CONTRACT PHARMA
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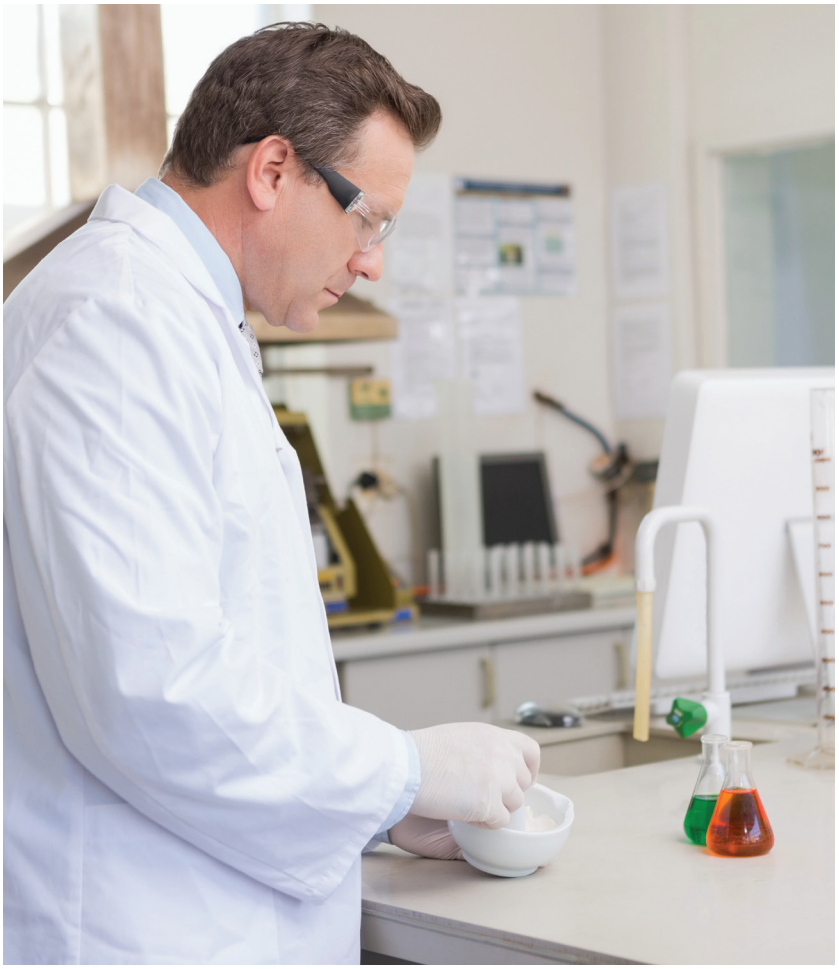
ELEMENTAL IMPURITIES

Where we were then, where we are now, and where are we going?

In an effort to improve and modernize the USP General Chapter for Heavy Metals <231>, the USP published a stimuli article in the January-February 2010 issue of Pharmacopeial Forum, [Vol36, (1)], that provided rationale in support of safe limits for certain elemental impurities in pharmaceuticals and dietary supplements. In that same issue, USP proposed three new General Chapters on Elemental Impurities Limits —<232>, Procedures <233>, and Dietary Supplements Metals Limits <2232>. The following is a timeline of events thus far.

The Elemental Impurities test procedures <233>, and Limits <233> and <2232>, for the analysis of pharmaceuticals and dietary supplements were approved for publication in the Second Supplement to USP 35 on June 1, 2012, with an official date of December 1, 2012. However, because the General Notices provision making these applicable to all USP/NF articles appeared in a revision of USP 37/NF 32, compliance with these chapters was to take effect on May 1, 2014.

In June 2013, the ICH Q3D Elemental Impurities Working Group issued Step 2b of its Guideline for Elemental Impurities. Immediately following, in September 2013, the USP Elemental Impurities Expert Panel reviewed these Step 2b limits, and recommended revisions to General Chapter <232>. Then, on December 27, 2013, the USP announced its approval of General Notices section 5.60.30, Elemental Impurities in USP Drug Products and Dietary Supplements, with an official date of December 1, 2015.



Subsequently, in January 2015, USP announced that it intended to establish January 1, 2018 as the new date of applicability of Elemental Impurities Limits General Chapter <232>, and General Chapter <2232> Elemental Contaminants in Dietary Supplements. This new date served to align the implementation of General Chapter <232> more closely with that of the ICH Q3D Guideline, which was issued in final form in December 2014.

