Application of an intelligent, on-line sample preparation system for meeting the USP 232, USP 233 and ICH Q3D requirements, using ICP-MS

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Overview

Purpose: To demonstrate easiest method validation and compliance with USP chapters <232> and <233> as well as robust, high throughput routine analysis.

Methods: Thermo Scientific™ iCAP Qc™ ICP-MS coupled to the ESI prep*FAST*™ auto dilution system.

Results: All information required for method validation can be easily obtained from the 21CFR part 11 compliant Qtegra Intelligent Scientific Data Solution. The *prep*FAST simplifies sample preparation and reduces manual interaction.

Introduction

Legislation for measuring elemental impurities in drug products is currently under revision by a number of regulatory authorities, driven initially by the United States Pharmacopeia (USP) in the form of USP Chapter <232> - Limits and USP Chapter <233> - Procedures. The implementation date for meeting the demands of these regulations is at present ,1st January 2018. This poster will describe application of an auto dilution system for on-line preparation of calibration standards and samples with ICP-MS detection in accordance with the requirements of USP <232>, <233> and ICH Q3.

Methods

USP chapters <232> and <233>

The two above mentioned chapters govern the analysis of elemental impurities. Whereas chapter <232> defines limits for the maximum exposure as a consequence of drug intake, chapter <233> describes methods for their determination. Two methods based on Inductively Coupled Plasma – Optical Emission Spectroscopy (ICP-OES) and – Mass Spectrometry (ICP-MS) are described in detail, but also validation criteria for other methods are outlined.

Due to the generic definition of Permitted Daily Exposure (PDE) values for different elements, each drug has individual requirements for calibration. Using prescriptive auto-dilution, a single stock solution can be used for all calibrations. The prescriptive auto-dilution feature can also be used to perform any required dilution from the sample solution as obtained for example after microwave assisted closed vessel digestion and thus reduces human interaction with the samples as a potentially untraceable error source.

Mass Spectrometry

The iCAP Qc ICP-MS coupled to the prep*FAST* system (Figure 1) with an SC-2DX autosampler (Elemental Scientific, Omaha, NE, USA) was used for acquisition of all data. The iCAP Qc was operated in He KED mode for all analytes. Instrumental parameters are listed in Table 1. The *prep*FAST system was integrated into the instrument to minimize sample flow pathways.

Data Analysis

Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ software was used to control the ICP-MS instrument and the prepFAST sampling and dilution device. The Qtegra software also allows the quantitative assessment of the data as well as the generation of dedicated reports that automatically calculate and highlight the relevant results for method validation according to USP chapter <233>.

FIGURE 1. prep*FAST* connected to the iCAP Q (left). ESI SC-2DX autosampler (right).

TABLE 1. Instrumental Conditions

Parameter	Value
iCAP Q	
Nebulizer	PFA-ST
Nebulizer Gas Flow	1.02 L·min^{-1}
RF Power	1550 W
Interface setup	Ni Cones, High Matrix Skimmer insert
Cell Gas Flow	4.8 mL·min^{-1} 100% He
KED voltage	3 V
prep*FAST*	
Sample loop	1.5 mL
Time per analysis	68 s

Results

Prescriptive Dilution for different J value calibration

Although according to chapter <233> a two point calibration is sufficient, the different maximum daily dosages of drug compounds mean that a different calibration curve is required for each product. Prescriptive Dilution allows generation of different calibration levels out of a single higher concentrated stock solution, so that calibration for different drug products can be easily and automatically accomplished (Figure 2).

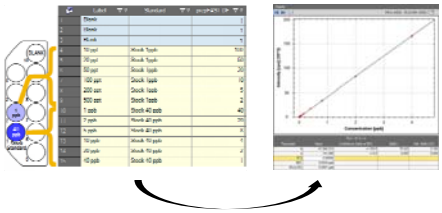

FIGURE 2. Prescriptive Dilution to generate different calibration levels using stock solutions with *prep*FAST.

In a similar manner, prescriptive dilution can be used to dilute each sample before analysis without performing manual interactions.

Method Validation

For compliance with chapter <233>, apart from the correct result for a spiked sample (Accuracy), a validation procedure has to be completed for each drug product or compound.

Among the characteristics to be validated, the precision of the method has to be addressed. According to chapter <233>, six replicates of a sample spiked @ J need to be analyzed, with a resulting relative standard deviation (RSD) below 20%. Using the reporting tool inside Qtegra ISDS, a dedicated report (see Figure 4) can be created that directly calculates and displays the results and can be used for straightforward validation. In a similar manner, the intermediate precision or ruggedness of the method needs to be addressed through repetition of the former experiment on a different day, instrument or analyst.

