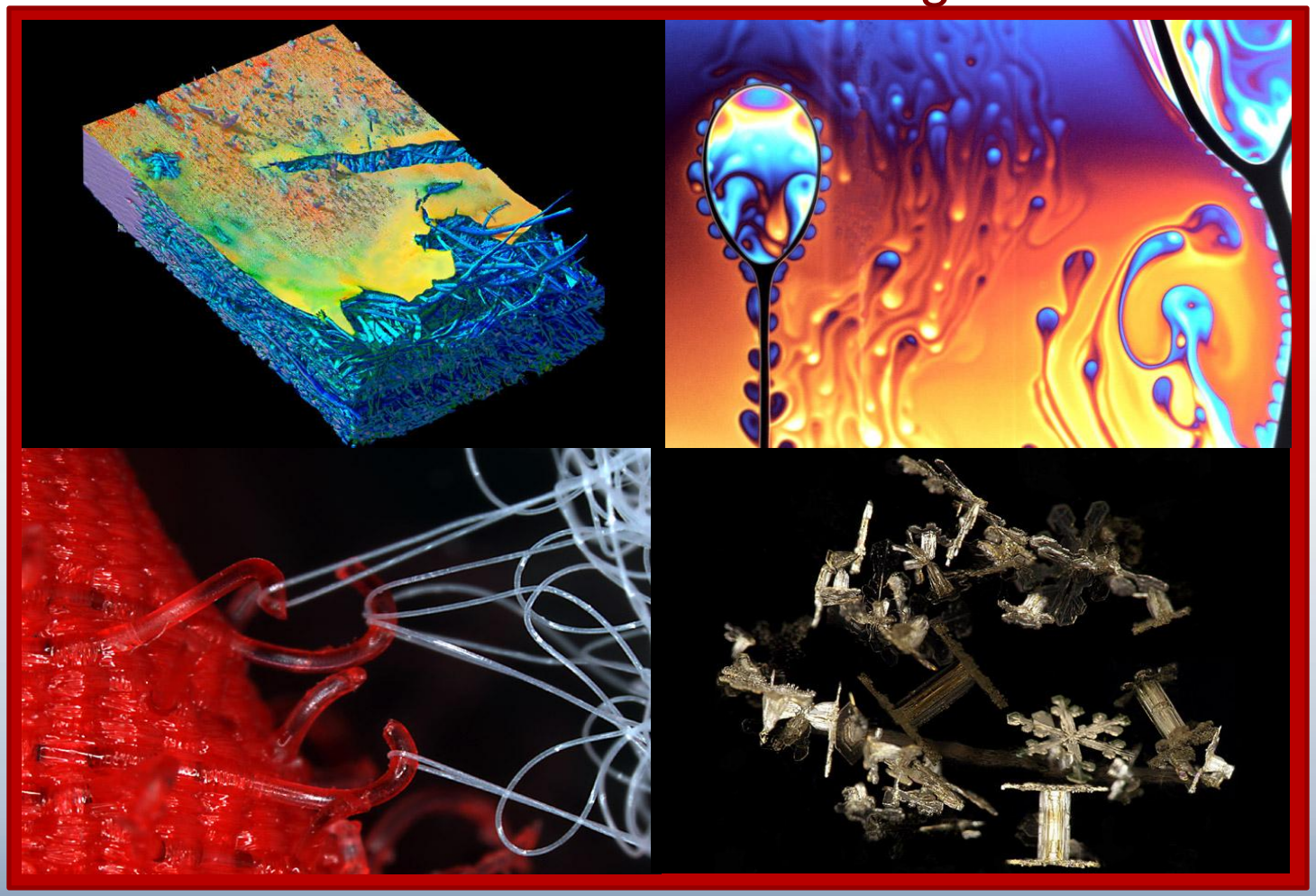
2010 – Another Year of Bioanalytical Activity and Movement Towards Harmonization…

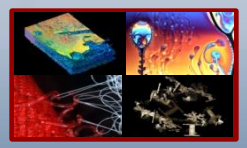
…and SQA gets involved



Presentation Outline

1. SQA and 2011 Annual Meeting
2. Harmonization of the Bioanalytical Method Validation Guidances
   - Summary
   - The Players
   - Meetings
3. EMA and FDA Perspectives and Announcement about Harmonization
4. EMA and FDA BMV Guidances – A Summary and Comparison
5. The Participation of BASS / SQA in the BMV Harmonization Initiative
6. BASS / SQA's Position on Aspects of a BMV Guidance
7. Proposal for a Global Bioanalytical QA Alliance
8. Recent FDA 483s and Warming Letter Discussion

Magazine Cover
Velcro



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Animal Health	• Learning from 483s
Bioanalytical	• Global harmonization of BioAnalytical method validation • Incurred Sample Reanalysis (ISR)
Biotechnology	• Investigational process for small and large molecules • Defining and auditing protein characterization • Biotech and Regulations: The New, The Old, What is needed
Computer Validation	• Archiving of electronic records • Validation world has expanded beyond GxP's • Expectations of the EPA for Computers in GLP • Virtualization of servers - regulatory expectations for control, configuration management, IQ, data integrity and security, validation challenges

JW Marriott Hill Country

Check it out at: **http://www.sqa.org/am2011**

Good Clinical Practices

- The FDA proposal on reporting Fraud - how will the industry comply?
- Outsourcing Quality--what's at risk?
- Part 11 and clinical trial sites
- The new FDA investigator inspection program
- Regulatory agencies and sharing of information (FDA-TGA-EMA)
- Good Clinical Laboratory Practices (GCLP)
- Assessing Investigator Responsibilities in light of the new Guidance (Oct 2009)
- FDA's increase in auditing IRB's

Good Laboratory Practices

- Timing of approval of individual scientist reports relative to approval of the non-clinical study report
- Validation of digital image technology
- Pathology peer review prior to study pathologist report being approved.

Check it out at: **http://www.sqa.org/am2011**

Medical Device	• The status of CDRH, an update on 2010 CDRH initiatives, and the regulatory path for 510(k) medical devices • FDA oversight of foreign clinical device trials including the recent HHS OIG report
University	• GLP and non-GLP Environments in the University • Computer validation, electronic records and Part 11 compliance in University and Academic.
Miscellaneous	• Interface of ISO and GCP/GLP • Current 483 Warning letters • Electronic notebooks • GAMP 5

Check it out at: **http://www.sqa.org/am2011**

Harmonization:

It is an opinion of the FDA that that BMV guidance harmonization is desirable and that the FDA and the EMA should work together.

It is important to consider how to get to harmonization so what is correct can be achieved in a reasonable amount of time. Moreover, representation for harmonization needs to be global.

Dr. Viswanathan suggested:
"Keep it simple, focused, unified and global."

EBF:

http://www.europeanbioanalysisforum.eu

European Bioanalytical Forum

EBF is an organization comprised of bioanalytical scientists working within the pharmaceutical industry R&D.

