Meeting Report

Recent Trends in Product Development and Regulatory Issues on Impurities in Active Pharmaceutical Ingredient (API) and Drug Products. Part 2: Safety Considerations of Impurities in Pharmaceutical Products and Surveying the Impurity Landscape

Karen M. Alsante,[1] Kim C. Huynh-Ba,[2] Steven W. Baertschi,[3] Robert A. Reed,[4] Margaret S. Landis,[1,9]
Scott Furness,[5] Bernard Olsen,[6] Mark Mowery,[7] Karen Russo,[8] Robert Iser,[5]
Gregory A. Stephenson,[3] and Patrick Jansen[3]

INTRODUCTION

The *American Association for Pharmaceutical Scientists* (*AAPS*) *Workshop on Predicting and Monitoring Impurities in API and Drug Products*: *Product Development and Regulatory Issues* was held on 13–14 October 2012 at the McCormick Place in Chicago, IL, USA. The goal of the workshop was to discuss control strategies of chemical and physical changes of active pharmaceutical ingredients (API) and drug products in the drug development process. These changes can affect both the safety and efficacy of drugs; therefore, the ability to rapidly predict and assess the potential for drug product performance changes for impurity formation and the associated safety concerns are important parts of speeding the development of innovative drug therapies without compromising quality.

Dedication: This manuscript is dedicated to the memory of the late Karen Russo, Ph.D. (United States Pharmacopeial Convention)

[1] Pfizer Global Research and Development, Groton, Connecticut, USA.
[2] Pharmalytik Newark, Newark, Delaware, USA.
[3] Eli Lilly and Company Lilly Research Laboratories, Indianapolis, Indiana, USA.
[4] Celsion Corporation, Lawrenceville, New Jersey, USA.
[5] United State Food and Drug Administration, Washington, District of Columbia, USA.
[6] Olsen Pharmaceutical Consulting, LLC, West Lafayette, Indiana, USA.
[7] Merck and Co., West Point, Pennsylvania, USA.
[8] United States Pharmacopeial Convention, Rockville, Maryland, USA.
[9] To whom correspondence should be addressed. (e-mail: margaret.s.landis@pfizer.com)

The workshop comprised four different sessions. Each session focused on separate fundamental issues to build a comprehensive understanding of the physical and chemical processes that affect drug impurities and drug degradation products, the control of impurities, and the impact of these factors on safety and regulatory areas. Taken together, this comprehensive understanding is used to achieve a more robust development approach that enables predictability with a concomitant assurance of safety and efficacy. Innovative methodologies for development of effective stability control strategies were also presented.

This article summarizes sessions 3 and 4 of the *American Association for Pharmaceutical Scientists* (*AAPS*) *Workshop on Predicting and Monitoring Impurities in API and Drug Products*: *Product Development and Regulatory Issues* and addresses issues of safety considerations of impurities in pharmaceutical products and surveying the impurity landscape.

Sessions 1 and 2 of the *American Association for Pharmaceutical Scientists* (*AAPS*) *Workshop on Predicting and Monitoring Impurities in API and Drug Products*: *Product Development and Regulatory Issues* are summarized in *Recent Trends in Product Development and Regulatory Issues on Impurities in active Pharmaceutical Ingredient* (*API*) *and Drug Products Part 1*: *Predicting Degradation Related Impurities and Impurity Considerations for Pharmaceutical Dosage Forms* published separately.

SESSION 3: SAFETY CONSIDERATIONS OF IMPURITIES IN PHARMACEUTICAL PRODUCTS

This third session of the workshop discussed the safety and regulatory considerations of impurities in pharmaceutical products. Scott Furness (*United States Food and Drug Administration*

(*FDA*)) opened the session with a discussion of regulatory and scientific challenges of impurities for over-the-counter (OTC) drug products. As the FDA does not perform any pre-approval assessment of OTC monograph products before commercialization, there is a concern that these products may not meet current impurity monitoring expectations. Several initiatives are being carried out in this area including a collaborative monograph modernization effort among industry, government and the US Pharmacopeial Convention (USP).

Bernard Olsen (*Olsen Pharmaceutical Consulting*, *LLC*) continued the discussion with a presentation to discuss impurity investigations based on clinical phases of drug development. The process begins with initial human clinical trials and proceeds through the entire life cycle of a drug and describes how building impurity control into a manufacturing process involves a cross-functional effort with key inputs from multiple departments.

Following Bernard, Mark Mowery (*Merck and Co.*) gave an update on the activity around the development of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M7 guidelines for mutagenic, specifically genotoxic, impurities. It was emphasized that this guidance has the potential for significant impact to the drug development workflow. The challenge is to assess accurately the rate of formation of this class of degradation products at levels that are lower than listed in Q3A and Q3B Guidances.

Karen Russo (USP) then introduced the key considerations for impurities in compendia testing and USP initiatives to address this area. She discussed the flexible monograph concept to accommodate multiple procedures and corresponding acceptance criteria, and monographs for dosage forms with degradation products that are not included the drug substance monograph.

Robert Iser (*US FDA*) concluded the session with an overview of challenges encountered during development of new generic drug product to assess the impact of process and degradation impurities on the quality, safety, and efficacy of the product being developed. He also introduced the FDA guidance available with respect to identification, control and qualification strategies for impurities in Abbreviated New Drug Applications (ANDAs).

ASSESSMENT OF IMPURITIES IN OTC MONOGRAPH PRODUCTS: REGULATORY AND SCIENTIFIC CHALLENGES (CONTRIBUTED BY SCOTT FURNESS, US FDA)

The American public has ever-increasing expectations for FDA to guarantee the safety of all drug products used by US consumers, OTC monograph drug products should not lag behind with regard to the quality of regulatory standards required with drugs marketed under an approved application. Unlike the FDA's application review process for New Drug Applications and ANDAs (1), the FDA does not perform an individual assessment of quality for OTC monograph drug products before they are allowed to be marketed. Manufacturers of these products typically assess quality through conformance to the corresponding USP monographs (2). As any drug manufacturer could unknowingly produce drug substances and drug products that contain impurities at a toxic level, the lack of modernized, up-to-date impurity standards renders impurities in OTC monograph products as one of the

most concerning safety issues given the lack of any pre-review quality assessment.

A number of potential solutions to this concern are being considered. To begin with, new impurity requirements could be proposed in certain specified USP monographs for OTC products. Although such a risk-based approach has the advantage of focusing changes on those USP monographs for OTC products containing drug substances and drug products known to have toxic impurities, it will only address a small fraction of drug substances and drug products and the concern of impurities in OTC products is a known systemic problem throughout the regulatory construct. Secondly, new regulations could be proposed amending *Title 21 Code of Federal Regulations* (*CFR*) *Section 330.1* (3) to include new impurity requirements as a condition for "general recognition as safe, effective and not misbranded." Although this would be the most comprehensive of all of the potential solutions considered by far, it remains unclear whether compliance with any new requirements can be assessed with a cGMP inspection alone, given the absence of any pre-review quality assessment. Another option considered was engagement of the USP to modernize the compendial monographs for OTC drugs, as well as to strengthen USP General Chapter <1086>: Impurities in Drug Substances and Drug Products and USP General Chapter <467>: Residual Solvents.

