenge remains of how to properly formulate LBDDS, and more specifically, self-emulsifying drug delivery systems (SEDDS), which are notoriously difficult to formulate from scratch.

LBDDS delivery mechanism

LBDDS use the body's own mechanisms to effectively deliver drugs. As an example, when the body digests a fatty meal, the lipids and fats are dispersed through the gastrointestinal tract (GIT), where they are emulsified and subsequently absorbed. During the digestion process, lipophilic solubi-

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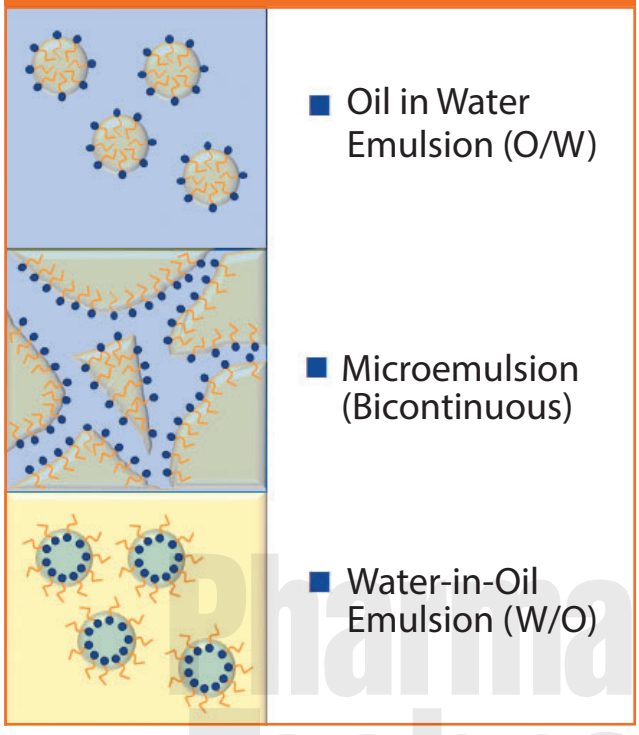
Figure 1: Microemulsions exhibit a stable region.



lized vitamins and nutrients are absorbed. LBDDS and more specifically, SEDDS, work using this same mechanism. The encapsulated formulation releases from the capsule in the stomach or intestine (which may be targeted through enteric or sustained release coatings); the oils are emulsified and stabilized by the surfactant phase to form small droplets, which consequently allow for rapid absorption of the drug into the body. Once dispersed, these are effectively an oil/water (O/W) emulsion. One could start with a predispersed O/W emulsion; however, a formulator cannot encapsulate an O/W emulsion effectively because it is inherently unstable from a thermodynamic perspective, and over a relatively short amount of time it will fully separate. To overcome this tendency and to formulate a truly stable system requires creating a microemulsion, which no longer has a defined oil and water phase, but rather a bicontinuous phase. Unlike traditional O/W or water/oil (W/O) emulsions, these are thermodynamically stable, clear, low viscosity, and exhibit a high capacity for drug solubilization. The stable region is drawn theoretically in **Figure 1**.

Microemulsion regions are also drawn using the classic fishtail diagram (see **Figure 2**), where the Winsor Type IV emulsions have the right blend of oil, water, and surfactant to maintain an equilibrium bicontinuous system. In these systems, there are no true droplets, but rather single digit nanoscale structures that coexist. The Y-axis on the diagram in **Figure 2** may be the surfactant blend (hydrophilic surfactant and hydrophobic surfactant) or the temperature of the system.

It is these Winsor Type IV microemulsions that may be encapsulated effectively. Once these stable microemulsion systems inside of the capsules meet with the aqueous environment of the GIT, the system shifts to an O/W emulsion. Depending on the formulation, droplets can range from tens of nanometers to millimeters in diameter. These droplets encapsulate the poorly water-soluble drug and allow for absorption of the API as the oil is digested, forming micelles and other complex colloidal structures. In theory, this approach works well, but in reality, it can be challenging to isolate stable microemulsion regions within a given system in order to build formulations.

Formulating stable systems

SEDDS, which create tiny nano-scale droplets upon contact with the GIT, are highly effective, and a number of APIs have been recently approved that use this formulation approach (e.g., Rydapt, Neoral, Avodart, Norvir). However, what is yet to be comprehensively studied is the effect of excipients on the formulations. Although it is generally accepted that an oil-phase, primary surfactant, and secondary surfactant are required to effectively formulate these products,

Figure 2: A fishtail diagram shows microemulsion regions; O is oil; W is water; S is surfactant.