The scope of EBF is on bioanalysis of small and large molecules with 'bioanalysis' being defined as:

- Quantification of drug and metabolites in body fluids and tissues
- Quantification of safety biomarkers amenable to conventional Bioanalytical techniques
- Bioanalytical characterization of NBEs
- Common practices - outside the IP area - on procedures, science, LIMS, validation, quality (GLP),

The EBF regularly meet to discuss on regulatory issues and aspects and present joint opinion s towards regulatory bodies and their peers.

EBF:

http://www.europeanbioanalysisforum.eu

Hot Topics:

- GBC
- EMA Draft Guidance on BMV
- Dried Blood Spots
- Anticoagulant counterions and of choice
- Definition and Quality level
  [Screening ↔ Qualified ↔ Validated Assay]
- Ligand Binding Assays
  [ISR, Parallelism, Curve Fitting]
- Design of Experiments in LBA
- Integrated PK/PD analysis
- Determination of Metabolites (MIST)
- Challenges of acylglucuronides analysis
- Stability in blood

CVG:

Calibration and Validation Group

CVG is a non profit members based scientific organization having the mission To participate with industrial, academic and regulatory bodies to provide education and forums for discussion of calibration and validation practices throughout the nation (Canada).

Objectives:

- To provide a forum to discuss related issues in the art and science of instrument calibration and method validation
- To provide a forum to discuss related issues in the art and science of instrument calibration and method validation
- Recent developments in analytical techniques and instrumentation, stability studies, method development and GMP/GLP issues are also discussed to address the different analytical needs of members

http://www.cvg.ca

GBC:

The intended purpose of the GBC is to use a science-based approach in developing harmonized practices that global health authorities may accept; thus eliminating local requirements that are in conflict and impede getting new drugs to patients.

The group plans to grow in qualified representatives as a consortium having the greatest relevant experience while dropping any industry or regulatory identities. They will form working teams with specific topics with the intent of providing recommendations at a global meeting with the objective to put forth white paper summaries.

Highlights of 4th Regulated Bioanalysis Workshop "Discussing, Reviewing, Sharing Perspectives, Providing Potential Solutions and Agreeing upon a Consistent Approach on the Recent Issues in Regulated Bioanalysis "

[CVG and Canadian LC-MS Group]

A workshop for companies involved in providing bioanalytical data associated with bioavailability, bioequivalence, pharmacokinetic, and comparability studies.

The focus of the meeting in 2010 was Global Harmonization Activities. The session included regulatory updates and global harmonization perspectives from:

- Dr. Brian Booth, US FDA
- Dr. CT Viswanathan, US FDA
- Louise Mawer, U.K. MHRA
- Dr. Jan Welink, EMA representative
- Eric Ormsby, Health Canada
- Arthur Leonardo Lopes de Silva, Brazil ANVISA

These perspectives were also presented from leaders in the industry, and the EBF

Key issues described and consensus obtained in the 2009 meeting and published in the 2010 paper were:

1. Manually integrated chromatograms.

2. Impact of the presence of metabolites on quantitation.

3. Effect of hemolysis.

4. Procedure for investigation.

5. Anticoagulant used in the study – Must be consistent with the validation, otherwise additional testing is required; namely, the anticoagulant must be consistent between the validation and the sample analysis.

6. Blood Stability testing – A Collection process stability experiment that should be performed during method validation to ensure method integrity during sample analysis.

7. Ion Suppression and Matrix effects – Best to correct by using a stable-labeled internal standard, or less ideally, by reducing the flow rates and/or use of smaller ID HLPC columns (such as 1mm).

8. Assessing Contamination – The consensus was to maintain the 20% LLOQ criteria, but there was no consensus on how to determine the impact of carryover. The later will be assessed during the 2010 meeting.

9. Non-linear calibration models – Meeting consensus was to use a quadratic fit for a large dynamic range and potential linearity problems should never be masked. It was conveyed that no 483s have been reported for using a quadratic fitting model throughout an entire study.

10. The 2009 ASMS Regulated Bioanalysis Interest Group Workshop (RBIG) is posted on the ASMA Regulated Bioanalysis Forum at www.asms.org

11. The 2009 APA Conference report is available at: Ackerman and Bradley Applied Pharmaceutical Analysis 2009 Conference, *Bioanalysis (2010) 2(2), 185-188.*

Significant Discussions Elevated during the Meeting

In as much as the globalization of bioanalysis has been driven by the scientific community, it was conveyed that globally harmonized instructions should be of equal interest to both the regulators and practitioners of bioanalysis.

Dr. Bansal raised some big questions that require consideration; namely:

What would be the global regulatory guidance?

Publication type (OECD or ICH)?

21 CFR 320.29 [Bioavailability and Bioequivalence Requirements] are currently under revision as announced by Dr. Viswanathan during the morning session of April 22.

FDA: Electronic data capture *[The FDA is now looking for pilot data during audits and will be keying into Part 11]*

Brussels Meeting, 2009 – Plea for a world-wide globalization of BMV guidance document.

Upcoming Meetings on Regulatory Findings, Method Development Challenges, and Innovations in Bioanalysis

The 1st Conference in Asia Pacific
on Recent Issues in GLP Regulated Bioanalysis
"Bringing together scientists from across Asia Pacific and the rest of the world to discuss, review, share perspectives, provide potential solutions and agree upon consistent approaches on the recent issues in GLP regulated bioanalysis"

January 12-13, 2011, Shanghai, China
Pre-Conference Short Course: January 11, 2011
Post-Conference Site Visits and Tour: January 14, 2011

The 5th Workshop on Recent Issues in Regulated Bioanalysis
"Discussing, Reviewing, Sharing Perspectives, Providing Potential Solutions and Agreeing upon a Consistent Approach on the Recent Issues in Regulated Bioanalysis "

April 13-14, 2011, Montreal, Canada
Short Courses: April 11-12, 2011
Hotel Marriott Chateau Champlain

Current Regulatory Positions on Harmonization - AAPS Nov 2010

FDA: **Dr. Viswanathan:**

Harmonization is “Common Sense”

First harmonize the existing documents, then globalize

The FDA does not want to be too prescriptive in the guidance content

There must be flexibility in the Guidance

Regulators will drive the harmonization time lines, not consortiums. But the CVG can help this process:

- Useful input
- Help bridge Science / Policy
- Representative and inclusive representation
- Ability to unify based on science and practicality
- Help in understanding industry practices

Current Regulatory Positions on Harmonization - AAPS Nov 2010

FDA: **Dr. Viswanathan:**

Tone: Moderate and Progressive

Timeline: Current administrative hold-ups.