In an effort to address concerns about OTC monograph product impurities in a comprehensive fashion and to engage industry stakeholders to the extent possible, the FDA has been actively working with the USP on a number of different fronts. To develop a science- and risk-based approach to prioritize those compendial monographs presenting the greatest risk to public health, the FDA's Compendial Monograph Modernization Task Group (MMTG) was formed in October 2010 (4). That task group identified a number of the highest priority compendial monographs for modernization, and has subsequently communicated these recommendations to the USP. As a result, a number of these highest priority compendial monographs for OTC monograph products are actively being revised and published in the *Pharmacoepial Forum* (5), including compendial monographs for Acetaminophen, Chlorpheniramine Maleate, Diphenhydramine Hydrochloride, Diphenhydramine Citrate, and Pseudoephedrine Sulfate. The USP has also formed an Expert Panel charged with the responsibility of revising General Chapter <1086>, Impurities in Drug Substances and Drug Products (6). Such revisions will potentially impact all compendial monographs. In addition to modernizing this General Chapter to meet modern impurity standards, some elements of this document could be moved to a required General Chapter below <1000>, thus potentially making a number of new requirements enforceable in a cGMP inspection. Lastly, in a 2011 USP/FDA OTC Drug Substances and Drug Products Workshop (7), the USP suggested that the use of Performance-Based Monographs (PBMs) might be a useful means of modernizing the compendial monographs for OTC monograph drugs in a more expedient fashion. PBMs specify tests and acceptance criteria, but the procedures only define the criteria needed to show the procedure is acceptable (e.g., specificity requirements, relative standard deviation, etc.). Although the use of this approach has the advantages of providing analysts flexibility in choosing the most optimal methods for their given formulation as well promoting faster monograph

modernization, the enforceability of such a PBM has been called into question by the FDA.

IMPURITY INVESTIGATIONS BY PHASE OF DEVELOPMENT—WHAT AND WHEN? (CONTRIBUTED BY BERNARD OLSEN, OLSEN PHARMACEUTICAL CONSULTING, LLC)

The degree and level of rigor associated with impurity investigations are often dictated by the phase of development of the project. All sources of drug impurities that must be considered during development are depicted in general terms, for both drug substances and drug products, in Fig. 1. For marketing authorizations, potential impurities that reach certain levels arising from the synthetic process, degradation, interaction with drug product excipients, or introduced from the container/closure system should be investigated to establish an effective impurity control strategy.

At early stages of development, it is impractical to investigate all impurities (8). In-depth investigations are not usually necessary to ensure safety with regard to impurities during early clinical trials. Many pharmaceutical companies focus on the most likely potential impurities and impurities actually observed during initial phases of development. The most likely potential impurities from the synthetic route are the intermediates, solvents, and reagents used in the final steps (9). Predictable by-products and degradation products, especially major degradation products, identified in early stress studies are also often investigated.

During later phases of development, the drug substance synthetic route becomes finalized and in-depth studies are performed to determine the origin and fate of impurities (10). The knowledge from these studies provides a basis for choosing which impurities are significant and need to be monitored routinely with specified limits. Control of some impurities at intermediate stages can be justified with impurity rejection data demonstrating effective downstream removal of the impurity. This approach and others can also be used for potentially genotoxic impurities. Specification limits based on process capability *vs.* limits justified by safety will continue to be an area for discussion between industry and regulatory

authorities. Justification of eliminating routine limits for impurities, shown to have negligible risk of appearing in the drug substance or product (11), is also an area for regulatory discussion.

Stress degradation studies are usually repeated in later development phases to identify degradation products and pathways in both the drug substance and drug product. The extent and timing of in-depth stress studies varies widely by company (12,13). A thorough understanding of drug degradation behavior can be used to aid in design of a formulation and the packaging and storage requirements necessary to maintain quality.

Risk assessment for new or greater levels of impurities is an important part of change control during development and post-approval manufacturing. Changes in site, scale, vendors, and process conditions should be evaluated for their potential risk of affecting impurity profiles and stability. As an example, cyclohexylamine in dicyclohexylcarbodiimide (DCC), a commonly used peptide-coupling reagent, can lead to formation of a cyclohexylamide impurity. If cyclohexylamine is not present in DCC used during development but appears in material from a new vendor, a new impurity may need to be addressed. Therefore, risk assessments for starting material or reagent vendor changes need to include possible impurities that the purchased material may introduce. Similar considerations apply to changes in excipient vendors.

POTENTIAL GENOTOXIC DEGRADATION PRODUCTS: ICH WORKING GROUP UPDATE (CONTRIBUTED BY MARK MOWERY, MERCK & CO., INC.)

The development of the ICH M7 guidance (14) on mutagenic and genotoxic impurities has the potential to significantly affect drug development workflows across the industry in many areas including Chemistry, Manufacturing, and Controls Information, toxicology, drug metabolism, clinical development, and regulatory affairs. The issues involved in dealing with potentially genotoxic impurities are particularly interesting when considering degradation products of both the drug substance and drug product.
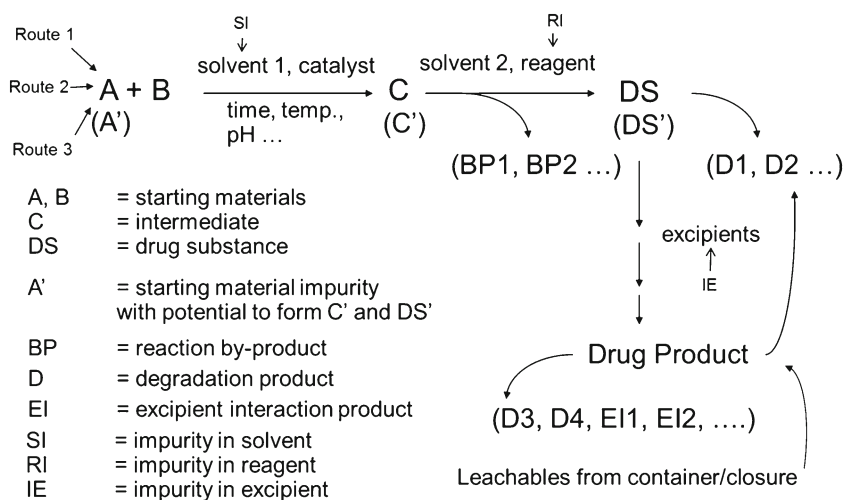

Fig. 1. The potential sources of drug impurities during development for both drug substances and drug products

Controlling genotoxic degradation products to levels dictated by current guidances can be particularly challenging because of the potential for continuous growth of the degradation product over time, complexities associated with assessing that potential in an accelerated fashion, and the limited mechanisms available to reject or eliminate common degradation pathways (such as oxidation or hydrolysis) to parts-per-million (ppm) levels.

As shown in Table I, the control limit for a confirmed genotoxic degradation product can be orders of magnitude below the applicable ICH identification thresholds defined by the ICH Q3A and Q3B guidances (15,16). However, the process of confirming whether a degradation product is genotoxic begins with knowledge of the chemical structure. Developing methodology and workflows to identify all degradation products at these very low limits is clearly not practical, and in many cases may not be possible. As a result, the challenge for the drug development scientist is to utilize a scientifically sound, risk-based approach (11) to accurately assess and address the risk of formation of potentially genotoxic degradation products at levels that may be orders of magnitude lower than dictated by the current structure identification thresholds in a reasonable timeframe.

The current direction of the ICH M7 guidance with respect to degradation products provides a framework for sponsors to form strategies for performing appropriate risk assessment and mitigation for potentially genotoxic degradation products. The guidance accomplishes this through building on the concepts of "potential" and "actual" degradation products as already introduced in the current ICH guidances. The risk of low level mutagenic degradation products forming in the drug substance or drug product can be assessed by identifying significant degradation products from developmental studies (i.e., "potential" degradation products) such as forced stress and accelerated stability, based on risk for persistence as "actual" degradation products in the final drug substance or drug product.