WHERE WE ARE NOW: THE ICH Q3D GUIDELINE

Before going any further, it is important to understand that the primary objective of this guideline is to establish harmonized, safety-based limits for elemental impurities, especially those with the highest toxicological concern. It provides for the selection of elements to control, as well as a methodology for establishing safety-based limits with permitted daily exposures (PDEs) for specific elements. This guideline also directs the use of an appropriate, risk-based approach in ensuring control for elements likely to be present in drug products and ingredients, serving as a harmonized guideline to ensure globally consistent control of elemental impurities.

The ICH Q3D Guideline applies to new finished drug products as defined in ICH Q6A and Q6B, and new drug products containing an existing drug substance(s). There are three parts to this ICH Guideline: (1) the evaluation of the toxicity data for potential elemental impurities, (2) the establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern, and (3) the application of a risk-based approach to control elemental impurities in drug products. The guideline thus presents a process to assess and control elemental impurities in a drug product using the principles of risk management,

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as described in ICH Q9. The process provides a mechanism for developing a risk-based control strategy to limit elemental impurities in the drug product.

In developing the Guideline, the Elemental Impurities Expert Work Group (EWG) specifically did not mandate, nor expect, the screening of all metals. Rather, they designed it so that the risk assessment would be the linchpin of the compliance strategy. They reasoned that knowledge of a product, and its manufacturing process—type of excipients, catalysts, equipment, maximum daily dose, route of administration, dosing regimen—would provide sufficient information for assessing risk.

Using the information derived from the risk assessment, a testing strategy could be developed, making it unnecessary for each individual drug component, or every elemental impurity to be tested. Thus, they envisioned using a screening methodology to identify elemental impurities of less than 30% of the PDE to support the need for no further testing. Also, using knowledge of the product, process, and sound science, elemental impurities that could be excluded, would be excluded. For example, an elemental impurity such as Osmium, which is extremely rare in occurrence, would be excluded and not screened, as it would not be introduced by a drug component, process, or equipment.

USP AND ELEMENTAL IMPURITIES

Elemental impurities are controlled in official drug products, drug substances, and excipients according to the principles defined, and the requirements specified in USP General Chapter <232> Elemental Impurities—Limits, which lists 15 elemental impurities that must be controlled. Procedures for the analysis of these elemental impurities are described in USP General Chapter <233>, Elemental Impurities—Procedures. General Chapter <233> describes two analytical procedures (Referee Procedures 1 and 2) for the evaluation of the levels of the elemental impurities as a limit test. The chapter also describes criteria for acceptable, alternative procedures.

However, the two referee procedures described in <233> provide only "general guidance" in carrying out analysis for elemental impurities. This can be problematic, as both procedures lack sufficient detail to easily and readily perform the testing. Take, for example, samples requiring an "Indirect Solution", that is, a closed vessel microwave digestion. This can pose significant analytical problems, as in some instances, even under the most aggressive conditions, samples simply do not fully dissolve, and in other instances, the digestion procedure itself may cause problems with specific elements.

WHERE WE ARE GOING: REQUIREMENTS IN A GLOBAL ENVIRONMENT

To discuss what steps should be taken for elemental impurities, stakeholders from industry, excipient manufacturers, the FDA, EMA, USP, and Pharma Europa (EP) met in late March/early April 2015 at USP headquarters in Rockville, MD. Speaking from the Excipient Manufacturer's Perspective, David R. Schoneker of Colorcon and IPEC-Americas opened up the workshop with the keynote presentation discussing IPEC's efforts in developing a "generic" database of elemental impurities found in excipients.

However, given the manufacturers' trade names or specific product identities, such a database would be agnostic, at best. During the various breakout sessions, he, along with other excipient manufacturers, provided some information regarding this database. It was clear from what was said that many excipient manufacturers were reluctant to provide concise information as to what excipients had been tested, what methods were used, and what the specific results were.

One of Mr. Schoneker's direct comments was that most of the data developed by excipient manufacturers was the result of using leaching methods, as opposed to a total acid digestion, or extraction for sample preparation. The rationale behind this was that the leaching was based upon bioavailability, rather than total elemental impurities present.

