The Finalized BMV Guidance: What's New For NDAs and BLAs

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At Long Last….

The final BMV guidance published 5/2018

BMV Guidance 2013, BMV Guidance 2001

Crystal City 5 Conference 2013 (Baltimore, Md)

Crystal City 1-4 (Crystal City Va)

Federal Register Feedback 2014

More than 5000 comments received

Remember---FDA is using BMV 2018

Not BMV 2001, 2013 or ICH M10!

What is Validation About?…..

We are trying to Answer These Questions

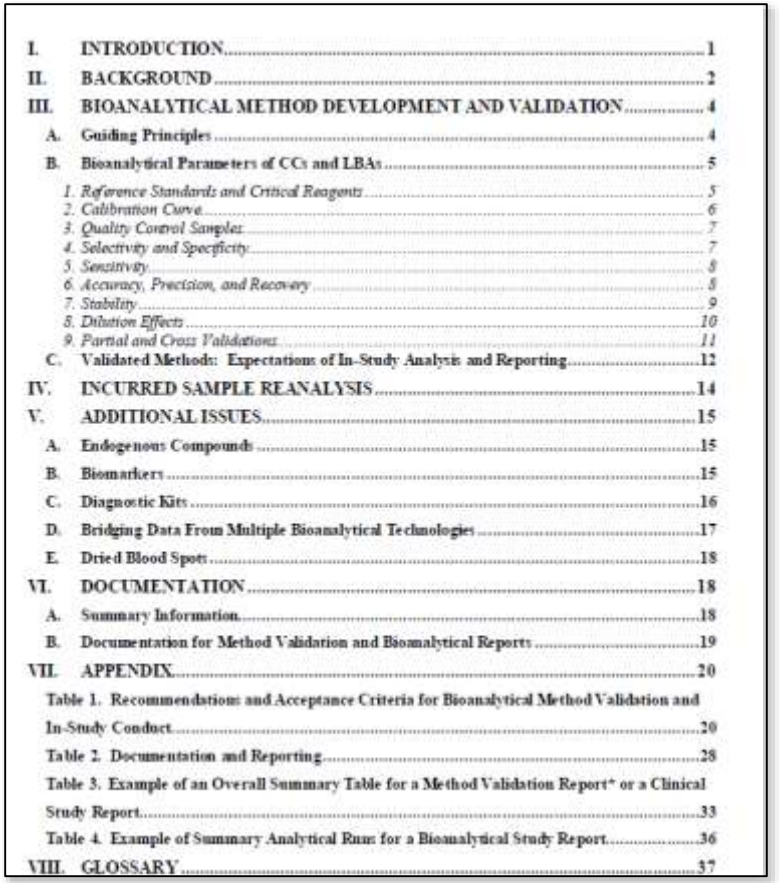
Does the method measure the intended analyte(s)?

What is the range of measurements that provide reliable data?

What is the variability in these measurements?

How does sample collection, handling and storage affect the reliability of the data?

Some Old, Some New



Organization….

1. Text

Prose about familiar BMV issues

- Reference standards/critical reagents, Calibration curve, QCs, Selectivity and Specificity, Sensitivity, Accuracy, Precision Recovery, Stability, Dilution Effects, Partial/Cross validations, ISR
- General principles

Organization….

2. Tabular presentation

- Specific presentation of validation/study specifics
  - Validation parameters, in-study expectations
  - Quick & Easy (?)
- Documentation-what should be where
- Sample Tables around organization of data

Validation and Study Elements

Table 1. Recommendations and Acceptance Criteria for Bioanalytical Method Validation and In-Study Conduct (refer to sections III.A and III.B for additional information).