Once the structure of a potential or actual degradation product is identified, the M7 guidance would require an *in silico* structure activity relationship evaluation to determine the potential for genotoxicity and the need for further confirmatory toxicity evaluations. Focusing structural identification efforts on only significant potential degradation products that are reasonably likely to persist to actual degradation products provides a mechanism by which the genotoxic risk can be mitigated during product development and registration. However, while the designation of actual degradation products is

reasonably straightforward, the process by which significant potential degradation products are determined varies substantially across the industry and many scientifically sound approaches involving *in silico* methodologies, accelerated stability, or forced stress testing are viable, as discussed by other presenters at this Workshop.

Although the specific experimental studies used to assess potential degradation products may vary, it is imperative that the sponsor maintains a consistent and aligned approach to structure identification. Nonetheless, using these general concepts, the M7 guidance provides a generally accepted risk-based approach for evaluation of potential degradation products. Furthermore, because control of hydrolytic and oxidative degradation to ppm levels may be exceedingly challenging over the shelf life of many drug products, employing a well-designed strategy to address this risk earlier in development can also limit the risks associated with late phase genotoxic degradation product identification.

KEY CONSIDERATION FOR IMPURITIES IN COMPENDIA TESTING (CONTRIBUTED BY KAREN RUSSO, US PHARMACOPEIAL CONVENTION)

This mission of the USP is to establish public standards to support the identity, strength, quality and purity of official articles for which there are USP-NF monographs. The standards in the monograph apply at any time in the life of the article from production to expiration. Standards for certain types of impurities, such as residual solvents and elemental impurities, are presented in General Chapters (17), while the Monographs (18) contain specific tests, procedures and acceptance criteria, collectively known as the specification. Tests for impurities are among targeted article-specific standards tests. The term "impurities" is a general term and includes process impurities, degradation products, residual solvents, and elemental impurities.

Monographs for drug substances are intended to mainly address process-related impurities. In cases where there is more than one impurity profile for a drug substance, because of varied synthetic pathways, a flexible approach can be used to accommodate multiple procedures and corresponding acceptance criteria. Monographs for dosage forms are intended to address degradation products. It is not necessary to quantitate process impurities already addressed in the drug substance monograph and that are not increased during stability storage.

Availability of well-characterized USP reference standards (19) is a key component of impurity testing. Reference standards can be used to identify and quantitate drug substance and drug product impurities. If a reference standard is not available, monographs may use relative response factors for quantitative purposes.

Many USP monographs are actually outdated and thus they may include impurity tests using older testing methodology (e.g., packed column gas chromatography methods, wet chemistry, or thin layer chromatography) or they may have no impurity tests detailed. As part of the monograph modernization effort, the USP is striving to strengthen the monograph content, especially with regard to impurities, through the replacement of older testing procedures with newer ones [e.g., high-performance liquid chromatography (HPLC) and ultra-high-performance liquid chromatography (UPLC)]. Additionally, the USP is working to introduce

Table I. Drug Substance and Drug Product ICH Identification Thresholds Compared with Control Limits for Chronic Dosing of a Confirmed Genotoxic Degradation Product

Daily dose	DS identification threshold	DP identification threshold	1.5 μg genotoxic threshold identification limit
<1 mg	0.10%	1.0%	0.15% at 1 mg
1–10 mg	0.10%	0.50%	0.015% at 10 mg
>10 mg–2 g	0.10%	0.20%	0.0015% at 100 mg
>2 g	0.05%	0.10%	0.000075% at 2 g

impurities tests, where none currently exist, and to increase the number of impurity reference standards.

IMPURITIES OF GENERIC DRUG PRODUCTS (CONTRIBUTED BY ROBERT ISER, US FDA)

When developing a generic drug product, current regulations allow for flexibility in the choice of inactive ingredients used to design the product. As stated in 21 CFR 314.94(a)(9)(ii), the applicant may use different ingredients, where allowed "provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product" [20]. Additionally, ANDA sponsors have flexibility in choice of ingredient suppliers and the choice of manufacturing process. With this flexibility comes responsibility, therefore it is incumbent that the applicants understand the impact of this flexibility with respect to not only safety but also product quality and performance.

One area that needs to be evaluated in terms of product safety and quality is impurities. Sources of impurities in generic products are no different than the sources in brand products. These sources include drug substance process impurities (intermediate or pre-cursor materials related to the drug substance), degradation products, impurities or residuals in excipients and other impurities that could be introduced throughout the proposed processes (e.g., residual solvents, carry-over reagents, or residual metals).

Guidance is available from the FDA with respect to identification and control of impurities in both the drug substance and the drug product. Two ICH guidance documents, Q3A Impurities in New Drug Substances [16] and Q3B Impurities in New Drug Products [15] have also been in place. Specific guidance for impurities in generic products is more recent including ANDAs: Impurities in Drug Substances [21], finalized in 2009 and ANDAs: Impurities in Drug Products [22], finalized in 2010. These guidances were written as "add-ons" to the ICH guidance documents as the FDA believes that much of the content in the Q3A and Q3B guidances apply to ANDAs.

One major component of the impurity guidances is a pathway to qualification for impurities. The ANDA guidances recommend that applicants provide a rationale for establishing impurity acceptance criteria including safety considerations. The qualification pathway laid out in the guidances includes:

1. Comparison to the brand or reference-listed product (RLD) using the same validated, stability-indicating analytical procedure
2. Demonstrating that the impurity in question is a significant (human) metabolite of the drug substance, assuming there are no quality or efficacy concerns with the level of the metabolite
3. Using appropriate scientific literature to justify a level as safe
4. Evaluation of the impurity using toxicity studies

Additionally, current limits for specified and unspecified impurities in USP monographs must also be considered. Further details on qualification can be found in the guidance documents and if questions arise, applicants should contact the respective review division in the FDA.

As noted, another source of impurities may come from the excipients used in the formulation. The impact of any impurities from excipients should be considered when developing the product. With respect to these impurities, ANDA applicants should determine if reactive impurities such as peroxides, formaldehyde, formic acid, etc. may be present and what impact the presence of these impurities may have on the stability and performance of the generic product. Available sources of information that may assist the applicants in terms of understanding the impurity profile of the chosen excipients includes stability studies, chemistry of the molecules involved, communication with vendors or the available literature. There are several publications currently in the literature that delve into reactive impurities that may be present in commonly used excipients including one from Crowley and Martini [23]. Additional sources of impurities that need to be assessed with respect to their risk to product quality, safety and performance include residual solvents and residual metals.

For residual solvents, there are a number of guidance documents and resources available for evaluating observed levels and criteria including ICH Q3C [24], USP General Chapter <467> [25], MAPP 5015.8 - Acceptance Criteria for Residual Solvents [26] and Residual Solvents in ANDAs: Questions and Answers [27]. For residual metals, ICH and FDA guidance documents are still being developed and finalized, however, some resources including the EMA Residual Metal Catalyst Guideline [28] and USP General Chapters <231>, <232>, and <233> [25] are currently available. With respect to setting appropriate limits for residual solvents and metals, both safety and quality impact should be considered and risk based approaches should be used.