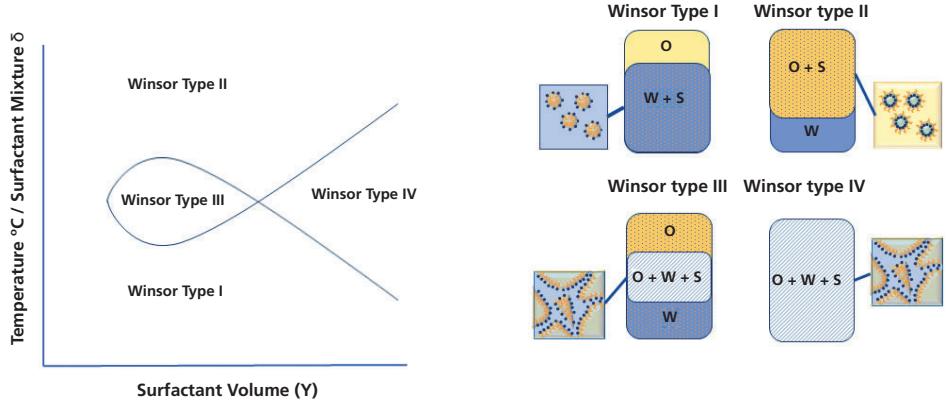


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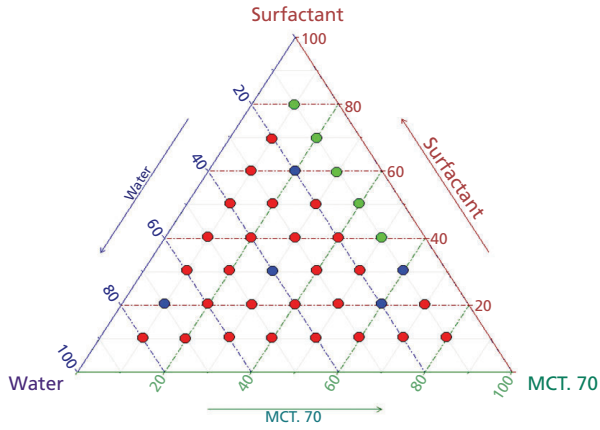
Figure 3: The stable regime in indicated by the green dots in the tertiary (oil, water, surfactant phase) diagram. The oil phase is a medium chain triglyceride (Kollisolv MCT 70, BASF).



scientists must often work with existing formulations. Otherwise, they must start from scratch, which can require hundreds if not thousands of experiments.

With the aim of reducing the amount of experimentation and the time required to evaluate the applicability of SEDDS for different formulations, the author and his colleagues developed an approach that may be useful in future work. Their research, summarized in this article, used a high-throughput robotic system to establish tertiary phase diagrams (**Figure 3**) to determine stable regimes within these surfactant, oil, and water phase diagrams. Then different formulations using different surfactants, oils and aqueous phases were evaluated within this stable range to determine their applicability.

Within the stable region indicated by the green dots in **Figure 3**, a series of formulations were crafted to comprehensively study the effect of excipients on the formulations by varying the oil phase, aqueous phase, and surfactant/blend phase. An aqueous phase was studied because, in most encapsulations (particularly with softgels), moisture ultimately enters the system and reaches an equilibrium with the non-ionic surfactants, sometimes at concentrations greater than 5% w/w. The approach of formulating with an aqueous phase of 10% (either as water, ethanol, or others) builds robustness into the formulation and enhances the ability to maintain stability in the future. This phase may be either water or ethanol; ethanol allows for higher levels of drug solubility and better miscibility between the phases but may pose additional formulation challenges, such as the handling of flammable solvents during manufacturing.

Next, the oil phase, which is primarily responsible for solubilization of the drug and is the primary ingredient that is digested, was designed to be varied based on the solubility of the drug, rate of digestion (e.g., medium chain triglycerides digest faster than long chain), and the concentration, which further affects the digestion rate.

Finally, the surfactant phase was designed. This phase is primarily responsible for the stability of the system as a microemulsion as well as the size and stability of the droplets after the microemulsion "breaks" to form an O/W emulsion. Typically, and in the case of these examples, one would use a hydrophilic and a hydrophobic surfactant to balance the phases and enable the formation of a true microemulsion; this case was also tested by high-throughput screening. The results of these efforts were 10 stable formulations that can be used at multiple temperatures, aqueous/moisture levels, and different applications, as shown in **Table I**.

Formulation test results

Formulations were tested using model drug compounds and studied for stability, robustness, dispersibility, and digestibility using *in-vitro* models (1). These were further corroborated by observing *in-vivo* absorption using a rat model.

Table I. Stable formulations (F1 to F10) for self-emulsifying drug delivery were designed to aid formulation of lipid-based drug delivery systems for poorly water soluble APIs.

	Medium chain triglyceride (Kollisolv MCT 70, BASF) (%) (w/w)	Soybean oil (%) (w/w)	Maisine 35-1 (%) (w/w)	Corn oil (%) (w/w)	Glycerol monocaprylocaprate(%) (w/w)	Polyoxyl 40 hydrogenated castor oil (Kolliphor RH40, BASF) (%) (w/w)	Poloxamer 124 (Kollisolv P124, BASF) (%) (w/w)	Polyoxyl 35 castor oil (Kolliphor EL, BASF) (%) (w/w)	Glyceryl Monooleate (%) (w/w)	Water (%) (w/w)	Ethanol (%) (w/w)
F1	-	27.5	27.5	-	-	35	-	-	-	-	10
F2	10	-	-	-	-	68	-	-	12	10	-
F3	40	-	-	-	-	42.5	-	-	7.5	10	-
F4	10	-	-	-	-	-	-	68	12	10	-
F5	40	-	-	-	-	-	-	42.5	7.5	10	-
F6	10	-	-	-	-	-	68	-	12	-	10
F7	-	10	-	-	-	68	-	-	12	10	-
F8	-	-	-	10	-	68	-	-	12	10	-
F9	10	-	-	-	12	68	-	-	-	10	-
F10	40	-	-	-	7.5	42.5	-	-	-	10	-

Figure 4: Digestion rates of the formulations (F1 to F10).