Parameters	Validation Recommendations		In-Study Analysis Recommendations
	Chromatographic Assays (CCs)	Ligand Binding Assays (LBAs)	
Calibration Curve	Elements: • A blank (no analyte, no IS), a zero calibrator (blank plus IS), and at least six non-zero calibrator levels covering the quantitation range, including LLOQ in every run. • All blanks and calibrators should be in the same matrix as the study samples. • The concentration-response relationship should be fit with the simplest regression model. Acceptance Criteria: • Non-zero calibrators should be ± 15% of nominal (theoretical) concentrations, except at LLOQ where the calibrator should be ± 20% of the nominal concentrations in each validation run. • 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each validation run.	Elements: • A blank and at least six non-zero calibrator levels covering the quantitation range, including LLOQ per validation run. • Calibration curves are usually run in duplicate. • Additional calibrators may be used as anchor points. • All blanks and calibrators should be in the same matrix as the study samples. • The concentration-response relationship is usually fit with a four- or five-parameter logistic model. Other models may be acceptable with justification. Acceptance Criteria: • Non-zero calibrators should be ± 20% of nominal (theoretical) concentrations, except at LLOQ and ULOQ where the calibrator should be ± 25% of the nominal concentrations in each validation run. • 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each validation run. • Anchor points should not be included in the curve fit.	Elements: • A blank, a zero, and at least six (in duplicate for LBAs) non-zero calibrator levels covering the expected range, including LLOQ per analytical run. • All blanks and calibrators should be in the same matrix as the study samples. • The in-study analysis should use the same regression model as used in validation. Acceptance Criteria: • CC: Non-zero calibrators should be ± 15%, except at LLOQ where the calibrator should be ± 20% of nominal concentrations in each run. • LBA: Non-zero calibrators should be ± 20%, except at LLOQ and ULOQ where the calibrator should be ± 25% of nominal concentrations in each run. • CC and LBA: 75% and a minimum of six non-zero calibrator levels should meet the above criteria in each run.
	Only data points that fail to meet acceptance criteria may be excluded. Exclusion should not change the model used.		

Continued

Documentation

Table 2. Documentation and Reporting (refer to sections III.B and VI for additional information)

Items	Documentation at the Analytical Site	Validation Report*	Analytical Study Report*
System Suitability	• Dates, times, QCs or samples used for suitability testing	• Not applicable	• Not applicable
Synopsis	• Not applicable	• Synopsis of method development (e.g., evolution of methods with multiple revisions, unique aspects) • Overall summary information	• Not applicable
Reference Standards and Critical Reagents	• Certificate of analysis (CoA) or purity, stability/expiration data, batch number, and manufacturer • Log records of receipt, use, and storage. • If expired, recertified CoA, or retest of purity & identity with retest dates • Internal standard CoA, purity or demonstration of suitability	• Batch/lot number, purity, and expiration (see appendix VII, Table 4) • If expired, purity and stability at the time of use and retest dates	• Batch/Lot number, purity, and expiration (see appendix VII, Table 4) • If expired, purity and stability at the time of use and retest dates
Stock Solutions	• Log records of preparation, and use • Storage location and condition	• Brief description of preparation • Preparation dates • Stock solution stability • Storage conditions	• Brief description of preparation • Preparation dates • Stock solution stability • Storage conditions
Blank Matrix	• Records of matrix descriptions, receipt dates, and storage • Records of interference checks • Matrix effect results	• Description, lot number, receipt dates • Description of interference check • Matrix effect results	• Description, lot number, receipt dates • Description of interference check