The important question is how the guidance will address new technologies and policies over time

Beyond Harmonization:

- Unified single global guidance
- Adopting harmonized documents by various regulatory authorities
- If a country does not adopt, it will fall behind…It's that simple

Current Regulatory Positions on Harmonization - AAPS Nov 2010

EMA: **Dr. Michael Berntgen**

Currently reviewing > 50 sources of comment regarding the Draft BMV Guidance

Forwarded the Draft BMV Guidance to FDA for Review
Summary of overview of the comments to be published on EMA web site

EMA committed to international collaboration including interactions with regulators and ICH and associated activities

Committed to work with FDA to harmonize the BMV guidance

Current Regulatory Positions on Harmonization - AAPS Nov 2010

EMA / FDA Approach to Eventual Globalization of BMV Guidances

EMA / FDA Confidentiality Agreement in Place ✓

EMA / FDA interaction ✓

EMA request for FDA to provide feedback on draft guidance ✓

EMA / FDA to harmonize guidances [near future]

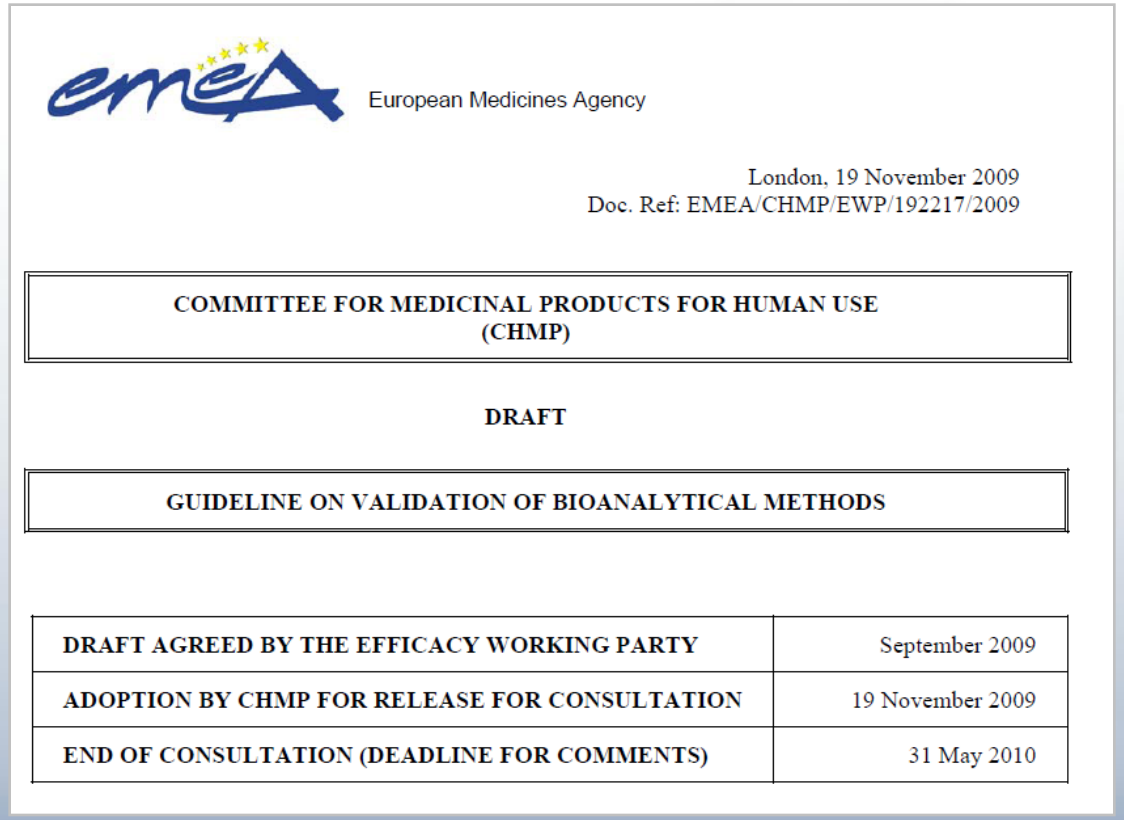
FDA to provide EMA with draft revised guidance [second phase *Vish*]

Beyond → Globalization towards a single global guidance document

Bioanalytical Method Validation (BMV) Guidance Revisions

EMA – 2009, Comments review 2010

FDA – Revision ongoing, target late 2011



European Medicines Agency

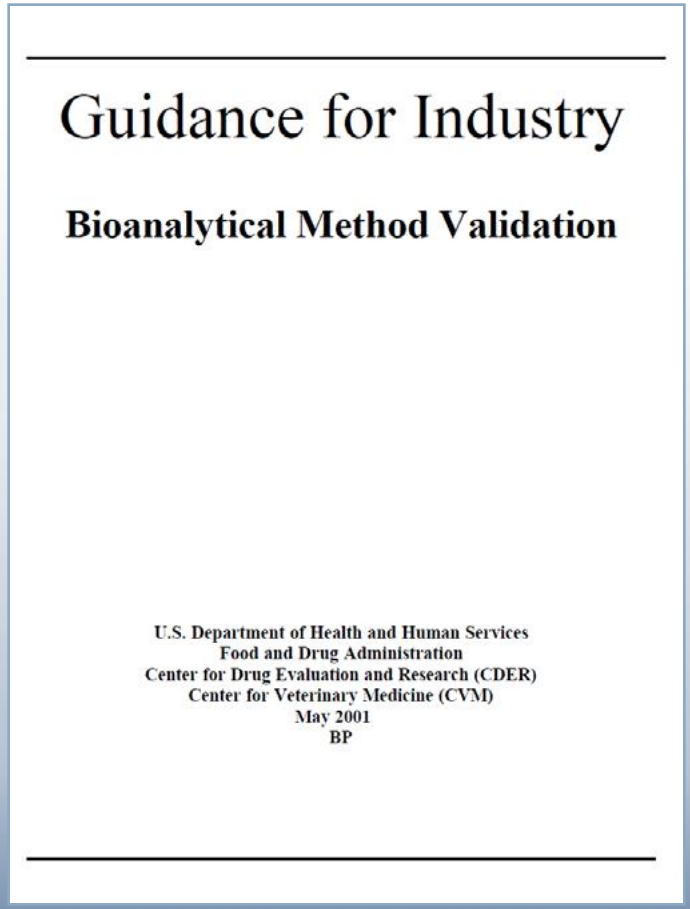
London, 19 November 2009
Doc. Ref: EMEA/CHMP/EWP/192217/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON VALIDATION OF BIOANALYTICAL METHODS

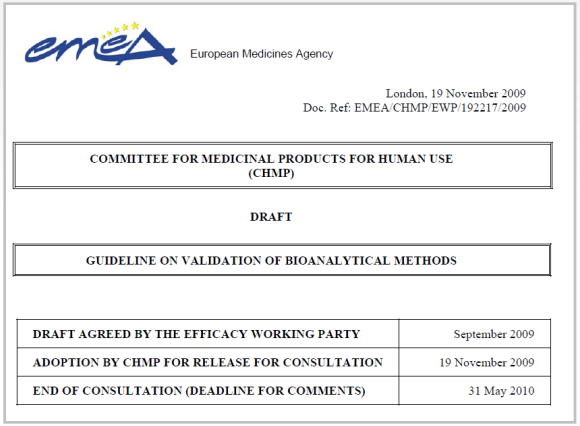
DRAFT AGREED BY THE EFFICACY WORKING PARTY	September 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 November 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2010



Guidance for Industry

Bioanalytical Method Validation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
May 2001
BP