Table 2 shows the spike results obtained for a drug product administered orally with a maximum daily dose of 10g. The sample was dissolved using a closed vessel microwave assisted digestion procedure similar to reference 1. The attainable instrumental detection limits are also shown in the table.

TABLE 2. Detection limits and spike recoveries.

Element	IDL [ng· mL-1]	Recovery, Precision [%] (N=6)	Recovery, Ruggedness [%] (N= 12)
Cd	0.0002	102.1; 1.7	102.2; 1.2
Pb	0.0001	103.8; 1.5	102.2; 2
As	0.007	101.3; 1.7	101.4; 1.3
Hg	0.002	104.1; 1.3	102.2; 2.2
Ir	0.0002	103.0; 1.2	102.1; 1.3
Os	0.0004	101.2; 1.3	99.8; 1.9
Pd	0.0005	103.3; 1.8	103.9; 1.4
Pt	0.0003	102.7; 1.2	102.2; 1.1
Rh	0.00007	101.9; 1.7	102.4; 1.2
Ru	0.0001	102.8; 1.9	103.1; 1.4
Cr	0.003	N/A	N/A
Mo	0.002	101.0; 1.9	102.0; 1.7
Ni	0.009	102.2; 1.8	102.4; 1.4
V	0.001	100.1; 1.8	100.1; 1.4
Cu	0.01	101.7; 2.1	101.9; 1.5

Driven by Qtegra ISDS

Qtegra Software Concept

Using a Qtegra template the user only needs to type in the number of samples. Parameters for subsequent quality control checks (e.g. drift checks or internal standard recovery) are automatically set and actively monitored by the software (Figure 3).

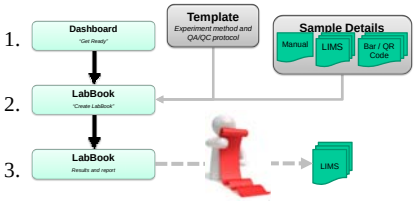

FIGURE 3. Qtegra software concept

Access rights can be controlled through different user levels and all changes are automatically tracked through Audit Trails in the software.

Comprehensive Report Generation for Method Validation

The Qtegra software contains a dedicated toolset to generate customized reports that allow preparation and display of data for almost immediate method validation:

- **Summarize LabBook and Instrument specific information:** The history of a data set can be controlled and all relevant information can be displayed.
- **Create sample and analyte specific tables:** Larger data sets can be filtered so that only one sample is displayed in a dedicated table. Individual tables can be created for different analytes e.g. the big four (As, Cd, Hg and Pb) and other impurities separately.

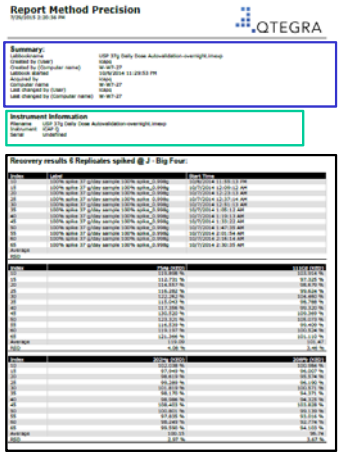

FIGURE 4. Qtegra generated report for method validation

- **Multi-LabBook Query:** Filtering over multiple LabBooks is also possible in order to track/compare data acquired on different days or by different users. In this way, the ruggedness of the method can be directly assessed (see Figure 5).

FIGURE 5. Multi-LabBook Query inside Qtegra ISDS

Conclusion

The Thermo Scientific iCAP Q equipped with an ESI Autosampler and prep*FAST* sample introduction system was validated for use with USP chapters <232> and <233>. The reporting tool inside Qtegra ISDS allows for rapid method validation. The system provides the following benefits:

- **Ease of Use:** With the prescriptive and intelligent dilution provided, any manual sample preparation and data post processing is minimized.
- **No Impact on Bench Space:** The integrated dual valve assembly is mounted directly beneath the sample introduction system, minimizing sample pathways.
- **High Throughput:** The iCAP Q ICP-MS in combination with the ESI prep*FAST* sample introduction system is the ideal system to measure samples in a high throughput laboratory.

References

- Application Note 43174: Analysis of Pharmaceutical Products for their elemental Impurities Using the Thermo Scientific iCAP Q ICP-MS

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