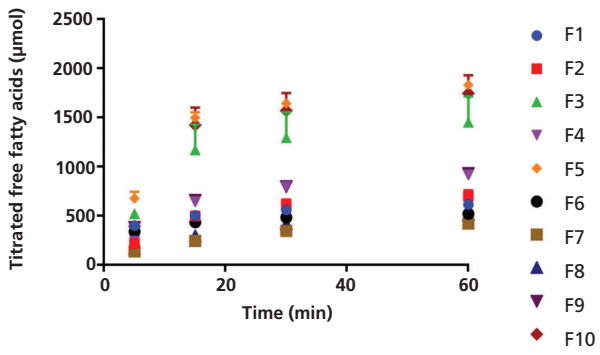
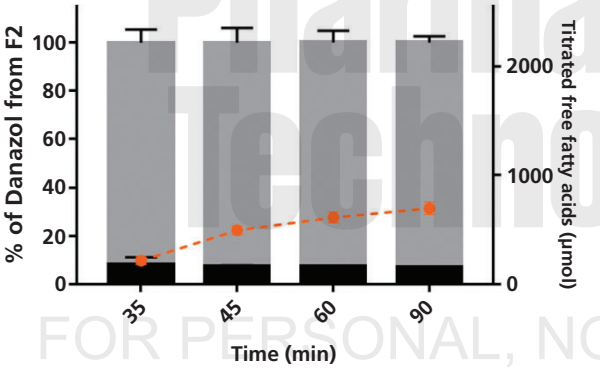


Figure 5: Digestion over 90 minutes with formulation F2 (left) and F3 (right). The orange line is the titrated free fatty acid (digestion rate); the grey bar is solubilized and available API; and the black bar is precipitated, unavailable API.



Each of the formulations listed in **Table I** exhibits unique properties. The use of ethanol, in the case of F1 and F6, allows for higher drug solubility and rapid dispersibility in aqueous media. Those using potent concentrations of surfactant, such as a non-ionic oil-in-water solubilizer and emulsifying agent (Kolliphor RH 40, BASF) used in formulas F2 and F3, exhibit very small droplet sizes upon release (10s of nanometers) and highly stable micellar systems once the oil is digested, although it is important to note that they generally require a few minutes to fully disperse from the capsules. Similarly, those made with a non-ionic oil-in-water emulsifier and solubilizer (Kolliphor EL, BASF) used in formulas F4 and F5, exhibit small droplet dispersions, but a slightly faster digestion due to the faster digestibility of the surfactant. Formula F6 uses a liquid poloxamer surfactant (Kollisolv P124, BASF), which allows for rapid dispersion, but sacrifices stability of the oil droplets. By using other oils, such as soybean and corn oil (formulas F7 and F8, respectively), digestion rates may be varied (MCT being the fastest typically, soybean the slowest), and the solubility of the API may be tailored. Finally, co-surfactants, while a minor component, are key to maintaining the microemulsion. Several formulations are shown using glyceryl monooleate (formulas F2, F3, F4, F5, F6, F7, F8) and glyceryl monocaprylocaprate (formulas F9 and F10), offering different droplet sizes and digestion rates.

Best practices for testing formulations with an API

In order to test one of these formulations, it is generally recommended that the API be first saturated into the oil phase, which can be done by stirring overnight and filtering and testing API content by ultraviolet (UV) spectroscopy or high-performance liquid chromatography. Oil phases (oil + hydrophobic surfactant) and water phases (aqueous + hydrophilic surfactant) should be heated to approximately 60 °C and lightly mixed by hand; the microemulsions self-assemble. The resulting mirco-emulsion may then cool and be dispensed into soft- or hard-shell capsules. Generally, the oil phase will be preloaded with API for formulation. It is recommended that approximately 80% of saturation in the total formulation be used for the final formulation to maintain API stability.

Testing of these formulations can be challenging, because in a standard dissolution bath with UV filter it is often too difficult to parse the API concentration from the droplets, micelles, and other phases in the bath. Therefore, it is recommended that formulators test these using lipolysis, membrane-based absorption models (macroFlux, Pion) or cell-based methods, such as Caco-2. Using a lipolysis mode and the model drug Danazol (synthetic steroid, MP 224.2°C, 337.46 g/mol, LogP = 3.62), the varied digestion rates of the 10 formulations can be clearly noted, as shown in **Figure 4**.

Those formulations with a higher oil content, particularly those with medium chain triglycerides (Kollisolv MCT 70, BASF) exhibit the fastest digestion over one hour in intestinal media. Comparing the digestibility as well as the solubility of the API, one can compare formulations more succinctly. As an example, formulation F2, with high concentrations of Polyoxyl 40 hydrogenated castor oil (Kolliphor RH 40, BASF), disperses into nanoscale droplets and is digested slowly. Formulation F3, with the same ingredients but a much higher oil concentration, exhibits a much faster digestion rate and higher API capacity but sacrifices the size of the resulting oil droplets. Over a 90-minute digestion, these differences can be seen as graphed in **Figure 5**: the orange line is the titrated free fatty acid (digestion rate); the grey is solubilized and available API; and the black, precipitated unavailable API.

In summary, the formation of microemulsions is a challenge that can be overcome using modern methods such as robotic high throughput screening. These identified regions can then be utilized to craft functional pharmaceutical formulations capable of varied API loading, digestion rates, and dispersibility. The 10 new formulations described in **Table I** are available for formulators to place "on the shelf" as more challenging APIs come through the pipeline.

Reference

1. S.D.S Jorgensen et. al., *Eur. J. Pharmaceutics and Biopharmaceutics* 124, 116-124 (2018).

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Planning a Successful API Procurement Strategy

Selwyn Lustman, Lina Cogan, and Hamilton J. Lenox

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Sourcing hard-to-find ingredients and establishing a reliable supply chain can stretch the resources of a small- to mid-size pharma company. Building or contracting for the expertise to manage an API supply chain is crucial to drug development success.

The age of "blockbuster" medicine, when the market was ruled by multibillion-dollar drug manufacturers producing a small number of products in large quantities, has begun to expire. With its decline comes a new, more complex marketplace that favors generic drugs over branded giants, personalized therapies over one-size-fits-all medicine, and novel formulations and drug delivery systems over traditional approaches.