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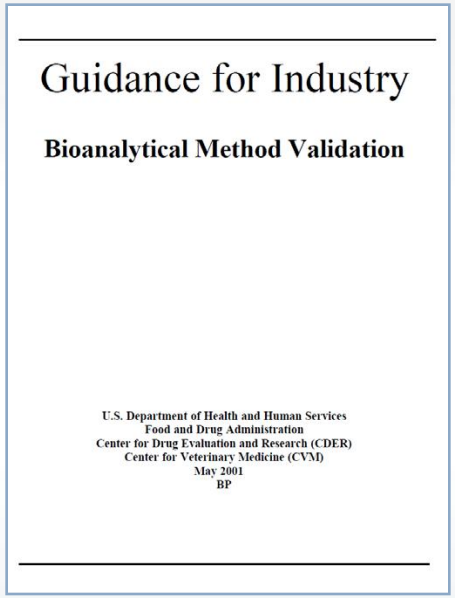


Guidance for Industry

Bioanalytical Method Validation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
May 2001
BP

There are differences between the Guidances, and there is a similar Indifference

FDA Guideline (2001) Focused on GC, Mass Spec, LC and respective tandem Methods. There was minimal guidance pertaining to LBA and molecular biological methods, except:

> "This guidance also applies to other bioanalytical methods, such as immunological [LBA] and microbiological procedures, and to other biological matrices…"

EMA Draft Guidance contained only a minimal sketch of guidance pertaining to LBA. Inference of yet to be determined two separate or a general fit's all guideline.

Some Current Differences Between EMA / FDA BMV Guidances

Impetus for Harmonization of Guidances

Subject	EMA	FDA
Reference Standards	Discusses isotopic expectations of labeled reference standards	No reference to isotopically labeled reference standards
Selectivity	Response of interference peaks < 20% of LLOQ	No Specific criteria
Selectivity	Includes tests for possible metabolic back-conversion	No specific tests recommended
Recovery	Not discussed	Required
ISR	Required; criteria provided	Not formally discussed in guidance, but enforced by FDA and described in Crystal City III conference paper
Carryover	Required	No discussed
Matrix Effect	Discussed specifics of evaluation and criteria	General statement that it should be investigated
Stability	Provides criteria of 15% from nomi nal concentration	No specific criteria provided
PK Outliers	Not recommended	Allowed

Other Current FDA – EMA Guidance Comparisons

ISR – Some additional points, and clinical samples:

EMA – "If PK parameters represent the end-points of a study, ISR is Recommended."

- In TK studies it is sufficient to address ISR once per species.
- For Human study samples the ISR should be carried out for "every subject or patient population," unless otherwise justified.
- ISR on BE studies should always be carried out.

FDA – ISR needs to be conducted on each "each species used for GLP Toxicology experiments" and using samples from a single study would be sufficient for all other studies of the same species.

Incurred sample variability is generally accepted as being greater in humans Than animals. Content regarding human samples is stated as (CC III WS): "The final decision as to the extent and nature of the incurred sample testing Is left to the analytical investigator, and should be based on in-depth under-Standing of the method, the behavior of the drug, metabolites, and any Concomitant medications in the matrices of interest."

Other Current FDA – EMA Guidance Comparisons:

GLP Studies and Human Samples:

FDA: Bioanalytical Methods for BA, BE, PK and DDI studies must meet Criteria in 21 CFR 320.29

> *The analytical laboratory conducting pharmacology/toxicology and other preclinical studies for regulatory submissions should adhere to FDA's GLPs (21 CFR Part 58) and to sound of quality assurance throughout the testing process*

EMA: Directive 2004/10/EC indicates that human bioanalytical Studies fall outside of the scope of GLPs

> *The validation of bioanalytical methods and the analysis of study samples should be preformed in accordance with the principles of GLP*

EBF Recommendations (Which Sample?):

- Method Validation;
- Upon any major method change (as per SOP);
- First time in new matrix (animal or human);
- First time in a new target population: first patient study;
- Disease state change in patient population;
- First time use of an existing method in a new laboratory;
- Whenever scientific reasons require retesting of ISR (i.e. special population);
- Process check;
- All BE studies;
- Incidental check in any other studies (human PK or DDI).

From Bioanalysis (2009) 1(6), 1049-1056

Reanalysis of Study Samples for PK Reasons

EMA: Not accepted

Normally reanalysis of study samples because of a pharmacokinetic reason is not acceptable. This is especially important for bioequivalence studies, as this may affect and bias the outcome of such a study.

However reanalysis might be considered as part of laboratory investigations, to identify possible reasons for results considered as abnormal and to prevent the recurrence of similar problems in the future. only exception: identification of sample analyte in pre-dose samples or placebo samples

Reanalysis of Study Samples for PK Reasons

FDA: Accepted

It is important to establish an SOP or guideline for repeat analysis and acceptance criteria. This SOP should explain the reasons for repeat analysis, which could include repeating analysis of clinical samples for regulatory purposes, inconsistent replicate analysis, sample(s) outside of the range, sample processing errors, equipment failure, poor chromatography, and inconsistent pharmacokinetic data.

Reassays should be done in triplicate if there is sufficient sample volume. The rationale for the repeat analysis should be clearly documented.

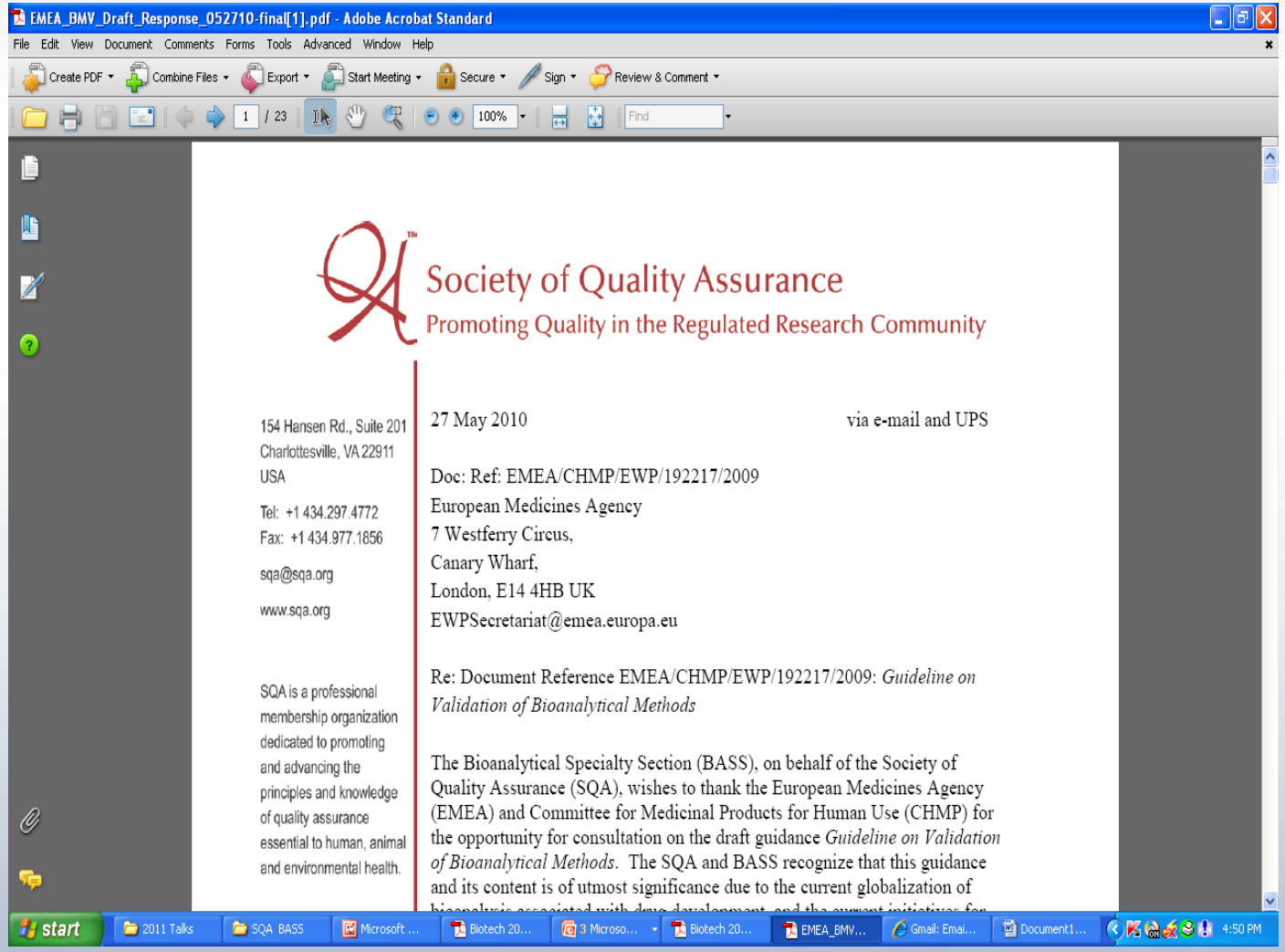
Other Current FDA – EMA Guidance Comparisons:

Specificity:

EMA:
Validated by using at least 10 sources of sample matrix, spiked at or near the LLOQ. Presence of endogenous antibodies to analyte may cause interference, and this and endogenous compounds must be considered and must no affect accuracy

FDA:
No recommendation

BASS Activities in BMV Harmonization Initiative:



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SQA is a professional membership organization dedicated to promoting and advancing the principles and knowledge of quality assurance essential to human, animal and environmental health.

27 May 2010 via e-mail and UPS

Doc: Ref: EMEA/CHMP/EWP/192217/2009
European Medicines Agency
7 Westferry Circus,
Canary Wharf,
London, E14 4HB UK
EWPSecretariat@emea.europa.eu

Re: Document Reference EMEA/CHMP/EWP/192217/2009: *Guideline on Validation of Bioanalytical Methods*

The Bioanalytical Specialty Section (BASS), on behalf of the Society of Quality Assurance (SQA), wishes to thank the European Medicines Agency (EMEA) and Committee for Medicinal Products for Human Use (CHMP) for the opportunity for consultation on the draft guidance *Guideline on Validation of Bioanalytical Methods*. The SQA and BASS recognize that this guidance and its content is of utmost significance due to the current globalization of

(1) Reply to EMA Draft Guidance (2) Opinion Paper

Line(s) No.	Comment and Rationale	Recommended Change
366-367	Regarding commercial kits. If a commercial kit is not initially validated by the vendor, it cannot be re-validated, as the wording suggests. Additionally, a kit is used for its materials/reagents during a method validation, and this should be clarified.	Recommend clarifying that all of the principles for a method validation apply when using a kit for reagents. Note that many kits do not contain matrix QC samples, but do contain controls. Matrix QC samples therefore need to be prepared, qualified, and validated, as with any method validation. Recommend that this be clarified in the guidance. Commercial kits usually come with expiration dates for its reagents. The earliest expiration date of a kit's reagents should not apply to all reagents, especially reagents that impact a method, and would require a partial validation or at least a qualification of the reagent before continued use of the method, such as an antibody, conjugated materials, blocking buffers, and coated plates. This should also apply to changes in lot numbers. Recommend that this be clarified in the guidance.
388, 398, 491	Regarding the reference to a "study plan" and/or "protocol."	Recommend consistent use of terminology within the guidance, particularly in light of definitions specific to FDA GLP regulations vs. OECD GLP principles.
Section 5.2	Regarding acceptance criteria of an analytical run. Immunoassays and/or ligand-binding assays (LBAs) acceptance criteria are not described here. Furthermore, there are additional LBA experiments that need to be defined and included for LBA.	Recommend that LBA acceptance criteria for applicable experiments need to be defined. The use of, and treatment therefore, should be similar to that of LC/MS assays, which is why LBA methodology is part of this draft guidance (as it should be). Refer to the rationale and recommendations described for other previous comments

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SQA Opinion Paper on global harmonization of the bioanalytical method validation guidances

"The current bioanalytical landscape is ripe for the global harmonization of a bioanalytical guidance document."

Keywords: bioanalytical method validation ■ FDA/EMA regulations ■ method validation guidelines ■ global harmonization ■ Society of Quality Assurance (SQA)

This opinion paper states The Society of Quality Assurance's (SQA) recommendations for the global harmonization of bioanalytical practices and provides some detailed areas for consideration in this exercise.

Background

The US FDA's 2001 Bioanalytical Method Validation (BMV) Guidance [101] and the subsequent 'Crystal City' workshop consensus white papers [1–6] have formed the basis for establishing

and published in an editorial the same year [7]. Platforms for discussions via meetings and workshops have since been established to drive this paradigm [8–10].

Current situation

The current bioanalytical landscape is ripe for the global harmonization of a bioanalytical guidance document. Key aspects of this landscape include:

- Pharmaceutical companies and CROs are conducting regulatory bioanalysis internationally.

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Stephen Rogenthien

GLP Operations, Ricerca Biosciences, LLC

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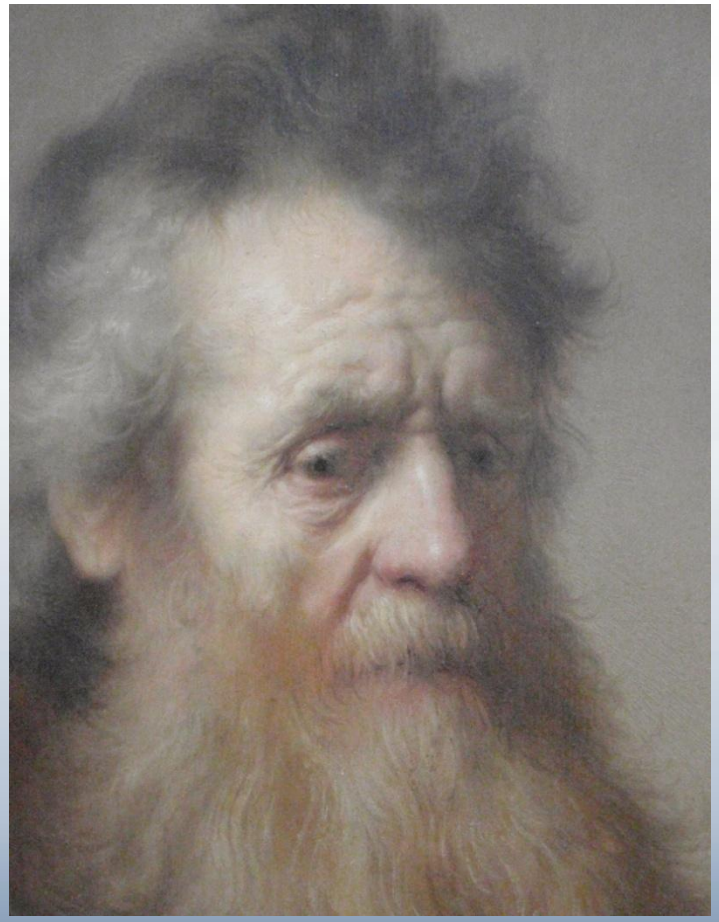
Published in Bioanalysis, December 2010

