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How to Qualify a 3rd Party Laboratory and Understand Conflicting Laboratory Results

Jana Hildreth
CEO & Technical Director
Blaze Science LLC



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Reasons for Testing

Before Manufacturing

- Verify identity
- Verify strength (for standardization, normalization)
- Qualify Supplier
 - Product quality
 - Potency
 - Uniformity
- Check for contaminants, adulterants



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Reasons for Testing

- After Manufacturing
 - Verify label claim
 - Purity, potency etc.
 - Quality Control of manufacturing process
 - Product uniformity
 - Product stability
 - Monitoring of degradation products or marker compound(s)
 - Compliance
 - ISO
 - GMPs



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Identifying Your Testing Needs

- **What is the goal of the analysis?**
 - ID Testing
 - Do you have the correct species or plant part (mandated by cGMPs)
 - Qualification of a new supplier
 - Conformation of **all** test results listed on C of A
 - Conformation that all test results meet product specifications you have set
 - QA Check to ensure product is not adulterated or contaminated
 - Litigation



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cGMP Requirements Under Subpart D – Equipment and Utensils

In this section it specifically outlines that you:

- (b) ...must calibrate instruments and controls you use in **manufacturing or testing a component or dietary supplement**. You must calibrate:
 - (1) Before first use;
 - (2) At the frequency specified in writing by the manufacturer of the instrument and control; or
 - (3) At routine intervals or as otherwise necessary to ensure the accuracy and precision of the instrument and control.



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Good Manufacturing Practices: Subpart D – Equipment and Utensils: What Records Must You Keep

- 1) **Calibrating instruments** and controls that you use in manufacturing **or testing** a component or dietary supplement
- 2) Calibrating, inspecting, and checking automated, mechanical, and electronic equipment
- 3) Documentation of any calibration



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What Initial Questions to Ask of a 3rd Party Laboratory

- 1) Do you have previous experience with this analyte(s) and particular or related matrix?
- 2) Are you accredited with any organization?
- 3) Do you have an independent QA unit? Do you have a quality manual and SOPs?
- 4) Do you have all the necessary equipment to do the work or will you be outsourcing any of the work to another lab?
- 5) Do you have training records demonstrating the person handling the sample is properly qualified?



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What Documents to Check When Auditing a Third Party Laboratory - General Controls

- 1) Is there an Organizational Chart and are there job descriptions for each laboratory position
- 2) Are all test procedures in writing and are they being followed?
- 3) Is there a training programs in place and is the training documented in writing?
- 4) Do they have a formal Quality Unit in place and an SOP for Internal Audits?



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What Documents to Check When Auditing a Third Party Laboratory - Equipment Control

- 1) Does the laboratory have the adequate equipment to perform the required testing?
- 2) Do SOP's exist for each piece of equipment for maintenance along with operation and calibration?
- 3) Are there visible labels on each piece of equipment used for measurement indicating when the last calibration was performed?
- 4) Are records of calibration easily accessible?
- 5) Do they have SOP's for scheduled performance verification of instruments used for testing?



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What Documents to Check When Auditing a Third Party Laboratory - Safety

- 1) Do they have a Safety Manual and documentation demonstrating each employee has been trained?
- 2) Are there first aid kits, operational eye washes etc. conveniently located?
- 3) Is there adequate procedures for disposal of waste?
- 4) Is there adequate ventilation?
- 5) Are chemicals stored appropriately - flammables, acids etc.
- 6) Do laboratory personal wear safety glasses and lab coats?



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What Documents to Check When Auditing a Third Party Laboratory - Reference Standards, Reagents, Media and Solutions

- 1) Is there a SOP for the receipt, log-in, handling, storage and expiration of standards, reagents, media and solutions?
- 2) Are the standards, reagents, media and solutions labeled with the proper name, date opened and expiry date?
- 3) How do they qualify their standards and supplier?
- 4) How do they determine the expiration date of the standard if it has not been supplied?



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What Documents to Check When Auditing a Third Party Laboratory - Sample Receipt etc.

- 1) Do they have SOP's for receipt, handling and storage of test samples?
- 2) Are there written procedures for disposal of samples
- 3) Is each sample assigned an unambiguous sample number when logged in?
- 4) Are samples logged in to a notebook or computer system and how is this information backed up?



What Documents to Check When Auditing a Third Party Laboratory- Records Management

- 1) Are records and reports adequately secured and retained for the required length of time
- 2) Do they have a SOP for Proper Documentation Procedures?
- 3) Are the chemist trained in this procedure and do they follow good documentation practices?
- 4) Do they identify the standard used, manufacturer, lot number and expiration date?
- 5) Do they identify the sample and site the specific method being used?