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Validation/Study Reports

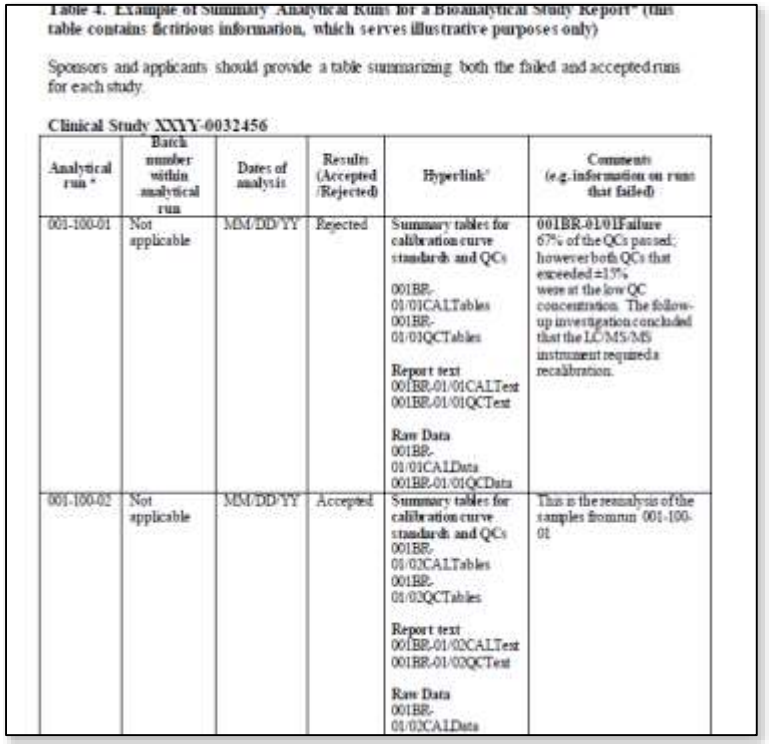


Table 4. Example of Summary Analytical Runs for a Bioanalytical Study Report* (this table contains fictitious information, which serves illustrative purposes only)

Sponsors and applicants should provide a table summarizing both the failed and accepted runs for each study.

Clinical Study XXYY-0032456

Analytical run *	Batch number within analytical run	Dates of analysis	Results (Accepted /Rejected)	Hyperlink*	Comments (e.g. information on runs that failed)
001-100-01	Not applicable	MM/DD/YY	Rejected	Summary tables for calibration curve standards and QCs 001BR-01/01CALTables 001BR-01/01QCTables Report text 001BR-01/01CALText 001BR-01/01QCText Raw Data 001BR-01/01CALData 001BR-01/01QCData	001BR-0101Failure 67% of the QCs passed; however both QCs that exceeded ±15% were at the low QC concentration. The follow-up investigation concluded that the LC/MS/MS instrument required a recalibration.
001-100-02	Not applicable	MM/DD/YY	Accepted	Summary tables for calibration curve standards and QCs 001BR-01/02CALTables 001BR-01/02QCTables Report text 001BR-01/02CALText 001BR-01/02QCText Raw Data 001BR-01/02CALData	This is the reanalysis of the samples from run 001-100-01

These are examples

You may see other examples

Using this table is not mandatory

Validation/Study Reports

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 x to y% x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 ≤ x% ≤ x%	
QCs performance during accuracy & precision	**Cummulative accuracy (%bias) in 5 QCs** QCs: Product A Product B/C	 x to y% x to y%	
	Inter-batch %CV QCs: Product A Product B/C	 ≤ x% ≤ x%	
	Total error QCs: Product A Product B/C	 ≤ x% ≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		

You will probably see Requests for something more like this…..

This greatly aids in review
--saves time

What's Covered--*Scope*

INDs, NDAs, BLAs, ANDAs and veterinary applications

- Parent/analytes
- Matrix: plasma, serum, urine, CSF etc.
  - Artificial/surrogate matrix?
- Nonclinical and clinical
  - PK, TK, pharmacology, PD, biomarkers
- Support Approval, Safety, Efficacy, Labelling