The result is an increasingly diverse and more complex industry. Small- and mid-sized drug development companies are vying to offer differentiated and innovative drug products in a crowded market. Such innovation requires increasingly specialized and hard-to-find APIs. Small, lean companies that specialize in pharmaceutical development, not supply chain logistics, often struggle to source unique ingredients from manufacturers around the world under aggressive timelines and in quantities suitable for each stage of development.

Intensifying regulatory pressure adds to these challenges. Previously, regulatory authorities focused primarily on the purity and integrity of the drug product itself; today's health authorities have extended their reach to incorporate a product's entire chain of custody.

In the United Kingdom, the Medicines and Healthcare products Regulatory Agency recently prioritized supply chain integrity in its five-year corporate plan (1). The European Commission's November 2013 update to its Guidelines on Good Distribution Practice of Medicinal Practice for Human Use also reflects a drive toward global traceability. Also in November 2013, the US Congress enacted the Drug Supply Chain Security Act, giving the FDA enhanced abilities to enforce elevated trackability and product verification standards.

These guidelines demonstrate how regulators have extended oversight over the entire supply chain, leading to a higher incidence of compliance actions. The number of warning letters issued in the United States more than doubled between 2012 and 2016 (**Figure 1**).

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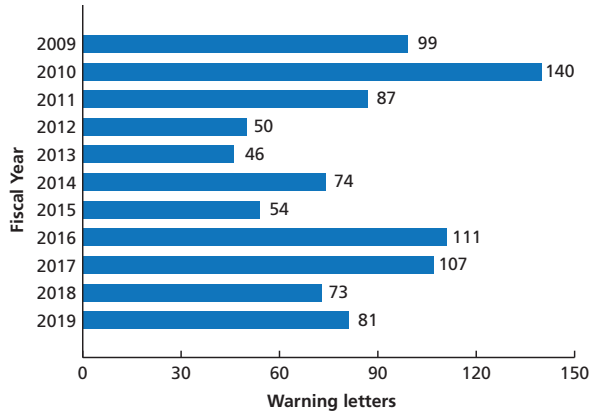
Figure 1: Warning letters issued against drug establishments in the United States. Data source: FDA Data Dashboard as of Aug. 15, 2019 (2).



Drug companies grappling with the challenges of API procurement must not only manage their own quality systems, but also must ensure the quality of their supply chain, including elements outside of their control. An API manufacturer with poor infrastructure or improperly applied standard operating procedures (SOPs) can introduce consequences for the entire drug development process, putting developers at risk for regulatory sanctions. Collectively, these challenges risk knocking even the most visionary drug development companies to the sidelines, struggling with API quality, logistical issues, or the complications of regulatory approval.

By understanding the challenges involved in sourcing hard-to-find APIs, developing transparent and scalable manufacturer relationships either independently or with support from a qualified expert, and maintaining end-to-end regulatory approval, drug developers can avoid unforeseen quality, logistical, and regulatory roadblocks.

Looking for a niche API in a haystack

The 505(b)(2) accelerated drug approval pathway was enacted in the 1984 Hatch-Waxman Amendments of the Federal Food, Drug, and Cosmetic Act to encourage innovation in the development of new formulations, indications, or delivery systems for existing active ingredients. Under the pathway, drug companies can use safety and efficacy information for APIs from studies of previously approved agents, allowing them to stretch the value of existing clinical knowledge and unlock novel drug applications.

Today's startup culture—enabled by modern technology and a surge in expired patents and exclusivity agreements—is behind an increase in 505(b)(2) applications (**Figure 2**). This competitive move toward innovation provides consumers with more treatment options; however, drug companies pursuing the 505(b)(2) pathway may have difficulty finding small batches of hard-to-find ingredients for research activities.

Many large, established API manufacturers do not offer the modest quantities that 505(b)(2) innovator companies need to sustain R&D programs. A less-established manufacturer may not have the infrastructure or expertise to produce an unfamiliar compound; developing that infrastructure takes capital that API manufacturers may not be willing or able to devote to a 505(b)(2) project, especially for a modest batch size.

Securing a hard-to-find API in a low volume requires an understanding of the current API manufacturing landscape. Subscription databases that track API-manufacturer capabilities and meetings at trade shows with API manufacturers may be cost-prohibitive for small players without in-house procurement capabilities.

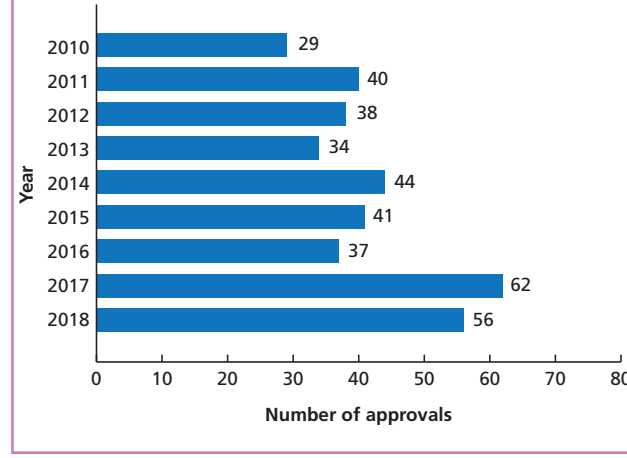
Scaling up supplier support

A small drug company may be able to find a manufacturer to supply a small quantity—say 50 kg—of a niche API for efficacy and safety testing. After that testing is complete and the formulation has proven successful, the drug company must contact the API manufacturer for a larger order—perhaps 750 kg—to prepare for commercialization. The original batch size of 50 kg is too small; running 15 batches of that size would take too long and cost too much. A request to increase volume to five batches of 150 kg may not be readily met.