As quality by design (QbD) becomes more of the norm in the generic industry, a comprehensive understanding of the sources of impurities will be part of an overall development process. In developing a complete Quality Target Product Profile (QTPP) for a generic product, impurities and their sources will likely need to be considered. The ICH Q8(R2) Guidance defines the QTPP as a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy [29]. As the QTPP is developed, applicants will link the desired product to Critical Quality Attributes (CQA) that need to be met to ensure product quality, safety, and performance. CQAs are defined by ICH Q8(R2) as physical, chemical, biological, or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality [29]. Degradation products could be classified as a CQA and, if classified as such, should be evaluated during development in terms of safety and efficacy impact to the product. Additionally, critical material attributes (CMA) of the drug substance and excipients may include impurities that affect the drug product CQAs. These CMAs should be investigated and understood during initial development as well as during the implementation of post approval source changes.

It is obvious that there are a number of challenges encountered during the development of a new generic drug product. Generic drug applicants should assess the impact of process and degradation impurities on the quality, safety, and

performance of the product being developed. There is FDA guidance available with respect to identification, control, and qualification for impurities in ANDA products. The compendia, available literature and comparative studies with the approved RLD are important in setting a baseline for the impurity profile of a given generic product. Additional considerations include differences in drug substance synthetic route and product formulation in a generic product as compared with the RLD. Understanding sources of impurities and product impact is part of an overall QbD approach and is necessary to ensure that desired safety, quality and performance targets are met for the generic product.

SESSION 4: SURVEYING THE IMPURITY LANDSCAPE

The fourth session of the workshop consisted of five talks specifically focusing on various aspects of impurity guidance, formation, and investigation. Regulatory expectations for characterization and control of impurities are not static, but continue to evolve. In parallel, impurity formation science and characterization strategies continue to evolve to stay current with on-going changing expectations and continue to provide improved quality programs and control strategies.

The first talk was given by Bernard Olsen (*Olsen Pharmaceutical Consulting*, *LLC*) on the topic of practical aspects at the interface of guidance and practice. Examples of inconsistencies were highlighted between ICH guidances on impurities, Q3A and Q3B, as well as the emerging draft guidance on genotoxic impurities. In particular, control requirements between API and drug product were highlighted. As guidances evolve, Dr. Olsen noted that one agency's guidance may get ahead of another agency's guidance, as was evident in the control of elemental impurities. Finally, a need to broaden the scope of guidances to include areas other than small molecules was noted.

The second talk was given by Steve Baertschi (*Lilly*), focusing on the rich oxidative degradation chemistry landscape. The importance of this area is second only to hydrolytic degradation in terms of the most common degradation chemistry observed in pharmaceutical systems. Various classes of reactive oxygen species (ROS) were mechanistically described and supported by relevant literature examples of the reaction chemistry. Finally, Dr. Baertschi proposed best practices for predictive and investigative approaches for delineating oxidative degradation products for drug molecules.

The third talk was given by Robert Reed (*Celsion*) and focused on fundamental considerations for photochemical degradation products, including light, package transmission and a pharmaceutical "system" that can translate the light into chemical transformation. ICH guidance has made photo stress testing part of the product development paradigm, and includes both stress testing and confirmatory testing requirements. Particular emphasis was given to the importance of recognizing that beyond drug molecule light absorption, other components of the formulation may serve as a mechanism to couple light energy into undesired photochemistry. Therefore, photostability testing should always be performed to assess the potential for photochemical reactivity of a drug product.

The fourth talk was provided by Gregory Stephenson (*Lilly*) on the relation of physical chemical changes to degradation and impurity formation. Physical changes considered include changes to the crystallinity of the API (e.g., amorphous content, solvation, disproportionation, and solubilized micro-environments) with consideration on the impact to product quality. Changes highlighted include increased chemical and photochemical reactivity, and potential changes in bioavailability. Specific examples were provided of each physical transformation and its impact on the API or drug product quality. Finally, it was highlighted that positioning API in an excipient environment only highlighted the possible changes that could occur, which suggests careful consideration of potential physical change impact on product quality should be part of a product development program.

The fifth and final talk was provided by Patrick Jansen (*Lilly*) and focused on distinguishing analytical artifacts from actual impurities. One of the challenges of forced stress testing is to assure that the degradation profile provides an accurate reflection of the degradation chemistry, and not being misdirected by artifact detection. Ultimately, analytical artifacts can be caused by any numerous events, such as trace metal contamination, reactions due to sample manipulation (such as sonication), external contamination or processes related to extraction processes. Specific examples of impurity investigations involving several of the situations highlighted above were described in the presentation. The importance of understanding the susceptibility of the drug molecule to events and environments that can cause analytical artifacts was emphasized as essential to a successful investigation outcome.

ICH IMPURITIES—AMBIGUITIES AND QUESTIONS IN PRACTICE (CONTRIBUTED BY BERNARD OLSEN, OLSEN PHARMACEUTICAL CONSULTING, LLC)

The ICH guidelines on impurities (15,16,24) have provided harmonized regulatory expectations for many years but some questions and inconsistencies remain. Some of the questions that arise regarding impurity levels and thresholds during drug development are discussed below.

Drug Substance Versus Drug Product Impurity Thresholds

There are inconsistent identification and qualification thresholds for impurities in drug substances and drug products, particularly for degradation impurities that may be common to both a drug substance and a corresponding product. The inconsistencies, expressed as total daily intake (TDI) of an impurity, are magnified at relatively low doses (see Table II). For example, with a daily dose of 1 mg, the qualification thresholds are 1.5 and 10 µg for impurities in drug substances and drug products, respectively. Should the ICH Q3A and Q3B guidelines be revised to make these thresholds more consistent? Other questions such as differentiating impurity thresholds based on use of the drug (e.g., chronic *vs.* acute therapy) also remain.

Thresholds and Limits Based on TDI

Levels of concern for potentially genotoxic impurities are currently based on TDI of the impurity. Levels below 1.5 µg TDI are considered safe (30,31). ICH thresholds for other impurities, however, are based on concentration. In the case

Table II. ICH Impurity Thresholds for Drug Substance (16) and Drug Product (15) Expressed as Total Daily Intake (TDI) of Impurity

Degradation impurity in a drug substance			
Dose (mg)	1	10	100
Identification threshold (TDI; μg)[a]	1	10	100
Qualification threshold (TDI; μg)[b]	1.5	15	150
Degradation impurity in a drug product			
Dose (mg)	1	10	100
Identification threshold (TDI; μg)[c]	5	20	200
Qualification threshold (TDI; μg)[d]	10	50	200

[a] Intake, 0.10% or 1.0 mg/day (whichever is lower)
[b] Intake, 0.15% or 1.0 mg/day (whichever is lower)
[c] For 1–10 mg/day, 0.5% or 20 μg TDI (whichever is lower) and for >10 mg/day, 0.2% or 2 mg TDI (whichever is lower)
[d] For <10 mg/day, 1% or 50 μg TDI (whichever is lower) and for 10–100 mg/day, 0.5% or 200 μg TDI (whichever is lower)

of potent drugs with low doses, the different basis for levels of concern creates an inconsistency in requirements. For example, an impurity at 0.2% in a drug substance dosed at 0.5 mg/day would have a TDI of 1 μg. This impurity would require qualification according to ICH Q3A even though patient exposure would be below the TDI of 1.5 μg considered safe as a genotoxic impurity (32). This inconsistency raises the question of whether thresholds for non-genotoxic impurities should be based on TDI instead of concentration.