If not for one of these purposes---*you can do whatever you want-FFP*

What' s Changed

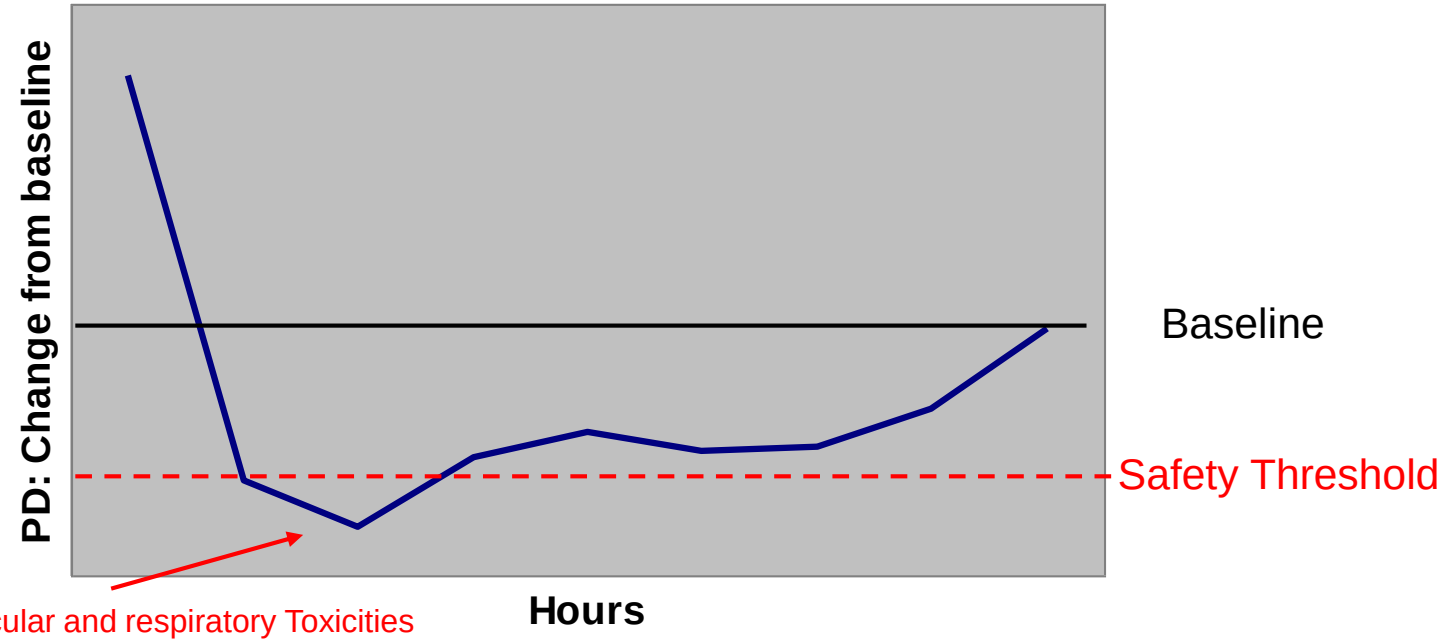
- ISR
  - Non clinical safety studies once per method per species (minimum)
  - Pivotal clinical studies in NDA/BLAs
  - All BE studies
  - Flat 7% was rejected: reverted to 10% of the first 1000 samples, and then 5% of samples over 1000 per study

Some of the "New" Things

1. Diagnostic Kits (aka commercial kits)
   - Typically designed for diagnosis of a condition in patients
   - Re-purposed for drug development
     - May not be suited to assessing the PK/PD time course of new drug/therapeutic
     - Sometimes they are fine (no additional validation is needed)
     - Sometimes they are not (e.g.1 point calibration curve; non-drug reference standard)
     - May need further validation

Diagnostic Kit Example

- Drug inhibits an enzyme that produces an endogenous messenger-common to both human and microbe



Diagnostic Kit Example

Plasma validation-Assay Problems

- 2-point calibration curve
- Reference std was not drug; structural dissimilarities.
- 2 QCs-non-drug-used; range of values listed
- No accuracy
- No QCs to monitor analytical runs during study sample analysis
- No stability!
  - Sample handling could have a significant (large) impact on PD biomarker
- No ISR
- No validation in urine

Some of the “New” Things

2. Biomarkers

- There was void here.
- Applicant responses range from almost no method validation to quite outstanding job
- Very important when using biomarkers to support decisions regarding approval, safety or efficacy or product labelling (dosing)

Some of the "New" Things

2. Biomarkers

Very broad category of analytes

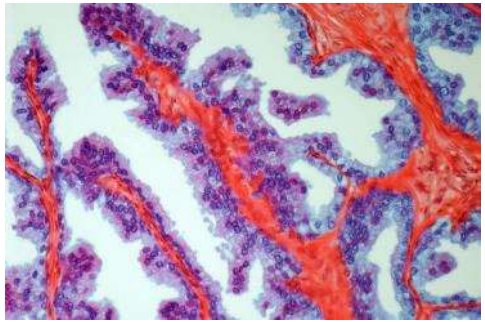
- When we use LCMS or LBA assays for drug-like molecules (e.g. testosterone)—should be pretty close to PK assay
- Other platforms/applications---parts of this approach may not apply
- Evolution ---Remember the questions