Companies that pre-qualified the API manufacturer by discussing scale-up requirements early on are in a good position. The manufacturer has bought into the expected growth curve and has the spare capacity to fulfill orders through every developmental phase.

Those companies are in the minority. Due to competitive pressures, many companies focus on testing and shepherding their product through R&D. Few are aware of the proper questions to ask when negotiating future capacity with a manufacturer, which often results in unpleasant late-stage

Figure 2: Number of 505(b)(2) approvals issued in the United States. Data source: GlobalData Intelligence Center (3).



FIGURES ARE COURTESY OF THE AUTHORS

discoveries: the API manufacturer doesn't have the capacity to scale, or they do but only with additional instrumentation and validation. Suddenly, the whole project is at risk.

Finding the right partner to match the phase of development and grow with the developing drug is crucial and can be difficult, without specific expertise.

Regulators will inspect every node in the chain of custody; drug companies must know that chain well and trust it completely.

You cannot afford non-compliance. Period.

While a drug in development has unique API, batch size, and financial requirements, all companies face similar challenges with regulatory oversight and identifying compliant API manufacturers. Assuming a manufacturer is competent because it has a customer list can lead to a false sense of compliance.

Even more reassuring is a facility with a certificate of good manufacturing practice (GMP), which drug companies can research using databases such as the European Medicines Agency's EudraGMP or FDA's Inspection Classification Database Search.

Having customers—or holding a certification—should not be a threshold of quality assurance. Have those customers filed complaints? Is the certification out of date? Is the manufacturer fraudulently claiming the identity of a certified establishment? A regulator's inspection report is no guarantee of compliance; it's not a promise. It's just one of many factors to consider when developing a potential vendor's risk profile.

The other factors require more digging to uncover. This difficult task makes it tempting for a small company to believe that an aging GMP certificate guarantees compliance. Sometimes it does, but when it doesn't, the consequences can be catastrophic. The API could be snarled in importation paperwork, sustain damage from improperly controlled temperatures, or be out of specification when it arrives, rendering it unusable. These outcomes could lead to stalled production, expired patents, lost investment, and a shredded reputation. Such doomsday scenarios are rare; however, digging—or due diligence—can eliminate the possibility of catastrophe.

It's likely not possible to visit every potential manufacturer; digging comes down to asking the right questions early and from afar. What SOPs are in place to ensure proper cleaning and sterilization in the facility? How are temperature specifications determined and controlled? How are products labeled? How are they transported and stored? How are rodents and other pests eliminated? How are staff trained and evaluated? How are deviations and complaints handled? What software is used and is it validated? How are data backed up and how often?

These questions are not about the manufacturing process per se, but rather about the ancillary systems that support it. These systems make up a manufacturer's holistic quality management protocol, and together paint a picture of that manufacturer's integrity. The best way to ensure that a product will arrive a high-quality, compliant compound with a transparent chain of custody is to do this digging or hire an expert to do it. The cost may pinch at first, but better the discomfort of a pinch today than the knock-out punch of catastrophe later.

Proceed with caution

It's hard to move fast in the drug development space, even on the 505(b)(2) pathway. Pre-qualifying a manufacturer for a specialized, low-volume API supply can slow down the process. Moving APIs from another global location to a facility takes domain expertise, experience with regulatory protocols, and access to the right players at the right time. Regulators will inspect every node in the chain of custody; drug companies must know that chain well and trust it completely.

Drug companies with large in-house sourcing and procurement teams can perform these functions internally. Smaller companies—operating without such a team—should follow this piece of advice: find a way to become, to hire, or to partner with a supply chain expert.

Becoming a supply chain expert will require time, which must be siphoned away from the original purpose of developing a novel drug therapy. Hiring an internal sourcing team is a good option, if that bandwidth is available. For most companies, partnering with an API procurement and supply chain expert is the most cost-effective route, particularly if that expert has a strong quality assurance program and incorporates on-site audits as part of its assessment criteria. These are specialists that understand regulations and have strong manufacturer relationships around the globe, which means small companies can negotiate like big ones, and those new to regulatory scrutiny are assured of continuous compliance.

Whatever the chosen approach, the key is to obsess over every detail throughout the supply chain, leaving nothing to chance, and taking no manufacturer's assurance of competence or integrity at face value. Don't gamble the success of an innovative new drug on a suspect supply chain; trust API procurement to those with the expertise to manage it.

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1. Medicines and Healthcare products Regulatory Agency, Corporate Plan 2018–2023 (April 24, 2018).
2. FDA, Compliance Data Dashboard, *https://datadashboard.fda.gov*, accessed Aug. 15, 2019.
3. GlobalData, Intelligence Center, *globaldata.com*. **PT**

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Market Dynamics Drive Agenda for CPhI Worldwide

The Editors of *Pharmaceutical Technology*

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New therapies, new technologies, global supply chain challenges, and political pressures draw pharma professionals to CPhI Worldwide. This major pharma industry event will draw more than 40,000 professionals to Frankfurt, Germany on Nov. 5–7, 2019.

Emerging therapies, business and political stresses, aging facilities, supply chain transparency, and regulatory oversight are some of the issues the bio/pharma industry currently faces. Mergers and acquisitions on both the pharma and supplier sides of the market, pricing pressures for innovator and generic drugs, new technologies including artificial intelligence and the industrial Internet of Things, the globalization of supply chains, and rise of digital medicine are factors shaping decision making in the bio/pharma laboratory, manufacturing plant, and boardroom.