Extent and Rigor of Drug Impurity Investigations

ICH Q3A and Q3B guidelines (15,16) contain subjective or ambiguous language such as "most likely to arise" and "might reasonably be expected" to describe impurities that should be investigated. The definition of a potential impurity as one that "theoretically can arise" also has multiple interpretations in practice. These descriptions can lead to much different levels of investigation performed by different companies or expected by different regulatory agencies. A balance is needed between doing an insufficient investigation of impurities *versus* wasting time and resources on examining all impurities that are theoretically possible. A chemistry-based impurity assessment coupled with appropriate analytical tools can aid in identifying actual impurities and choosing potential impurities for investigation (33,34).

Metal/Elemental Impurities

The ICH Q3D guideline (35) seems to be lagging USP proposals (36) for limits of metal impurities. The relative timing and scope of these two efforts is a concern for some industry groups (37).

Genotoxic Impurities

The ICH M7 working group on mutagenic and genotoxic impurities issued a step 2 draft consensus guideline in early 2013 (14). This draft includes duration of treatment as a factor in setting acceptable limits for marketed products and describes acceptable control mechanisms for genotoxic impurities (e.g., specifications, impurity purge studies, control at

synthetic intermediates) (38). Two *in silico* evaluations are recommended to discharge the risk of an impurity being mutagenic and the use of predictive data on similar compounds to discharge impurity risk may also be addressed. Note that this guideline does not apply to drug substances and drug products intended for advanced cancer indications.

Other Product Types

Several product types and/or impurity types are not addressed in ICH guidelines. Development of harmonized regulatory expectations for the following classes of products would be helpful: biological/biotechnological, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semi-synthetic products, herbal products, and crude products of animal or plant origin. There is also opportunity for clarification and harmonization of requirements for investigation of extractable/leachable impurities from product container/closures and packaging.

FUNDAMENTALS OF PREDICTING OXIDATIVE IMPURITIES (CONTRIBUTED BY STEVE BAERTSCHI, ELI LILLY AND COMPANY)

Oxidative degradation is the second most common pathway of drug degradation after hydrolysis (39) and is therefore of great interest to the pharmaceutical industry. Predicting oxidative degradation, both the likelihood and the relevant pathways, has proven to be a difficult task due to the numerous oxidative pathways available and the complexities involved. Excellent reviews of this topic are available in the literature (40,41).

The presentation highlighted the basics of oxygen chemistry, including the major ROS relevant to drug degradation, as well as recommendations for conditions and reagents for conducting rapid oxidative susceptibility screening. Oxidative susceptibility of some common functional groups were also reviewed and illustrated with relevant examples.

Oxygen and Reactive Oxygen Species

There are numerous ROS with the potential to cause oxidative degradation of drugs during storage, distribution, and patient use. The following species were considered and discussed in the presentation, including ground state oxygen, hydrogen peroxide/peroxides, hydroperoxy radicals, singlet oxygen, hydroxyl/alkoxyl radicals, superoxide radical anion, and ozone (see Fig. 2).

Ground State Oxygen. Oxygen in its ground state is relatively unreactive toward drug molecules due to the fact that ground state oxygen has two unpaired valence electrons (i.e., the multiplicity is a "triplet"), while most organic compounds have paired valence electrons (i.e., the multiplicity is a "singlet"); direct addition of triplet oxygen to a singlet molecule is spin-forbidden (41). Nonetheless, this spin restriction does not apply to electron transfer processes between electron rich functional groups and oxygen. For example, electron-rich phenolates are known to react directly with triplet oxygen to produce superoxide radical anion and a phenolate radical. Other electron-rich moieties that participate in such direct
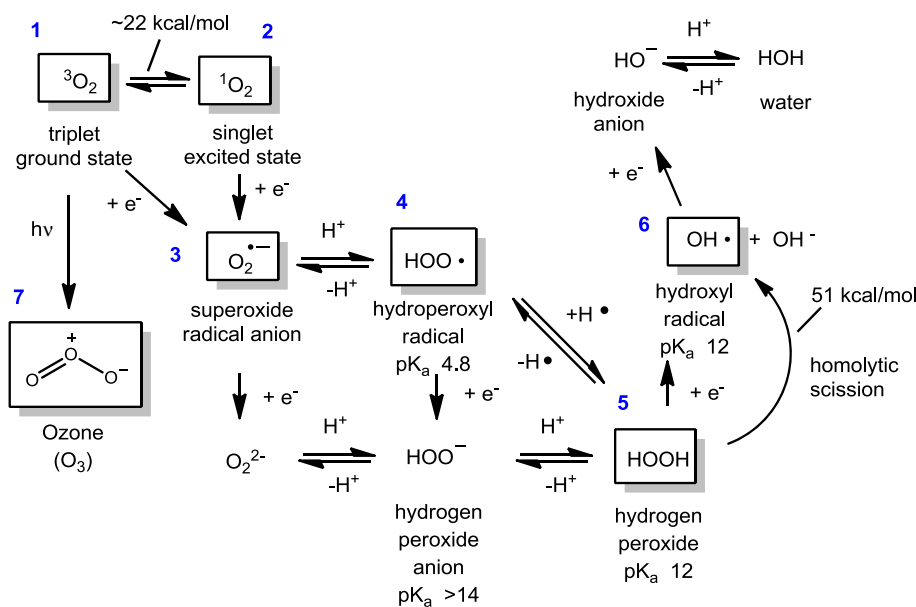
Fig. 2. Overview of oxygen and reactive oxygen species

reactions include unsaturated enamines and strained cyclic olefins (41).

Hydrogen Peroxide (and Alkyl Peroxides). Degradation by peroxides is the most common route of oxidation of formulated drug products, and also the most well understood. Hydrogen peroxide acts primarily by donating one oxygen (as O^+) to electron rich functional groups such as amines, thiols and thioethers, indoles, etc. Peroxides can also degrade to highly reactive hydroxyl radicals in the presence of low levels of transition metals (so called "Fenton" chemistry) or heat. Hydroxyl radical chemistry can be minimized by using 10% methanol in hydrogen peroxide stress tests as a radical trap, and by conducting the stress test at room temperature.

Hydroperoxy Radicals. Degradation by peroxy radicals, ROO·, often considered as the primary autoxidation pathway. for drugs, is the second most common route of oxidation of formulated drug products. Much has been written about the importance of peroxyl radical stress testing (42) and azonitriles are commonly used to mimic this pathway (43). Recent developments have revealed that undesired alkoxyl radical formation can occur under many peroxy radical stress conditions via radical termination mechanisms (44). The use of 5–10% methanol as a co-solvent during peroxy radical stress testing can scavenge the alkoxyl radicals and eliminate undesired side reactions from these highly oxidative species, such as (4) in Fig. 2 above.

Singlet Oxygen. Singlet oxygen is a highly reactive oxygen species that has no unpaired electrons and is therefore capable of direct reaction with many organic functionalities via two electron chemistry. While singlet oxygen is most commonly produced via photosensitization reactions, it can also be formed from radical termination reactions (e.g., via the Russell termination mechanism) (45). Examples of singlet oxygen-induced drug degradation were illustrated for the cases of epinephrine (46) and losartan (47).

Hydroxyl and Alkoxyl Radicals. Hydroxyl or alkoxyl radicals are highly reactive oxidants that can be formed from a one-electron reduction of hydrogen or alkyl peroxides. Transition metals, such as Fe(II) or Cu(I), can readily facilitate this reduction, and this chemistry is known as the Fenton Reaction (48). Fenton chemistry, while not a common oxidative degradation pathway *ex vivo*, has precedent in drug degradation chemistry (49).