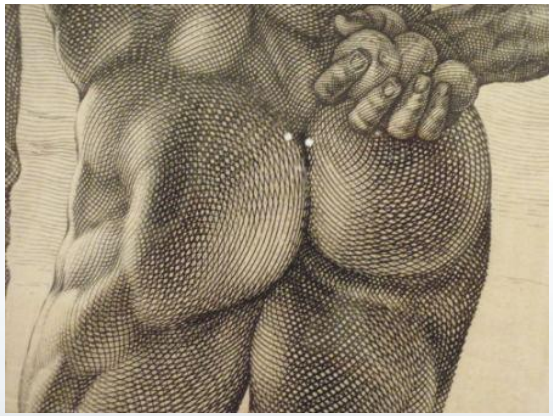
*"**Balance must be achieved between** scientific and regulatory concerns; between current and future bioanalytical technologies; between detailed prescription and flexibility; between absolute rigor and pragmatism. The SQA can play an important role in attaining such a balance..."*

***"...the Society of Quality Assurance wishes** to provide its perspectives and support towards a common understanding of the best approach to bioanalytical method validation and sample analysis."*

The Author's First Choices for the Photos in the Opinion Paper:

…….Declined by Journal





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EDITORIAL

SQA opinion paper on global harmonization of the bioanalytical method validation guidances

"The current bioanalytical landscape is ripe for the global harmonization of a bioanalytical guidance document."

Keywords: bioanalytical method validation ▪ FDA/EMA regulations ▪ method validation guidelines ▪ global harmonization ▪ Society of Quality Assurance (SQA)

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This opinion paper states The Society of Quality Assurance's (SQA) recommendations for the global harmonization of bioanalytical practices and provides some detailed areas for consideration in this exercise.

Background

The US FDA's 2001 Bioanalytical Method Validation (BMV) Guidance [101] and the subsequent 'Crystal City' workshop consensus white papers [1–6] have formed the basis for establishing best practices in bioanalysis. Pharmaceutical companies and contract research organizations have followed the recommendations in these documents as there were no other standards readily applicable to bioanalysis. For example, the International Conference on Harmonisation (ICH) Q2(R1) [102] standard was written for

Platforms for discussions via meetings and workshops have since been established to drive this paradigm [8–10].

Current situation

The current bioanalytical landscape is ripe for the global harmonization of a bioanalytical guidance document. Key aspects of this landscape include:

- Pharmaceutical companies and CROs are conducting regulatory bioanalysis internationally.
- Analysis performed in one country is usually part of submissions to others, since new drug applications and abbreviated new drug applications are no longer targeting local markets and patients, but international markets and global illnesses.

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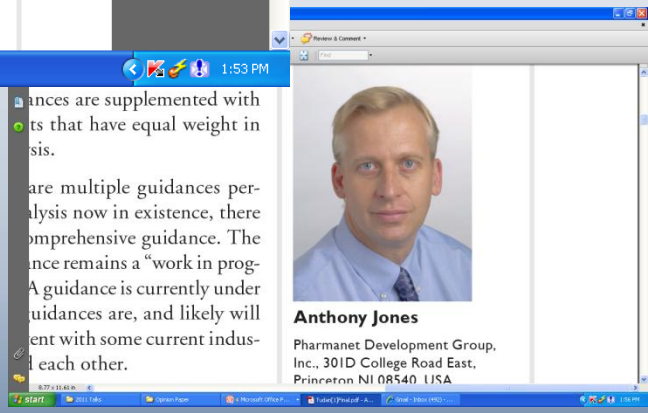
Pictures speak 1000 words, and so do committed SQA/BASS members…

The author's pics were mandatory



SQA Opinion Paper – Harmonized BMV Guidance Hot Topics

1. Human clinical samples
2. Incurred sample reanalysis (ISR)
3. Manually integrated chromatograms
4. Biomarkers
5. Metabolites
6. Stability
7. Immunoassays
8. Distinction between method validation and qualification

SQA Opinion Paper – Harmonized BMV Guidance Hot Topics

9. Outliers
10. Reanalysis [Including PK repeats]
11. Surrogate matrices
12. Dried blood spot analysis
13. Reporting of results
14. Matrix Effects
15. Solid tissues
16. Urine

1. Human clinical samples:

There is already some framework for clarification regarding guidance for the bioanalysis of human clinical samples, and it is the hope of the SQA/BASS that a globalized BMV guidance would provide a consistent, unified approach

BARQA - Good Clinical Laboratory Practice: A Quality System for Laboratories That Undertake the Analyses of Samples from Clinical Trials, 2003

MHRA – Good Clinical Practices: Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples, July 2009

DAIDS Guidelines for Good Clinical Laboratory Practice Standards, 2009* www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/GCLP.pdf

Ezelle *et al*. (2008) Guidelines on Good Clinical Laboratory Practice: Bridging Operations between research and clinical laboratories, J. Pharm and Biomed. Anal. 46:18-29

2. ***Incurred sample reanalysis* (ISR)**
3. ***Manually integrated chromatograms***
4. ***Biomarkers***
5. ***Stability***
   - Ensuring that stability assessments mimic actual sample processing steps and are not merely “checkbox” assessments against arbitrary times, conditions, etc.
   - Establishing a position on -70ºC, -20ºC, or both
   - Establishing whether stability must be conducted in the presence of other drugs when the administered drug is a combination product
   - Defining appropriate blood, urine, and solid tissue stability testing to ensure method integrity during sample analysis.
   - Identifying potential stability issues and their resolution prior to method validation and establish a position on how study results should be reported when stability is in progress

6. **Metabolites:**
- Clarification on acceptable practices associated with the effect of metabolites on quantitation

7. **Immunoassays**

8. **Distinction between method validation and qualification**
- Specifically, consensus should be obtained on whether a method should be validated or qualified, and if a method can be qualified, to what degree.
- Furthermore, consensus should be obtained on commercial kits that come ‘qualified’ for an intended use, but nonetheless are used as a ‘validated’ method. In these cases, the validation of a kit needs to be defined if it is expected to be distinguished from a qualified method.

9. **Outliers**

10. **Reanalysis [Including PK repeats]**

11. **Surrogate matrices**

12. Dried blood spot analysis

13. Reporting of results

14. Matrix Effects

- Including binding assays and methodologies to address them.
- The impact of hemolysis and lipemic effects on matrix effects should be considered and documented, if identified.