During this two-day workshop, presentations and discussions were held that provided further insight into what steps pharmaceutical companies and excipient manufacturers have taken, as well as what still remains to be done. These discussions have yielded valuable understanding into what approaches are being taken by pharmaceutical companies, both large and small, and the difficulties that they have encountered in their risk assessment testing efforts. Excipient manufacturers also spoke about issues specific to their products, elemental impurities, and the unique problems posed by excipients derived from natural sources. Adding to this were regulators from the FDA, who provided some knowledge into their perspective on compliance, and the evolving regulatory requirements for elemental impurities.

INDUSTRIES' EFFORTS AND PERSPECTIVE

Representatives from Bristol-Myers Squibb (BMS) gave a presentation on the Practical Implementation of USP <232> and <233> and ICH Q3D. In speaking about USP <233>, the speaker maintained that it was not prescriptive, but rather a guide as to what was required, without referencing implementation procedures. Consequently, it was discussed that in most cases, sample preparation is the key to method performance. From their experience at BMS, a method specific sample preparation procedure was necessary to carry out the determination of elemental impurities. It was pointed out that this would require method development and validation, and the presenter provided some suggestions as to how this could be approached.

Representatives from Merck made a presentation on the Concept of Elemental Impurities Assessment in Finished Dosage Forms by Total Extraction Testing. The presenter spoke about Merck's efforts in the development and validation of a method for use in all of Merck's finished drug products. The highlight of this presentation was that, rather than using closed vessel microwave digestions, an open vessel, wet acid "extraction" was implemented in sample preparation prior to ICP-MS analysis. The speaker indicated that "acid extraction" was allowed under USP<233>, and the data presented showed excellent spike recoveries for all 24 ICH elemental impurities. In closing, it was noted that Merck had made the decision to test everything, all excipients and finished drug products, to avoid any unforeseen regulatory issues.

At the various breakout sessions, a number of the large pharma attendees spoke about their companies' approaches to elemental impurities. Most indicated that they had initially begun

with a preliminary screening of selected excipients and finished drug products, but then had moved on to developing validated methods to support their risk assessments.

The attendees from Pfizer commented that the approach they had taken was to first use an initial screening procedure, and from this, a decision was made to develop and validate methods to test all excipients and finished drug products. They went on to state that this approach was intended to avoid any regulatory issues, and that over 1,000 excipients and drug products had already been tested. In closing, they indicated that, to date, they had no issues with elemental impurities.

Representatives from Actavis also offered their approach to elemental impurities. Like Pfizer, they intended to avoid any regulatory issues, and were well on their way in developing and validating elemental impurity methods for all of their finished drug products to support their risk assessments.

It is important to note that during these breakout sessions, throughout both days, individuals from the FDA continued to stress that data generated on elemental impurities, supporting any risk assessment, must be developed using fully validated analytical methods.

THE FDA AND ELEMENTAL IMPURITIES

Speaking on behalf of the regulators, representatives from the FDA gave several presentations. Dr. Vibhakar Shah, of FDA's Office of Policy for Pharmaceutical Quality, Center for Drug Evaluation and Research, gave a presentation on Elemental Impurities in APIs and Excipients - GMP Expectations. His presentation covered the statutory requirement for drug quality and regulatory requirements for drug products, APIs, and excipients. Speaking about these requirements, he went on to cover what FDA's GMP expectations for Elemental Impurities in APIs and excipient would be. Specifically, those expectations were:

- Availability of the on-site Risk Assessment Report, in accordance with the ICH Q3D recommendations, or an alternate approach that may be equal to, or better than, ICH Q3D, and deemed acceptable;
- Scientific data supporting the inclusion and/or deletion of elemental impurities from the specification limit(s)/specifications for the elemental impurities of concern based on process knowledge;
- Availability of method validation data demonstrating suitability of the test methods for intended use;
- Availability of product/process data demonstrating capability and reliability of the manufacturing process steps to remove or control elemental impurities consistently at, or below specified levels;
- Change control management for potential impact on elemental impurities profile; and
- Routine vs. full testing, and frequency of full testing for elemental impurities.

Based upon Dr. Shah's presentation, each drug product will require a risk assessment report, performed in accordance with ICH Q3D, covering the finished dosage form, API, excipients, and closure system, which is based upon sound scientific data that was obtained using validated elemental impurities analytical methods demonstrated to be suitable for their intended use.