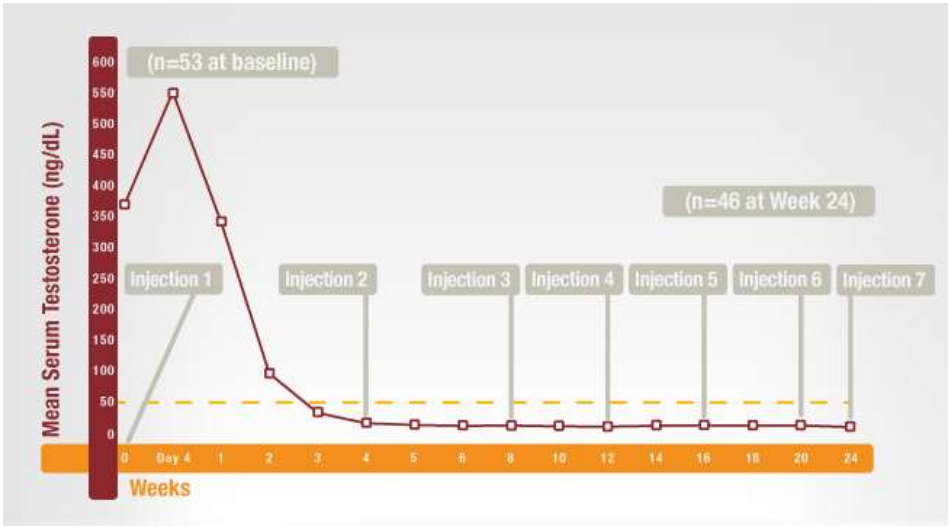
"The approach used for drug assays should be the starting point for validation of biomarker assays, although the **FDA realizes that some characteristics may not apply or that different considerations may need to be addressed**. "

Biomarker Example: Testosterone

…as a drug: testosterone replacement

…as a biomarker: prostate cancer





Biomarker Example: Testosterone

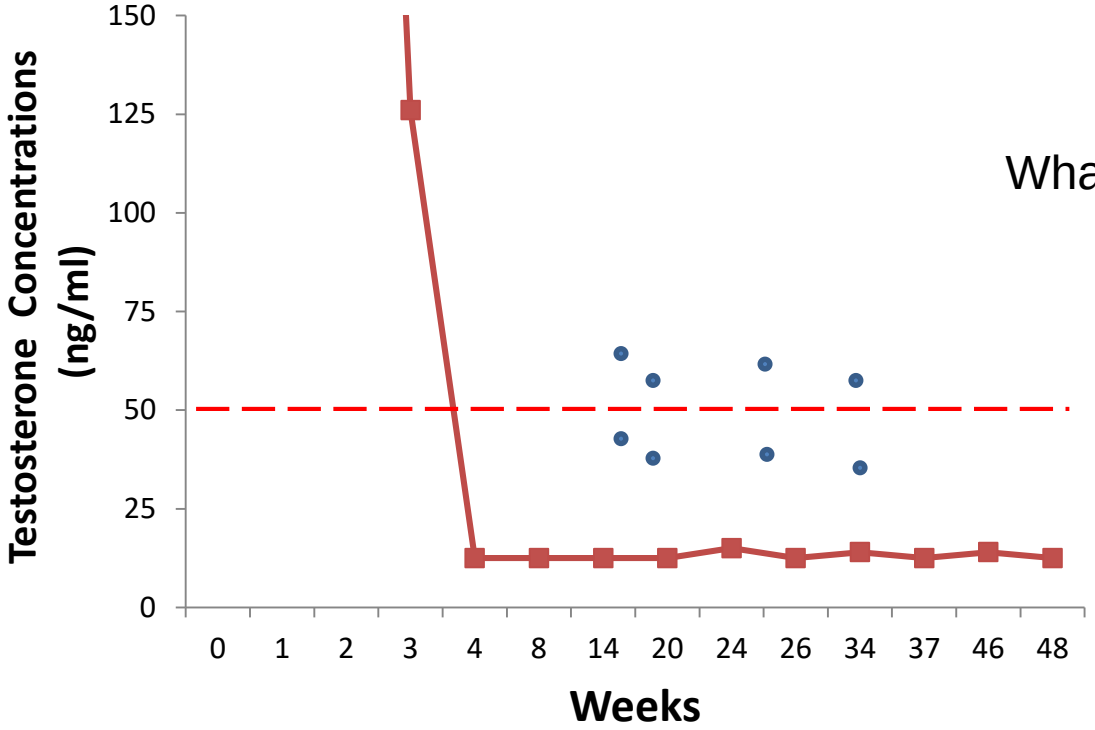
LC/MS assay

Phase 3 Efficacy Endpoint

Bioanalytical Issues

- Failure to reject analytical runs—calibrators in 57 runs
- Stability Failures
  - No Room Temp Stability below 200 ng/ml
  - Long Term Stability failure—only 34% were +/- 15%

Biomarker Example: Testosterone



What do these BA failures mean?

