Elemental Impurities Testing at a Pharmaceutical Company

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Strategies for Testing

- Finished product vs. Component Testing
- How many batches is enough?
  - New products vs. existing products?
- Type of testing
  - Full dissolution of sample?
  - Solids analysis?
  - What if a sample doesn't dissolve and solid analysis techniques are not available?
- Alternative techniques?

Finished Product vs. Component Testing

USP requires compliance in drug product, however, provides guidance on excipients and raw materials

ICH-Q3D also applies to drug products

Both permit either drug product testing or component testing

Product Testing

Drug product testing:
Eliminates need to assess processing equipment and packaging components
One analysis vs. multiple analyses for various components
Analysis of mixture may be more difficult than analysis of pure materials
A product failure would mean scrapping the entire batch of product
Difficult to re-work a product
Already takes into account contributions from processing equipment, water, packaging, etc.

Component Testing

Component Testing:
Pure materials usually easier to analyze than mixtures
Can isolate a "bad" batch of a material and thereby prevent entire product batch from failing
Requires multiple methods and analyses
Does not automatically incorporate contributions from processing equipment, water and packaging components

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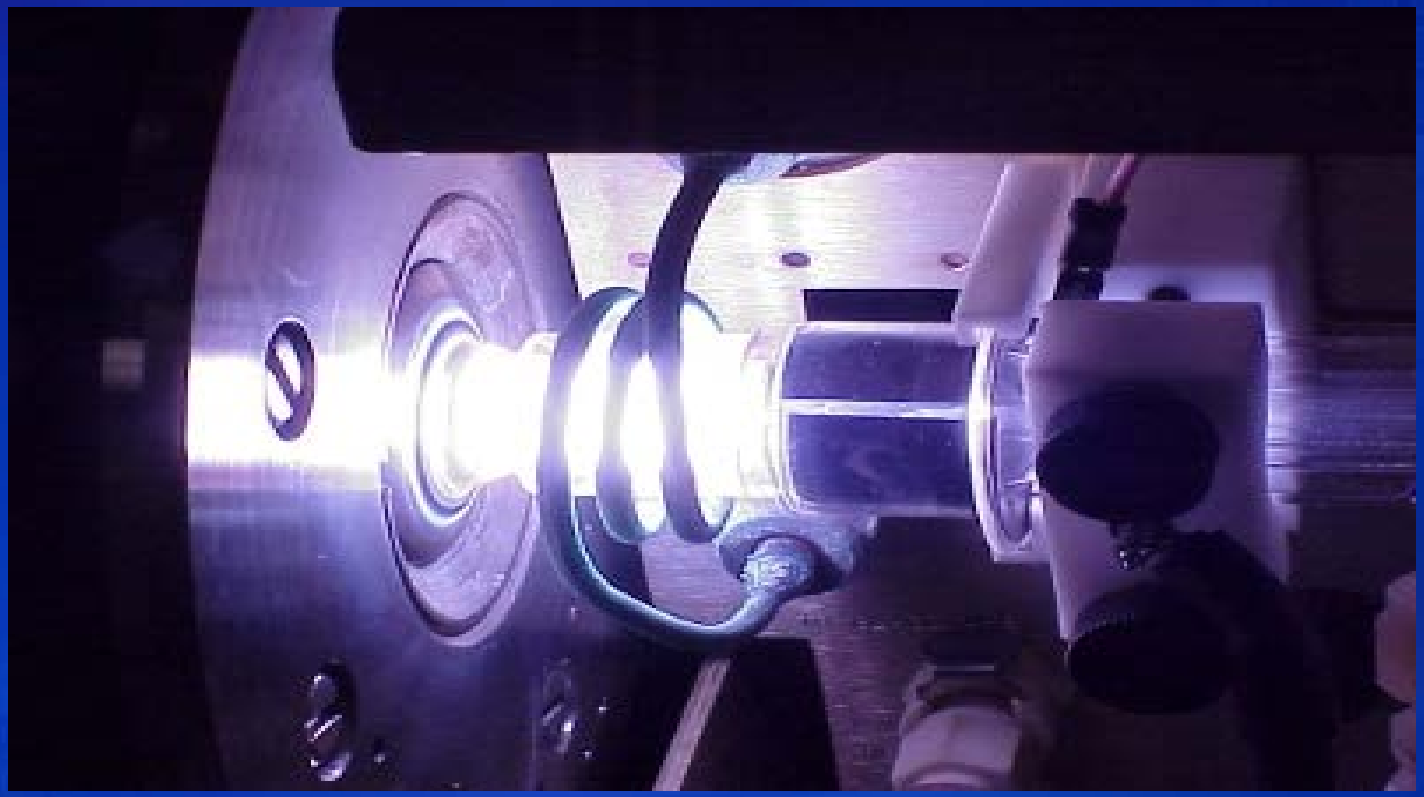
What Method to Use for Testing?