Superoxide Radical Anion. Superoxide radical anion $[O_2^-]$ is widely known in biological systems as an important oxidant and can be formed by single electron transfer from electron rich functional groups and transition metals. The pK_a of $[O_2^-]$ is approximately 4.8, and the protonated form is the hydroperoxyl radical $[HO_2]$. Superoxide radical anion acts as a radical initiator and readily forms hydrogen peroxide in solution.

Ozone. While examples of ozone-induced oxidation of drugs are few, there have been documented examples, presumably from production by automobile exhaust fumes and sunlight (50).

Conditions for Oxidative Susceptibility Testing

Conditions for *predictive* and *investigative* forced degradation studies were proposed (Table III). Predictive conditions were recommended as routine oxidative susceptibility tests, covering the three most important oxidative degradation pathways (peroxide mediated, autoxidation, and electron transfer). Investigative conditions were recommended as tools for probing oxidative degradation pathways and for creating larger amounts of specific oxidation products.

FUNDAMENTALS IN PREDICTING PHOTOCHEMICAL IMPURITIES (CONTRIBUTED BY ROBERT REED, CELSION CORPORATION)

The overall impact of photostability is evident from an examination of the USP 27 (2004) Reference Table "Containers for

Table III. Recommended Predictive and Investigative Degradation Conditions for Oxidative Susceptibility Testing

Predictive	Investigative
Peroxide mediated—0.3% H_2O_2, up to 3 days at RT	Peroxides—peracetic acid, mCPBA or Oxone (less than 30 min)
Autoxidation—AIBN (1 equivalent, 40°C, 3 days); VAZO 52 (30°C, 3 days)	Singlet oxygen—Rose Bengal or methylene blue, light, <30 min
	Fenton conditions—Fe(II) or Cu(I), 1–5 mM, 0.3–3% H_2O_2, <10 min
Electron transfer—Cu(II), 1–5 mM, 1 day, RT to 40C; Fe(III), 1–5 mM, 1 day, RT to 40C	Ozone—use ozone generator Other useful oxidative reagents—NaOCl or $KMnO_4$

Note: Consider protonation state of the molecule in all cases
AIBN 2,2′-azobis(2-methylpropionitrile), 2-(azo(1-cyano-1-methylethyl))-2-methylpropane nitrile, *VAZO 52* 2-(2-Cyano-4-methylpentan-2-yl)diazenyl-2,4-dimethylpentanenitrile, *mCPBA* 3-chloroperoxybenzoic acid

Dispensing Capsules and Tablets" (51) where a total of 743 pharmaceutical products are listed and 248 (33%) require light resistant packaging. Moreover, many of the products include drug substances that do not absorb light at >300 nm; therefore, since the light exposures are limited to wavelengths >300 nm, this suggests that with light degradation, the formulation, or "system" can play a significant role in the light sensitivity of a drug product. Therefore, developing a mechanistic understanding for what drives the photochemical degradation is critical to effectively control the quality of the product and address the specific requirements of each product. Excellent reviews of photochemical reactions and the role of the drug substance environment for introducing photochemical reactions are available in the literature (52,53).

The presentation highlighted the basics of photochemical reactions, including the ingredients for photochemistry, current industry guidance on photochemical testing, considerations of light sources and package transmission
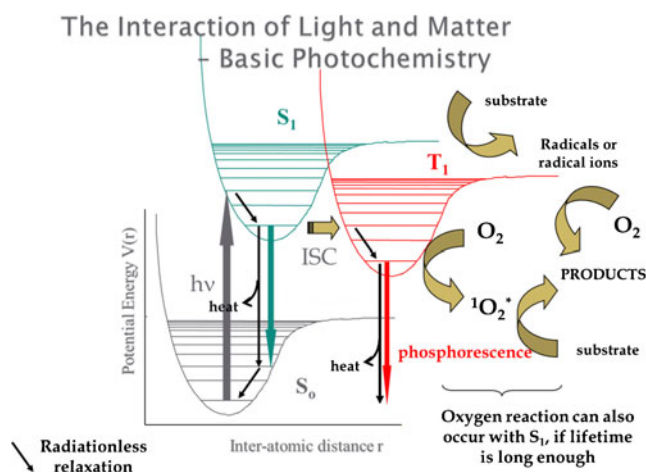

Fig. 3. Jablonski diagram demonstrating the initial light absorption ($S_0 \rightarrow S_1$) and potential pathways for relaxation of energy or subsequent reaction

properties, and the impact of formulations and diluents on photosensitivity of a drug product. Examples for each point were given to illustrate important points to consider when evaluating the photostability of a drug product.

Essential Ingredients of Photochemistry

The prerequisites to facilitate photochemical reactions involve overlap of light with absorptive properties of a drug molecule, or a drug product system (i.e., causative wavelengths). An important potential barrier, or control point, to the photochemistry is the transmission property of the package itself. In addition, the lifetime of the photochemistry has to be sufficient in length to allow reactive excited states to interact with oxygen or substrates (drug molecule or excipients) and produce undesirable products (Fig. 3).

ICH Guidance

ICH Q1B was finalized in 1997 to provide guidance to understand the implication of light on manufacturing, packaging, and storage of commercial API and drug product. The guidance emphasizes that photostability testing should be an integral part of stress testing and provides a systematic approach for conducting the test, both for forced stress and confirmatory testing studies. Since the guidance has been issued, several excellent papers have been published that suggest best practices for material presentation (54,55) as well as highlight some shortcomings of the guidance (56). Finally, the guidance does not address in-use considerations for protection from light, which has recently been considered for photosensitive injectables (57).

Light Emission/Package Transmission

The key challenge for control of potential photostability is the lack of a standard for light. The emission profile, both qualitatively and quantitatively, is quite varied, and real-life exposure is not well imitated with the light sources incorporated into the ICH Q1B guidance (58). Light sources also have the potential to change, as recently experienced with the introduction and adoption of compact fluorescent lights, which again may impact control strategies for light protection that were initially established. The transmission properties of package materials are also varied, and not well controlled. Of particular interest are low amounts of transmission for many package materials at wavelengths between 320 and 420 nm, which may open up a "window" for causative wavelengths to penetrate into a drug product. A case study was presented with six package materials to show that the sensitivity to UV or visible light sources cannot always be predicted and thus should be determined empirically.

Photochemical Systems

A common attribute considered for photochemical reactive potential is the absorptivity of the drug molecule above 300 nm. For example, the ICH guideline on photo-safety uses a 290-nm threshold for triggering the need to study the photo-safety of a drug product (58). However, there are numerous

examples of drug products listed in the USP where the drug molecule does not absorb at >300 nm, yet require a light resistant package. As is the case with most chemistries in drug products, one must consider the complete pharmaceutical system (e.g., including excipients, diluents, etc.) and the impact it may have on the photosensitivity of a drug product (59). Some specific examples were presented involving a photosensitive bisulphite adduct formation of epinephrine (46), a common impurity in sucrose (5-HMF) reacting with isoprenaline (60), ppb level iron mediated photochemistry of several drug compounds (61), and titanium oxide mediated photochemistry of multiple drug compounds (62).