With complex issues facing the pharma industry, decision makers charged with developing and delivering drugs to market will gather in Frankfurt, Germany on Nov. 5–7, 2019, for the annual CPhI Worldwide trade show.

The event, which in 2018 attracted more than 44,000 bio/pharma industry professionals from 165 countries to visit more than 2500 exhibiting companies, is an opportunity to meet with business contacts, learn about new technologies, and network with other drug development and manufacturing professionals in the industry (1).

The 2019 event at the Messe Frankfurt exhibition center in Germany will feature six events for APIs, excipients, and other ingredients (CPhI); contract services (ICSE); packaging (InnoPack); finished drug products (FDF); equipment (P-MEC); and bioprocessing (BioProduction), which are accessible through one visitor pass. A matchmaking service pairs buyers of bio/pharma ingredients, equipment, and services with exhibitors offering those products and services for onsite meetings. Free-to-attend conference programs include Insight Briefings, the World of Pharma Podium, and the Natural Extracts Podium. (See sidebar on page s40.)

M&A reshape bio/pharma dynamics

Mergers and acquisitions look to change the composition of the pharma industry and may shift the way bio/pharma companies conduct research, development, and manufacturing. Through the first half of 2019, both innovator and generic-drug companies announced deals to reposition their drug portfolios, strengthen their financial positions, or enter the emerging cell- and gene-therapy arenas.

CPhI Worldwide 2019 Schedule as of Oct. 3, 2019.

Time	Activity	Location
Tuesday, Nov. 5, 2019		
9:30–17:30	Exhibition Open	Messe Frankfurt
10:30–16:20	BioProduction Presentations	BioProduction Theatre: Hall 12
10:30–16:30	Pharma Insight Briefings	CPhI Theatre: Hall 6 ICSE Theatre: Hall 12 InnoPack and P-MEC: Hall 11
11:00–15:30	Natural Extracts Podium	Hall 4
11:00–16:15	World of Pharma Podium	Hall 8
Wednesday, Nov. 6, 2019		
9:30–17:30	Exhibition Open	Messe Frankfurt
9:50–15:40	BioProduction Presentations	BioProduction Theatre: Hall 12
10:30–17:00	Pharma Insight Briefings	CPhI Theatre: Hall 6 ICSE Theatre: Hall 12 InnoPack and P-MEC: Hall 11
11:00–15:30	Natural Extracts Podium	Hall 4
11:00–16:15	World of Pharma Podium	Hall 8
15:30–17:30	M&A Forum	Hall 4, Entrente Room
15:30–18:30	Women in Leadership Forum	Frankfurt Marriott
Thursday, Nov. 7, 2019		
9:30–16:00	Exhibition Open	Messe Frankfurt
9:50–14:20	BioProduction Presentations	BioProduction Theatre: Hall 12
10:30–13:40	Pharma Insight Briefings	CPhI Theatre: Hall 6 ICSE Theatre: Hall 12 InnoPack and P-MEC: Hall 11
View www.cphi.com/europe for schedule updates. All activities are at the Messe Frankfurt, unless noted.		

The corporate restructuring of bio/pharma companies has implications for the supplier side of the market. Two prominent deals included moves by contract development and manufacturing organizations (CDMOs) to play significant roles in the cell- and gene-therapy markets.

In May 2019, Catalent (Stand 121A82, ISCE) completed a $1.2 billion acquisition of Paragon Bioservices, a viral vector development and manufacturing company with expertise in adeno-associated virus vectors (2). In July, the company completed the purchase the of vaccine manufacturing equipment and facility assets and assumed the leases of two Novavax product development and manufacturing facilities (3).

Also in May, Thermo Fisher Scientific (Stand 121C80, ISCE) purchased Brammer Bio, a gene- and cell-therapies CDMO, for approximately $1.7 billion in cash. The acquisition will become part of Thermo Fisher's Pharma Services business (4).

Other deals involved the transfer of manufacturing assets from bio/pharma companies to contract manufacturers, signaling a shift to outsourcing of key development and manufacturing functions.

In August, Fujifilm Diosynth Biotechnologies (80B84, CPhI/Integrated Pharma Zone) acquired the Biogen Manufacturing ApS facility near Copenhagen, Denmark, adding a large-scale production facility with six 15,000-L bioreactors; an assembly, labeling, and packaging facility; and quality control laboratories and warehouses. Separately, the company announced a $10-million investment to establish an integrated continuous processing facility for non-GMP biopharmaceutical manufacturing at its Billingham, UK, location in June.

In June 2019, Catalent announced plans to purchase Bristol-Myers Squibb's oral solid, biologics, and sterile product manufacturing and packaging facility in Anagni, Italy (5). The company also announced an expansion of the its global spray-drying capacity through an agreement with Sanofi Active Ingredient Solutions at Sanofi's Haverhill, UK, facility, and plans to invest in formulation and controlled-release tablet and capsule manufacturing capabilities and capacity at its

Winchester, KY, site (6). In July 2019, Catalent Biologics started construction on a $112-million packaging facility that includes vial, bulk filling, and syringe/cartridge lines (7).

Lonza Pharma & Biotech (Stand 121C10, ICSE) announced on July 1, 2019 an agreement to purchase a sterile drug product fill and finish facility in Stein, Switzerland from Novartis. The facility will be the first sterile product finish and fill facility in Lonza's network for clinical supply and commercial launch (8). In addition, Lonza announced plans to add two highly potent API (HPAPI) production lines at its Visp, Switzerland site (9).

In May, Thermo Fisher Scientific announced an agreement to acquire a GlaxoSmithKline drug substance manufacturing site in Cork, Ireland for approximately $100 million. The site contains 270 cubic meters of reactor capacity, 10 production buildings, an R&D pilot plant, and lab infrastructure to support process development, scale-up, and physical characterization of APIs (10). The company also plans to invest $150 million at sites in Monza and Ferentino, Italy, and Greenville, NC, to add capacity for sterile liquid and lyophilized product development and commercial manufacturing (11).