15. Solid tissues

- Clarification to the extent that the validation of a method that is used for the analysis of an analyte(s) within a solid matrix is feasible only if the matrix being analyzed is a homogenate of the solid tissue, or if the collection of the tissue is controlled and validated.
- Otherwise, methods used for solid tissue analysis should be qualified rather than validated.

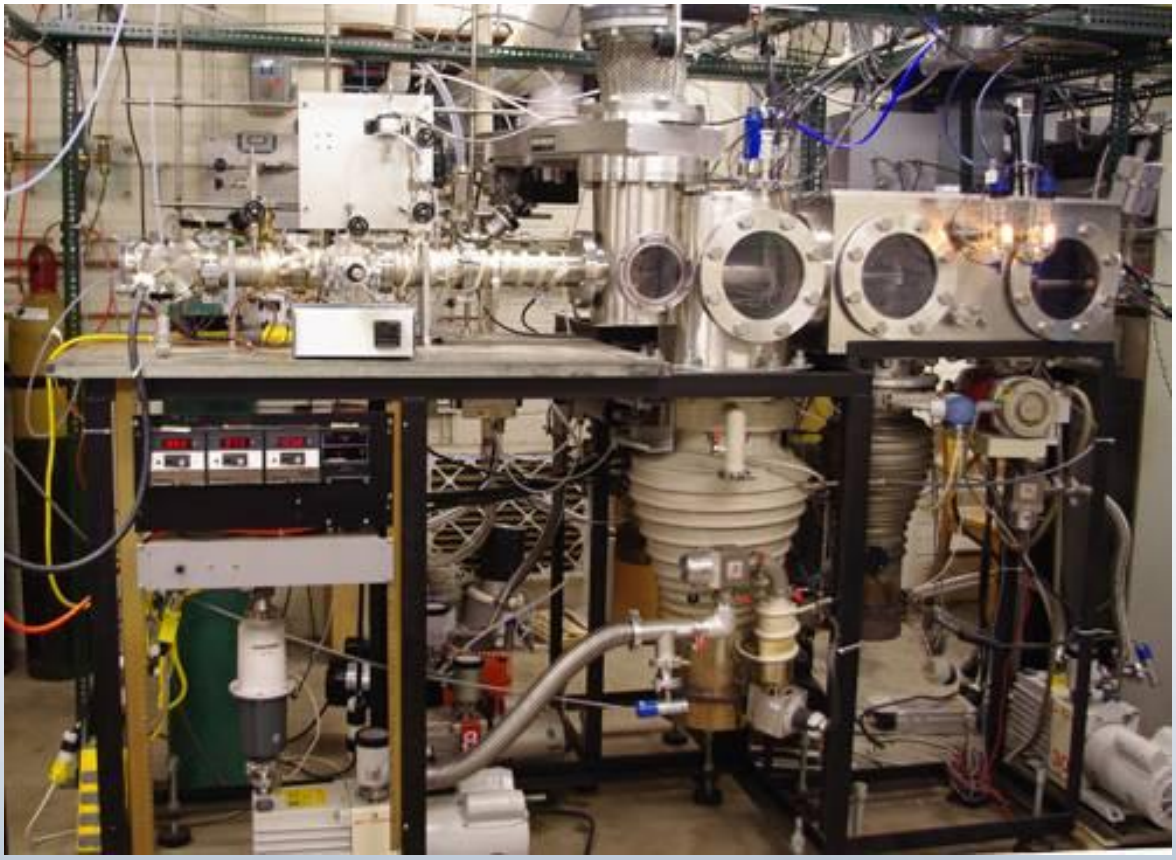
16. Urine

*"**Balance must be achieved between** scientific and regulatory concerns; between current and future bioanalytical technologies; between detailed prescription and flexibility; between absolute rigor and pragmatism. The SQA can play an important role in attaining such a balance..."*

QA Associations Around the World Share the Same Objectives:

- Safety
- Data Integrity
- Quality
- Global Health and Medicines

Does it feel and sound like this ?



Doesn't need to - Besides, remember 21 CFR Part 11? It's about the Data

LC-MS/MS Method and Validation Report Parameters

Cannot change (Part. Val.)

Non-tunable parameters

Mass Spectrometer (MS):	Sciex API 3000
Ionization:	TurboIonSpray
Ionization mode:	Negative
MS acquisition time:	3.5 min
Total cycle time:	3.5 min

Acceptable range defined within SOP and/or Protocol

Analyte	SRM Transition Monitored (0.2)	Dwell Time
Drug	m/z 272.1 → m/z 226.1	100 ms
D3-Drug (IS)	m/z 275.1 → m/z 226.1	100 ms

Stable-labeled IS m/z
= Drug + Isotopic mass (ie. 3 mu)

Check against method and chromatograms

Can change. Mass spec-Dependent.

Typical tunable parameters

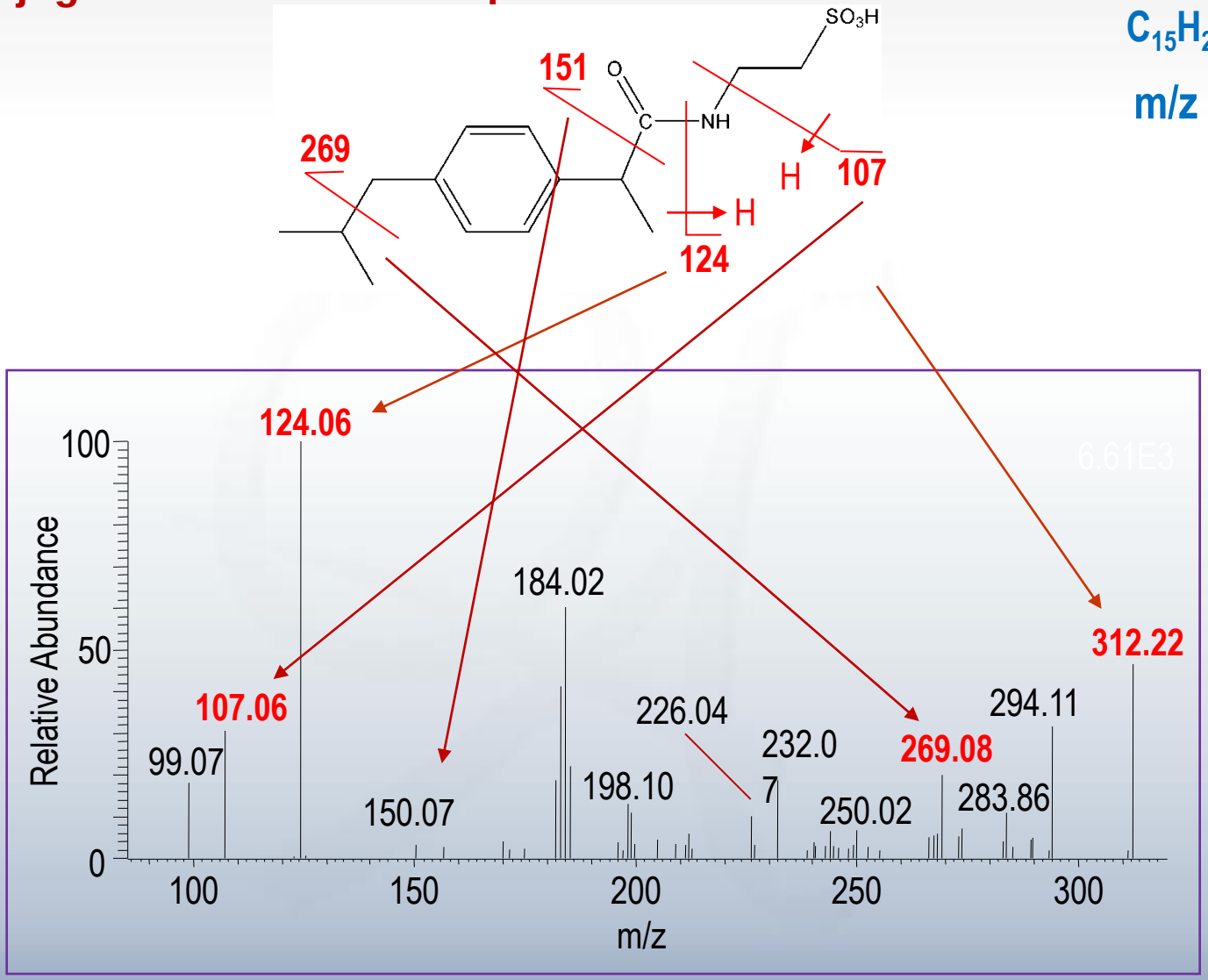
TurboIonSpray Temperature:	350 °C
IonSpray Voltage:	-3000 V
Declustering Potential:	-26 V
Collision Energy:	-39 eV