- ICH Q3D suggests use of compendial procedure
- USP <233> provides analytical procedure
- Use <233> for drug product OR component analysis
- USP working through the PDG to harmonize USP <233>

ICP-MS Usually Best Analytical Option; ICP-OES Second Best Option



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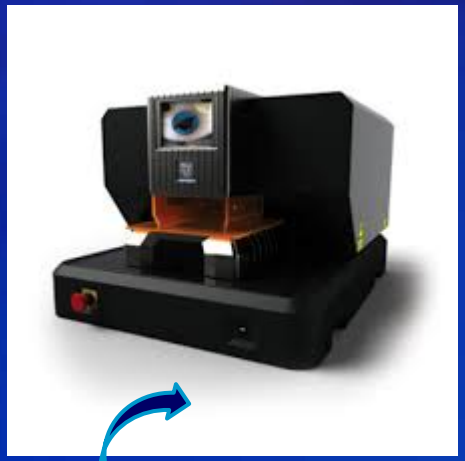
Alternative Techniques

- USP <233> allows for use of techniques other than ICP-OES or ICP-MS
- Use what works best for your samples and for which you have equipment
- Risk assessment should drive what testing you need to do, and determine what technique is needed

Potential Alternative Techniques



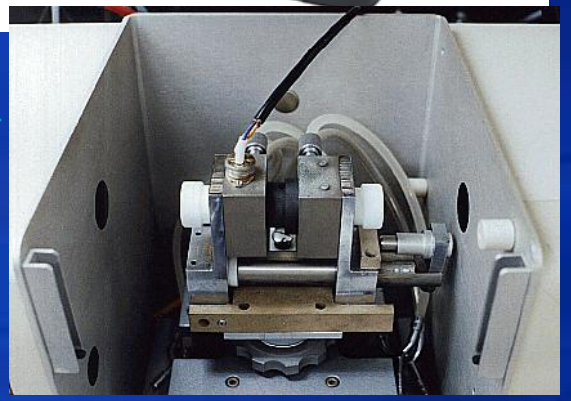
Laser ablation

Flame AA

Field portable, hand-held, bench-scale XRF instruments

LIBS

Graphite furnace AA



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http://www.tissuegroup.chem.vt.edu/chem-ed/spec/atomic/graphics/gfclose.jpg

http://vertassets.blob.core.windows.net/image/fc1733a8/fc1733a8-7cc1-4f2b-a353-a0a200e1aa16/ocean.jpg

http://www.panalytical.com/Epsilon-1.htm

https://www.esi.com/media/1076/nwr213.jpg

If Testing, How Many Batches is Enough

No firm guidance from health authorities—yet

ICH Q3D: at least 3 production-scale or 6 pilot-scale batches (recommended)

What if you have multiple suppliers of a given material?

Suggestion: do at least 3 production-scale or 6 pilot-scale batches of EACH supplier's material

What about new products?

use process justification/validation batches

use pilot-scale batches

use production-scale batches

Type of Testing

Options:

- full dissolution of sample
- solid analysis
- what else?

Sample Preparation Approaches (solid analysis does not normally need much sample preparation)

Microwave digestion

http://rs2.chemie.de/images/12758-76.jpg

Direct Dilution

https://www.sciencecompany.com/Assets/ProductImages/nc12973g.jpg

Microwave Digestion

- Closed-vessel preferred
- If using vented or open-vessel—need to make certain volatiles are not lost

What if a Sample Doesn't Completely Dissolve?

Factors to consider:

- what is the role of the analytical chemist?
- what do other industries do?
- what other types of samples are difficult to dissolve?

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What to do If the Sample Doesn't Dissolve?

Don't give up!

- Not appropriate to just say "it can't dissolve" and be done with it
  - make certain that, if you are filtering off solids, that there is no potential for that material to contribute to the concentration of the analytes of interest in the sample
  - Be able to avoid the "red-face" test—can you justify filtering off solids and going forward? If not, then do more work
- Other industries have been using ICP-MS for many years for trace metals determinations in sample matrices that are far more challenging than drug component or drug product analyses
  - Rocks are much harder to get into solution!

If a Sample Doesn't Dissolve In "Routine" Microwave Digestion Method

- Leverage approaches used by geological, environmental, semi-conductor (and other) industries
- Try different types of digestions
  - combinations of acids
  - add peroxide
  - pre-digestion
- Solid analysis: XRF, LIBS, LA (via ICP-MS or ICP-OES)

What about "Bioaccessibility?"

- The job of the analytical chemist is to provide the best results possible
  - results can be relied upon to make informed decisions
- It is the analyst's responsibility to provide results—NOT to make a decision regarding potential toxicity
- Decisions regarding "bioaccessibilty" should not be made in the analytical laboratory
  - Address by toxicologists and during development

Final Thoughts

- Time is running out!
- Risk Assessments need to be completed
- Leverage information in published literature, if possible, to fill “gaps”
- Remember: it’s a *RISK ASSESSMENT*

Thank you

Questions?