Contract services restructuring and refocusing

With the ongoing consolidation of bio/pharma companies, as well as pressure to get products to market faster, more drug companies are turning to contract service providers. The ICSE section of CPhI, located in Hall 12, will host more than 265 contract service providers, including analytical laboratories, clinical trial services, research services, formulation experts, manufacturers,

CONFERENCE PROGRAM ADDRESSES INDUSTRY TOPICS

Visitors to CPhI Worldwide can attend sessions presented by industry experts and sponsors. Key sessions—as of Aug. 26, 2019—are highlighted below. For a current list of sessions, visit www.cphi.com/europe/agenda.

Exploring Trends in Contract Manufacturing
Tuesday, Nov. 5, 2019, 10:30–11:40 , ICSE Theatre, Hall 12
As pharma evolves toward complex therapies with specific manufacturing needs, the role of the contract development and manufacturing organizations (CDMOs) has never been so important. With efficiency, cost, flexibility, and quality essential components of outsourcing, how are CDMOs evolving to remain competitive? Which technologies and strategies will provide the biggest returns?

The Future of Medicine: What Are the Therapies of Tomorrow?
Tuesday, Nov. 5, 2019, 10:30–11:40, CPhI Theatre, Hall 6
Oncology, auto-immune, cardiovascular, pulmonary, and mental health are all key therapy areas for Pharma companies. This panel will examine emerging therapies for the future pharma toolkit—both developing the new and repurposing the old.

Trends in Sustainable Pharma Packaging and Drug Delivery Devices
Tuesday, Nov. 5, 2019, 10:30–11:40, InnoPack and P-MEC Theatre, Hall 11

Understanding Cell and Gene Therapy Opportunity
Wednesday, Nov. 6, 2019, 10:30–11:40, ICSE Theatre, Hall 12
Cell and gene therapies provide treatment solutions to patients with previously unmet needs, and with regulators ready for an influx of product approvals in the coming years, the sector offers a significant commercial opportunity. This panel will discuss the investment opportunity for those looking to enter this ever-evolving sector.

Global Outlook: The Future of Biosimilars
Wednesday, Nov. 6, 2019, 10:30–11:40 , CPhI Theatre, Hall 6
Biosimilars are an indispensable tool for providing patient access to innovative, effective therapies whilst keeping healthcare costs sustainable. This panel will assess the global outlook: Europe's reasonably mature market, new Asian players, and the challenges to adoption in the United States.

Improving Patient Compliance and Adherence through Packaging/Device Innovations
Wednesday, Nov. 6, 2019, 10:30–11:40,
InnoPack and P-MEC Theatre, Hall 11

Made to Order: 3D Printing for Personalized Medicines
Thursday, Nov. 7, 2019, 10:30–11:40, ICSE Theatre, Hall 12
As the Pharma industry shifts from volume to value, addressing smaller patient populations and orphan diseases, 3D-printing technologies have a transformational role to play. With the promise of increasingly personalized and sophisticated solutions that offer significant benefits in terms of formulation, solubility, and controlled release, what does the future hold?

AI for Drug Discovery
Thursday, Nov. 7, 2019, 10:30–11:40, CPhI Theatre, Hall 6
The process for drug discovery and development is changing as finding viable new drug targets becomes increasingly complex. Artificial intelligence (AI), or machine learning, has been touted as a solution for helping drug development teams overcome challenges with data analysis. This discussion will provide an overview of the current state of play and the future potential of AI for Pharma.

Trends in Packaging and Devices for Biologics
Thursday, Nov. 7, 2019, 10:30–11:40
InnoPack and P-MEC Theatre, Hall 11

Podium and forum presentations
Developments in different regions and key issues facing the pharma will be addressed in sessions at the World of Pharma Podium (80B10). Topics include leadership in pharma, oncology therapies innovation, the healthcare digital wave, and the regulatory outlook. Regional topics include Brexit, the US market for cell and gene therapies, and opportunities in Africa and the Middle East, China, Japan, Korea, and India.

Other educational opportunities include discussions at the Natural Extracts Podium (Hall 4), a Mergers & Acquisitions Forum, a Women in Leadership Forum (separate fee required), panel discussions, presentations, and tours as part of the BioProduction event (BioProduction Theatre, Hall 12).

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and packaging services. In addition to meeting with current or potential suppliers, visitors to CPhI can hear panel discussions about trends in contract manufacturing, cell and gene therapy opportunities, and 3-D printing for personalized medicines at the ICSE Theatre in Hall 12. Insight Briefings will address analytical, formulation, and manufacturing functions, as well as sterilization, lyophilization, injectables and highly potent drugs, inhalation drugs, vaccines, and drug/device combinations.

Faster to market in a global supply chain

Increased demand for generic drugs is pressuring companies to deliver more product at lower prices. At the same time, regulatory authorities are stepping up oversight to ensure quality.

The scope of manufacturing and materials requirements for orphan drugs are different compared with blockbuster drugs. Shorter approval cycles reduce the amount of time available for process development and validation, sourcing material suppliers, analytical method development, establishing quality programs, and securing supply chains.

Several zones at CPhI Worldwide host exhibitors and conference programs to meet pharma company needs for ingredients, processing equipment, packaging, and finished dose formulations.