Recommendations for Phototesting

Photochemical reaction in pharmaceutical drug products is a core consideration for any development program. ICH Q1B has served to make phototesting an integral part of a drug development program, yet is constrained by the fundamental variability of light sources, and the translation of laboratory experiments into a robust control strategy. There is significant evidence that formulation systems, pharmaceutical packaging also play an important role in the photosensitivity of a product during product manufacturing, labeling or storage. A detailed understanding of the photochemical fundamental mechanism is foundational to providing a comprehensive solution for the quality of the drug product. Photostability testing should always be performed to assess the potential for photochemistry, regardless of the light absorptive properties of the drug molecule.

RELATION OF PHYSICAL CHANGES TO IMPURITY FORMATION (CONTRIBUTED BY GREGORY STEPHENSON, ELI LILLY AND COMPANY)

Pharmaceutical solids must be both chemically and physically stable to ensure delivery of the highest quality product possible. Chemical stability reactions are often studied as a function of changing humidity, temperature, and/ or with photo irradiation. Physical stability is defined as the resistance to changing of molecular arrangement or organization within the pharmaceutical solid. Physical instability involves phase transformations, a few common types of which follow:

- Amorphous to crystalline and crystalline to amorphous form conversions
- Polymorphic form transformations
- Changes in hydration and/or solvation state
- Salt form to free form transformation (disproportionation)

Physical transformation during stability testing can dramatically influence the mechanism of decomposition, thereby influencing the products produced and the rates of decomposition. Degradation usually initiates within amorphous regions, at defect sites within the solid, or within eutectics formed between the active substance and one of its decomposition products or even between the active and one or more excipients of the formulation. A typical solid-state reaction pathway involves the loosening of the molecules at the reaction site, a molecular change (i.e. degradation) and formation of a solid-solution followed by separation of the product or degradation product phase (63).

The role of water is important to understand when studying solid-state stability. Moisture often increases the rate of decomposition and/or physical transformation (64). Very few transformations are truly solid-state reactions (65), occurring solely within the crystalline solid. Typically, the reaction occurs in a much more mobile, liquid-like state rather than within the interior of the crystalline lattice. These reactions are often autocatalytic, where the products formed are miscible with the reactant resulting in eutectic formation or liquefaction, thus violating the criteria for a true solid-state reaction. The complexity of this process has been well captured in the study of the hydrolytic degradation of ranitidine HCl (66). Water can serve as a direct reactant (i.e., in hydrolysis reactions) or as a product. Commonly water acts as a plasticizer, influencing molecular mobility and diffusivity in amorphous regions. As reactions in amorphous solids are usually diffusion controlled (67), increasing water content by only a few percent can increase the rate of diffusion-limited reactions by several orders of magnitude, through its plasticizing effects.

Polymorphic transformations in marketed solid dosage forms have been observed and reported. There have been instances where the solid-state reactivity of one polymorph relative to another has been substantially different. Such reactions have been termed *topochemical* reactions, where the structure of the product is dictated by the geometry and proximity of the reacting sites within the crystal lattice. The most thoroughly studied topochemical reaction is the solid-state photo-dimerization β-cinnamic acid reported by Schmidt and coworkers (68). Such studies demonstrated the promise of "crystal engineering," where the geometrical restraints of the crystal lattice could be used predictably to produce products with a high degree of stereo- and regiospecificity (68,69). This work later culminated in the derivation of the *topochemical postulate* for which the photo-dimerization of a leukotriene B antagonist is one example (Fig. 4).

Similarly, solid-state transformation of amorphous pharmaceuticals to an undesired crystalline form is a common problem and these transformations can dramatically affect bioavailability of a pharmaceutical product, because of reductions in dissolution and solubility, potentially by 10- to 1,000-fold (70). Deliberate production of amorphous pharmaceuticals can result in outcomes worthy of their inherent physical and chemical stability risk and in other cases, "nuisance" amorphous components may be produced unintentionally during crystallization or processing steps such as milling that contribute to drug decomposition. Amorphous forms are usually less chemically stable than their crystalline counterparts because of the increased thermodynamic activity of the solid, increased molecular mobility of drug molecules of the solid, and its increased specific surface area affording increased accessibility to reactants and facile diffusion of oxygen and water molecules. Direct comparisons of crystalline *versus* amorphous form stability should be made to understand the degree of impact the lattice has on stability and the degree to which its presence impacts product stability (71).

Many substances form solvates or hydrates that can be desolvated to produce a crystalline or partially ordered crystalline form that retains much of the molecular ordering possessed by the initial solvate structure. Desolvates can be
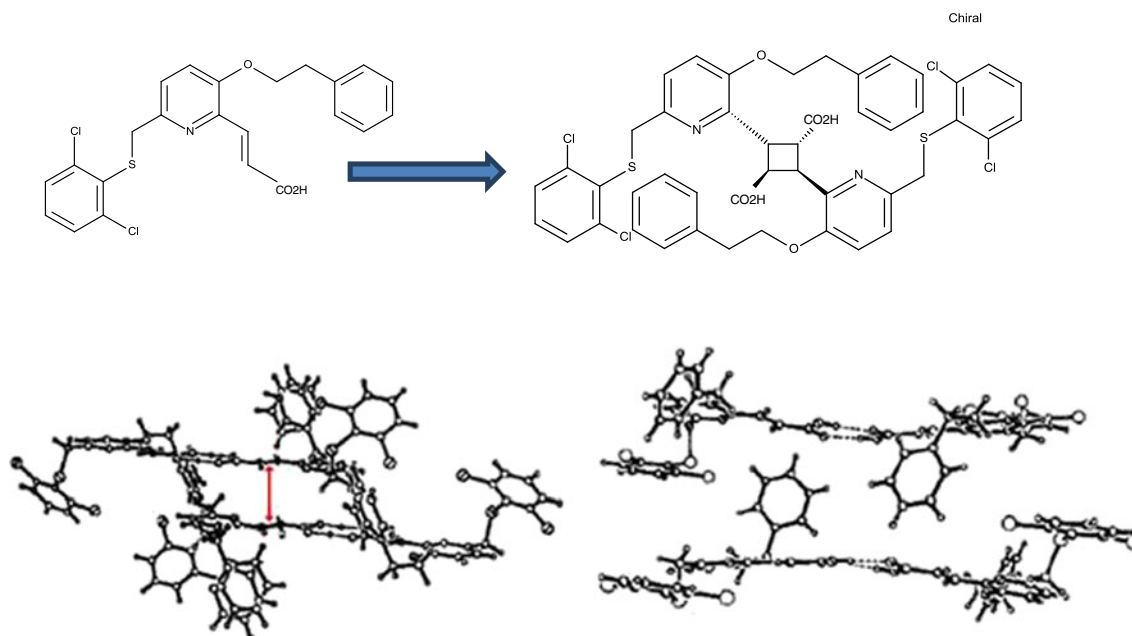
Fig. 4. The photochemical reaction of a leukotriene antagonist (*top left*) results in dimerization (*top right*). Comparison of the molecular packing of polymorphic form I (*bottom left*), and polymorphic form II (*bottom right*) illustrates the differential reactivity observed for the two forms (82)

produced in the final drying step of the drug substance or it might be inadvertently produced during the formulation process, such as during wet granulation or aggressive dry processing. The desolvation process produces a material that is highly flawed, containing voids, channels, and/or defective structures, which can be highly reactive (72). One classic example of desolvation-induced chemical instability is the case of oxidation of prednisolone 21-*tert*-butylacetate, where loss of solvent from the lattice results in a desolvated structure containing channels of sufficient size for facile oxygen diffusion. The arrangement of drug molecules within the lattice results in their hydroxyl group being oriented properly along the channel, facilitating efficient oxidation (73). It is most important to understand the different solid forms of the active drug substance that exist along each step of production and processing pathway, so that ultimately one might understand its impact on the final product's chemical and physical stability.