Accuracy is unreliable

Some of the “New” Things

3. New Tech/DBS

“Can we use new technologies in our development?”

Absolutely!

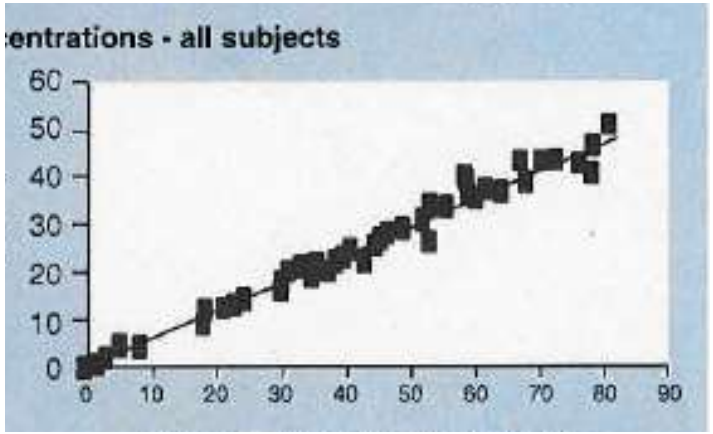
But we have to bridge (cross validate)

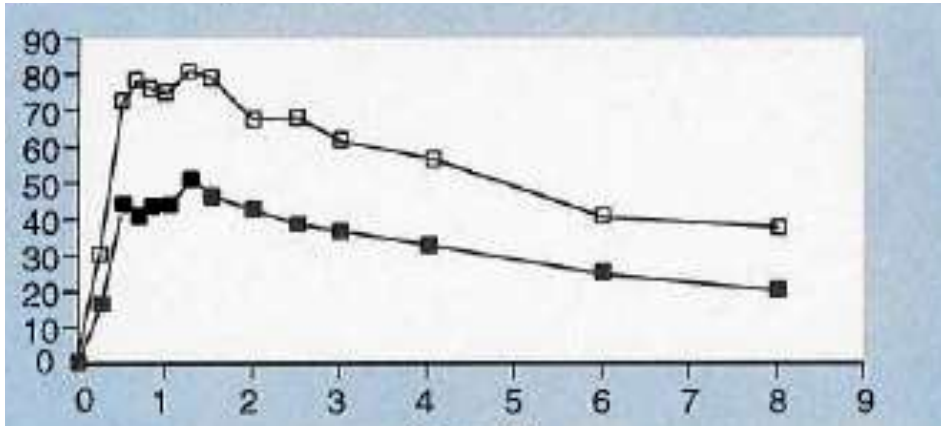
- might have a bias between platforms

Probably not needed if you use one platform for entire development

New Tech/DBS

How should you compare methods?





Some of the “New” Things

4. Endogenous compounds
   - Stripped matrix
   - QCs
   - Other approaches may be justified
   - Parallelism

Challenge Question 1

When conducting bioanalytical method development and validation for FDA submissions, analysts should use the:

1. 2018 FDA BMV Guidance
2. 2011 EMA Guideline
3. 2003 ANVISA Guideline
4. 2001 FDA BMV Guidance
5. 2019 ICH M10 *draft Guideline*

Challenge Question 2

When conducting bioanalytical method development and validation for biomarkers, the FDA expectation is:

1. 2018 FDA BMV Guidance should be strictly adhered to
2. Method validation for biomarkers is unnecessary.
3. The principles of 2018 FDA BMV Guidance should be used to guide you.
4. You should follow your gut instincts.

Summary

- The 2018 Guidance is now finalized and FDA will adhere to this document until ICH M10 is **finalized.**

- The Guidance provides recommendations about validation issues for chromatographic and ligand binding assays.

- The Guidance provides recommendations of new concepts about the use of diagnostic/commercial kits, comparing new/alternative platforms to established methodologies, and biomarker assays.

Thank you

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