45

Taurine-Conjugate Metabolite of Ibuprofen

$C_{15}H_{23}O_4NS$

m/z = 312



Ion fragments = m/z = **107**, **124**, 232, **269,** 294 mu

Proposal:

Global Bioanalytical Quality Assurance Alliance

A call for an alliance of the global Quality Assurance professionals for a unified quality assurance influence on the global harmonization of bioanalytical regulations and applications to human clinical samples, and the development of a global forum for educating QA professionals on the regulatory and technical aspects of regulatory bioanalysis

Through cooperation between the QA Associations around the world

Proposal:
Global Bioanalytical Quality Assurance Alliance

Proposed Objectives

Build a global QA professional alliance and Council

To provide a Unified Quality influence on the Global Harmonization of the BMV Guidances and Bioanalytical Regulations

To help demonstrate the Global Initiative

To Educate

To Communicate with Regulatory Agencies:

- **Feedback topics subsequent to Inspections**
- **Discussions and Clarifications**
- **Organization of QA meetings to include Agencies (FDA, MRHA, EMA..)**

Proposal:

Global Bioanalytical Quality Assurance Alliance

Proposed Objectives

Generating peer reviewed publications/documents to provide

- **Inputs from the Quality perspective to regulated bioanalysis**
- **Feedback on recent concerns/perspectives on current or upcoming developments in regulated bioanalysis**

To have QA assurance professionals from all Pharmaceutical Companies, CROs, Institutions, Universities equally represented in the education of and participation in the harmonization process

To best facilitate whether we are all aligned on the presentation/interpretation of the regulatory language

To provide leadership in devising adequate regulatory language

Network with Industry leaders, both scientific, quality and regulatory

Proposal:

Global Bioanalytical Quality Assurance Alliance

Getting Started, Initiating Dialogue and Alliance and Uniformity:

1. Letter to the Global QA Associations
2. Develop Consensus
3. Develop Action Plans and Hot topics list

   [New guidances, Bioanalytical regulatory and scientific hot topics, clinical samples, findings/interpretations, forums…]
4. Form an Alliance with two members from each association
5. Start meetings/sessions/forum
6. Letters to GBC, Agencies and Publications

Lessons from Recent 483's and Warming Letter

Final reports should be written from signed contributor reports – not draft.

Draft reports should not be sent to Sponsors for comment until all contributor reports are signed.

When draft reports are sent to Sponsors for comment, FDA expects the draft report and all correspondence from the Sponsor to be archived

[EPA has always required this under section 160.90: *"Correspondence and other documents relating to interpretation and evaluation of data, other than those documents contained in the final report, shall also be retained"]*

Reports must be written for all studies – even those terminated or if a compound is discontinued. The concern is that many of these compounds resurface at a later date.

Lessons from Recent 483's and Warming Letter

As per the pathologist exemption, only the slides and signed final report constitute the raw data. Therefore, without a signed report, there is no raw data or report.

Pathology Peer review should be done from only a signed pathology report.

If there is disagreement between the pathologists, the SD should reconcile the discrepancy in their final report.

FDA will continue to issue 483's for writing draft final reports based on unsigned draft contributor reports or peer reviewing pathology reports.

→Upon re-inspection, if the practice is still occurring, warning letters will be issued.

Lessons from Recent 483's and Warming Letter

Source reports should be archived upon completion.

→ Companies should not wait to archive source reports with the final report.

If a test site or testing facility sends data off-site:

- EPA and FDA expect the facility to maintain a copy.
- While this has always been the case in EPA, a current 483 was recently issued to a test site for not keeping a copy of the data.

FDA investigators are undergoing training on auditing electronic data.

FDA field staff has been trained on software validation and 21 CFR Part 11 inspection and enforcement.

Lessons from Recent 483's and Warming Letter

The FDA announced July 8 that it will "soon" begin conducting a series of "focused" inspections to evaluate industry compliance with and understanding of 21 C.F.R. Part 11

According to the announcement, the inspections will focus on Part 11 requirements relating to human drugs.

The FDA said it will conduct the inspections as per the enforcement discretion described the 2003 Guidance: "Part 11, Electronic Records; Electronic Signatures — Scope and Application."

In the announcement, the FDA said it:

> *"intends to take appropriate action to enforce Part 11 requirements for issues raised during the inspections that do not fall under the enforcement discretion discussed in the guidance."*

21 CFR Part 11

Part 11 Compliance Addresses:

- Where ?
- Who ?
- Security/Access
- Backup
- Archive
- SOPs
- Training
- Oversight
- Tested
- Ready Retrieval

Relevant Raw Data Must be:

- Accurate
- Complete
- Preserves Content, and
- Meaning

Audit Trail Must Record:

- Creation
- Modification
- Deletion

(Och) Ett Gott Nytt År

Kala Christouyenna!

Vrolijk Kerstfeest en een Gelukkig Nieuwjaar!

Nollaig Shona Dhuit

Buone Feste Natalizie

Est Joyeux Noel

Kellemes Karacsonyi unnepeket

Kung His Hsin Nien bing Chu Shen Tan

Fröhliche Weihnachten

Pozdrevlyayu s prazdnikom Rozhdestva is Novim Godom

Glædelig Jul

Feliz Navidad

Boze Narodzenie

Gledileg Jol

Hyvaa joulua

Feliz Natal