Another presentation, given by Dr. Danae Christodoulou, Acting Branch Chief of the FDA office of New Drug Products, and a member of the FDA's Elemental Impurities Working Group, covered Regulatory Expectations at Time of Registration and during Ongoing GMP Inspections. Touching on what the FDA's expectations for Elemental Impurities would be in relation to New Drug Product filings, she noted:

- The risk assessment for elemental impurities—Summation option—the contribution of components of the drug product to be included in the "Pharmaceutical Development Report", section P2.3 of the application;
- Specifications for elemental impurities, including "Heavy metals" to be set according to ICH Q3D limits;
- Testing methods and validation for controlled elemental impurities to be included in the corresponding drug substance and product sections of the application, sections S4.2 and 3, P5.2 and 3; and
- Excipient contributions to be included in their controls, or referenced to a Drug Master File (DMF) of the supplier, Type IV.

She also provided input as to current FDA expectations for elemental impurities, relative to GMP requirements. These include:

- Elemental impurities specifications in the drug substance(s) and drug product(s) set based upon results from testing;
- All test methods used to assess elemental impurities are to be fully validated analytical methods;
- These methods, and their validation, are to be available at the manufacturing site during GMP inspections, and also included in the drug application; and
- If any additional testing, i.e. skip lot testing, etc., was/is performed to confirm "minimal levels" of elemental impurities, the results and test methods used are to be available during GMP inspections.

TIME LINES FOR COMPLIANCE

With the USP establishing January 1, 2018, as the new date of applicability of the Elemental Impurities Limits General Chapters, and FDA setting December 2018, as the expected date of compliance for existing products, it appears there is some time to prepare. But there are other dates that can have a significant impact, especially in the global marketplace, and for new drug products. In both Europe and the US, the EQDM/EMA and FDA deadlines for compliance of new marketing authorization and new drug applications, respectively, with ICH Q3D are each set for June 2016.

In addition to these dates, there are other timelines that can have a significant impact with compliance. In many cases, the analytical methods used may require validation, rather than verification. The additional time spent developing and validating the method, as well as allocating analytical resources must also be factored in, as many labs simply do not have internal ICP-OES, ICP-MS, or microwave digestion capabilities readily available.

Also, bear in mind that while there are a number of contract laboratories capable of GMP analytical work using these

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analytical techniques, their capacity is not infinite, and they may already be scheduled at maximum usage. Thus, as a cautionary measure, all these issues should be factored into the plan for developing and validating analytical methods to support risk assessment for elemental impurities.

CLOSING THOUGHTS ON AN APPROACH

So what approach should one take in getting a handle on elemental impurities? With the ICH Guideline recommendation in mind, a good starting point would be acquiring knowledge about your own manufacturing processes. Readily available information, such as the type and age of equipment, process reagents, catalysts, as well as information from suppliers (when and if available) should be used to begin assembling a risk assessment. Supporting this, should be some sort of initial screening program. However, in most instances, a substantial amount of work will be needed to carry out the development of suitable methods for elemental impurities.

Bear in mind, that while USP<233> has two "Referee Procedures", these procedures are not prescriptive for any specific API, excipient, or finished drug form. In the most basic approach, method verification is required to demonstrate the suitability of the "Referee Procedure" used. However, based upon the PQRI stakeholder conference, there are also other considerations. Specifically, the manner in which the FDA will interpret the application of USP<233> and ICH Q3D, which has moved to step 5 – implementation. The FDA's focus with USP<233> appears to be in the direction of generation of method validation data to demonstrate the suitability of the test methods for intended use for elemental impurities. Method development, along with "full validation of analytical methods" will, in most cases, be required.

While one might be led to believe that using either of the two "Referee Procedures" of USP <233> would entail a minimal amount of verification to demonstrate suitability, more may be necessary. For example, the method chosen may need to be modified in some way to address specific matrix issues. This modification would now result in a full validation being required. Also, many have found the "Referee Procedures" in <233> to be too generic, or not suitable for their matrix. Subsequently, method development and validation have become necessary more often than not. Finally, it is this writer's opinion that, in light of the recent comments from FDA regulators, the requirements regarding the analytical methods used to assess elemental impurities appear to be coming clearly into focus, and pointing in one direction to the development of drug product/API/excipient specific methods that have been demonstrated to be suitable for their intended use through a complete validation. We would all be well served to prepare. **CP**