Perhaps even less often discussed is the potential for a salt to dissociate to its free form within the formulation itself. Such reactions have been termed "disproportionation" reactions. These reactions are quite common, for example with weakly basic active ingredients that form highly water soluble salts under acidic conditions, but are very insoluble at neutral pH in their un-ionized form.. Standard solid-state analytical tools, like PXRD and ssNMR, can be used to analyze, detect and quantify levels of free forms and estimate levels of dissociation. A quality-by-design model that can predict the balance between different driving forces for disproportionation with limited experimental data has been developed (74).

Ultimately, solid-state transformations, like chemical decomposition, are typically worsened through addition of excipients, bringing with them moisture, impurities, reactive impurities and extraneous agents that can significantly modify the pH environment of the pharmaceutical candidate in the

formulated product. Due diligence in determining the solid phases of the API, their thermodynamic relationships to each other and impact of the differences on impurity formation should be considered in any solid form stability work completed.

DISTINGUISHING ANALYTICAL ARTIFACTS FROM IMPURITIES (CONTRIBUTED BY PATRICK JANSEN, ELI LILLY AND COMPANY)

Forced degradation studies are typically used to determine the potential degradation products that may form during formal stability studies conducted on drug substances and drug products. Occasionally, impurities are detected in forced degradation studies that, upon further investigation, are actually artifacts resulting from a variety of sources. These may be artifacts due to trace metals, due to any various sample manipulations (such as sonication), due to external contamination of a sample resulting in an artifact, and due to artifacts formed during extraction procedures, such as formylation of reactive amines in presence of acetonitrile and a catalyst.

For a specific case study, an unknown impurity was detected in multiple lots of an API and observed at variable levels in samples prepared in different laboratories. The validity of the unknown impurity in the analyzed samples was confirmed through a series of cross-laboratory preparation experiments. Reaction of the API with Cu(II) salts was found to definitively produce degradation of the API to the unknown impurity in good yield. It was concluded that the unknown impurity resulted from trace levels of Cu(II) on the glassware used to prepare the samples. The artifact impurity was determined to be a dimer, resulting from free radical coupling of a phenol. The artifact formation could be

eliminated by thorough rinses of all glassware prior to sample preparation.

Similarly, in a second case study, levels of unknown impurity were found in analysis of the API and shown to be often irreproducible and possibly related to certain auto-injection systems and HPLC systems plumbed with stainless steel. A positive control experiment exposed the API parent to Cu(II), Fe(III) and several other metals during forced degradation studies. Cu(II) reaction produced very high levels of unknown impurity. Addition of ethylenediamine tetra-acetic acid (EDTA, 10 mM) to the sample injection solvent completely eliminated the unknown impurity from chromatogram and was therefore used to eliminate further impurity formation. Through results of the study, it was estimated that there could be levels as high as 0.7% Cu(II) on the contaminated glassware.

Copper catalysis to produce degradation impurities are known and well documented. In a certain case study, solutions of an API prepared in mobile phase were observed to be unstable and exhibited formation of a dimer (75). The root cause was determined to be trace levels of Cu(II) in the mobile phase solvent. Exclusion of acetonitrile, use of EDTA, and/or rigorous pre-cleaning of glassware eliminated the dimer formation. Similarly, investigations of GSK842879A suggested the parent compound and an impurity strongly chelated with Cu in solution, resulting in distinct chromatographic peaks that were deemed new impurities (76). Extensive rinsing of the HPLC system with 5 mM aqueous EDTA prior to analysis served to eliminate all anomalous impurity peaks.

There have been numerous cases of artifactual oxidation products produced when both copper and acetonitrile were present in a pharmaceutical sample. Removal of either copper or acetonitrile eliminated the oxidative degradation observed. Reactions of these type are known and described in articles detailing Cu(II)/acetonitrile complexes used to actively polymerize phenols. Specifically, Mrahashi *et al.* describes specific copper complexes formed from copper salts and acetonitrile that are convenient and highly useful catalysts for the aerobic oxidation of unactivated hydrocarbons (77).

Variability in impurity levels can also be traced to differences in sample manipulation and processing. In a specific case, the formation of an impurity was tied to the use or absence of sonication for sample preparation. Further investigation revealed the impurity to be a tertiary hydroperoxide and the observed impurity was then adequately reproduced using the Fenton Reagent ($Fe(II)/H_2O_2$) in single digit percent yields. Generation of a radical through sonication was invoked as the driving force for impurity formation (78).

Artifacts and impurities can readily appear in sample preparation procedures that involve extraction procedures. In a known example, a cyproheptadine chloromethochloride adduct formed from reaction of a secondary amine within the API scaffold with a component of the extraction solvent, methylene chloride (79). A related example details the formylation of a secondary amine during the sample preparation procedure. The reaction was determined to be catalyzed by light and sonication in the presence of titanium dioxide, a common tablet excipient. Deuterium labeling studies confirmed that the carbon atom of the formyl group was derived from acetonitrile solvent. The problem was ultimately overcome by eliminating acetonitrile from extraction solvent and agitation *versus* sonication of the pharmaceutical samples (80). In a poignant example of a successful artifact investigation, the source of

contamination was shown to be an extractable of the safety filter of the pipette bulb, specifically 1,2-diphenylguanidine (81). It is highly recommended to extensively and systematically rule out potential sources of external contamination when investigating new impurity and artifact formation.

Ultimately, artifacts can be caused by any numerous events, such as trace metal contamination, reactions due to sample manipulation (such as sonication), external contamination, or processes related to extraction processes. These events are often difficult to rapidly recognize and conclusively investigate. It is important to consider hints that new impurities might be artifacts, such as variability of analytical results, inability to reproduce impurity levels in different laboratory environments or inability of specific scientists, using slightly different equipment or procedures, to reproduce impurity artifact presence and levels. Specifically, look for the presence of trace metals (particularly copper) and the occurrence of API oxidation in the presence of copper impurities and acetonitrile-based solvents. As early as possible in the development process, a researcher should understand a drug's susceptibility to metal catalyzed oxidation, which can aid in a more rapid resolution of any artifact issues that may occur in standard analytical studies.

CONCLUSIONS

The conference sessions summarized in this white paper (Part 2 of 2) covered a variety of important aspects involved with safety considerations of impurities and surveying the impurity landscape in pharmaceutical products. The practical considerations of impurity testing for compendia, generic, and OTC products, defining the appropriate impurity investigations at different stages of development and clarifying the ICH guidelines for impurity thresholds and TDI recommendations were discussed. In many talks, guidelines and recommendations for dealing with genotoxic impurities received special attention. Focus was then drawn to the broad landscape of pharmaceutically relevant impurities by several experts in the field. A thorough discussion of reactive oxygen species that can impact pharmaceutical products and the predictive and intevestigative protocols used to decipher their degradation liability was presented. Basic fundamentals of photochemistry were reviewed and the potential impact of light absorption to affect all pharmaceutical products was discussed. Important recommendations concerning the importance of understanding physical form transformations and how to deconvolute analytical artifacts and transient, analytical-based impurities were delivered.

Together with Part 1, these white papers present a holistic view of the current scientific and regulatory environment regarding the prediction and monitoring of impurities in API and drug products, with special emphasis on product development and regulatory issues.

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