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What Documents to Check When Auditing a Third Party Laboratory: Handling of OOS

- 1) Is there a SOP and form for reporting out-of-specification test results?
- 2) Does the SOP require an investigation of all out of specification result be documented prior to any retesting?
- 3) Who makes the decision on retesting the sample if no mistakes can be found in the procedure used and reporting?
- 4) Are all activities pertaining to the OOS result(s) documented adequately?



"OF COURSE YOU CAN'T REPLICATE MY EXPERIMENTS. THAT'S THE BEAUTY OF THEM."



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Main Causes for Conflicting Laboratory Results

- 1) Analytical Method
- 2) Reference Material
- 3) Instrumentation
- 4) Human Error
- 5) Fraudulent activity



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Main Causes for Conflicting Laboratory Results: Methods

- 1) Different Methods
 - Different extraction technique, selectivity, detector etc.
 - Specific vs non-specific method (HPLC vs CPC)
- 2) Method lacks ruggedness
 - Validated vs Non-Validated
- 3) Method is not "Fit for Purpose"
 - Use of AOAC or USP method developed for different matrix



Main Causes for Conflicting Laboratory Results: Example of Specific Vs Non Specific Methods

1) Saint John's Wort

Non-Specific:

EP UV method yields around 0.3% value for "total naphodianthrones" and can easily be fooled by adding red dye

Specific:

INA HPLC/UV method measures specific compounds (Hypericin and psuedohyperiin) and typical yields 0.15%-0.2% total hypericins



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Good Reasons for Using Non Specific Methods

- 1) No other method exists or is practical (ORAC)
- 2) The cost and equipment needed to the perform the analysis is low
- 3) The time to needed to perform the analysis is fast and the equipment is easy to use (CPC vs Enzymatic HPLC for Chondroitin)



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Bad Reasons for Using Non Specific Methods

- 1) The method yields higher results which is good for marketing

- 2) The method can be easily duped - can't detect adulteration with inferior materials or plant parts
 - Melamine substitution for protein
 - Grape skin added or completely substituted for Bilberry
 - Carrageenan added or completely substitute for Chondroitin Sulfate



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Method Used Lacks Ruggedness

- 1) Sample size is too small or not representative of lot
- 2) Wrong solvent used to extract analyte
 - Ginsenosides from Ginseng root are extracted more efficiently with water but MeOH is the solvent of choice when dealing with Ginseng extract
- 3) Analyte not fully soluble or stable in solvent used
- 4) Filter used binds analyte of interest
- 5) Too small a quantity of neat calibration standard available for accurate weigh measurement



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What You Need to Do In Order to Comply with cGMPs Prior to Relying on a C of A

- 1) Qualify the supplier by establishing the reliability of the supplier's certificate of analysis through confirmation of the results of the supplier's tests or examinations
- 2) The certificate of analysis must include a description of the test or examination method(s) used, limits of the test or examinations, and actual results of the tests or examinations



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cGMPS: What you Need to do to Qualify a Vendor

- 1) Conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient
- 2) Confirm the identity of other components and determine whether other applicable component specifications in the cGMPS are met



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What you Need to Know When Establishing Product Specifications

- 1) Conduct appropriate tests or examinations
- 2) Rely on a certificate of analysis from the supplier of the component that you receive, provided that you have qualified the vendor and their C of A
- 3) Ensure the tests or examinations used are “fit for purpose” and “scientifically valid”



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What Laboratories Should Look Like





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New Technologies





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Upcoming Answer To Fast Turn Around Time





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Reasons for Conducting a SLV

- 1) To ensure viability of a method before doing a collaborative study
- 2) Provide evidence of reliability if collaborative data unavailable or not
- 3) Practicable to run To demonstrate that a method newly introduced into your laboratory is being properly performed
- 4) As a laboratory proficiency check



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Existing Protocols and Guidelines For Method Validation

- 1) International Conference on Harmonization (ICH)
- 2) AOAC SLV Guidelines
- 3) USP/NF 29/24 - 30/25
- 4) ISO/IEC Guide 25
- 5) FDA Guidance for the Validation of Chromatographic Methods
- 6) ETC.



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Conclusion

- 1) The testing of dietary supplements is a systematic series of logical steps
- 2) Determining validity of a method is more than copying a method from a journal
- 3) Methods suitable for one matrix may be unsuitable for another matrix
- 4) Changing a method does not mean the method retains validity
- 5) DS method development requires creative problem solving
- 6) You get what you pay for so don't lab shop!



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Questions????

Thank You !

Contact Information:

Jana Hildreth

CEO and Technical Director

Blaze Science Industries, LLC

janah@socal.rr.com

310-920-4517 (phone)

www.bsillc.org