The CPhI segment of the event in Halls 4, 6, 8, 9, and 10 hosts more than 1275 manufacturers and suppliers of APIs, excipients, fine chemicals and intermediates, natural extracts, custom manufacturing, and integrated pharma. For generic-drug manufacturing, the FDF section in Hall 9 features more than 450 suppliers in the finished dosage supply chain including Big Pharma, contract manufacturers, out-licensing specialists, end-product distributors, and end-user agents.

In addition to the exhibits, free educational sessions include panel discussions on the therapies of tomorrow, the future of biosimilars, and artificial intelligence for drug discovery. Topics scheduled for Insight Briefings at the CPhI Theatre in Hall 6 include opportunities in emerging markets and China, data integrity, quality by design, biomolecule purification, and novel excipients. Other sessions will examine dry powder inhalation, cannabis-based drug development, plant-based ingredients, amorphous silica gel, and bioavailability enhancement.

Manufacturing equipment is showcased in the P-MEC section in Hall 11, which also features LABWorld, a zone focusing on laboratory equipment and analytical biotechnology. InnoPack, also in Hall 11, features pharmaceutical packaging innovations. Panel discussions at the InnoPack–P-MEC Theatre will cover trends in sustainable pharma packaging and drug delivery devices, packaging and devices for biologics, and improving patient compliance and adherence through packaging/device innovations. Other topics include polymers for container closure systems, plastic vials and syringes, high viscosity/high volume drugs, pre-fillable syringes, particulate analysis, and new packaging and closure options.

To address the challenges for biologic-drug manufacturers, the BioProduction show—with more than 50 exhibitors in Hall 12—will feature exhibits and conference sessions.

Attending CPhI Worldwide

The scope of CPhI Worldwide requires advance planning to enable visitors to maximize their time at the event. The event organizers offer three registration packages: Visitor, VIP, and VIP Exclusive. Registration, travel, hotel, Visa information, and other details about attending the event can be found at *www.cphi.com/europe*.

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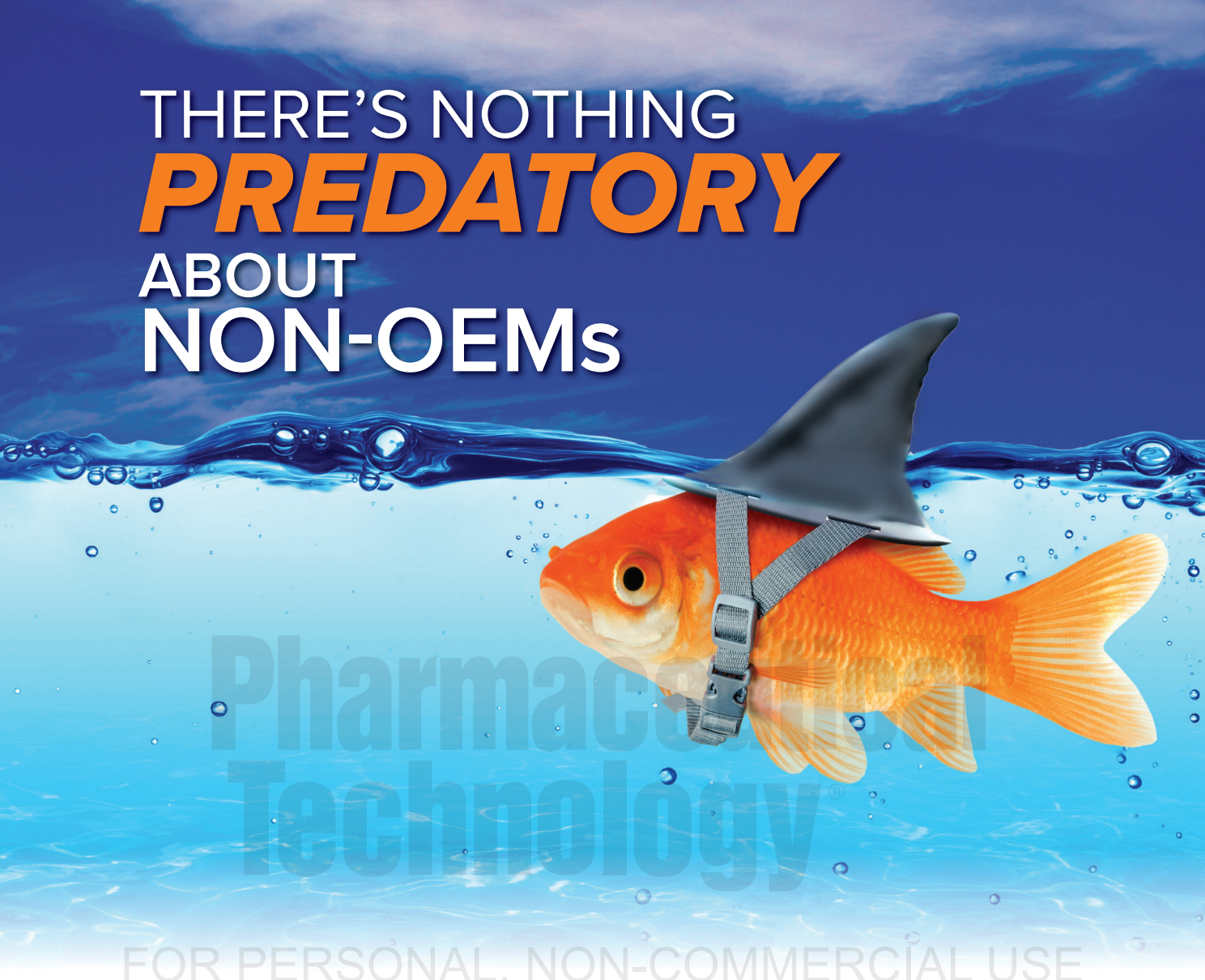

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