From Engineering Validation to Qualification of Biomarkers, an FDA Success Story

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AIMBE/NIH Meeting
Biomarker Qualification vs. Drug Development

- What impact are regulatory qualification processes having on collaborative efforts to develop and qualify new biomarkers?

- What is the most effective path for regulatory acceptance of biomarkers?

- Should additional biomarker qualification acceptance paths be developed?
What impact are regulatory qualification processes having on collaborative efforts to develop and qualify new biomarkers?
Biomarker Qualification

• Make sure that biomarker information in regulatory submissions is acceptable to regulatory agencies.

• The concept of qualification in this case is circumscribed to the requirements of regulatory review.

• Not all biomarkers need to be qualified, and not all biomarkers may be qualified through a biomarker qualification regulatory process.
Qualification in this case is circumscribed to the requirements of regulatory review.
From Pilot to Process at the FDA

- Pilot Biomarker Qualification Process started in 2005.
- Draft Guidance issued in October 2010.
Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical
Qualification in the Guidance

• **Definition:** A conclusion that within the stated *context of use*, the results of assessment can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

• **Regulatory implication:** If a biomarker is qualified,
  – Analytically valid measurements of it can be relied upon to have a specific use and interpretable meaning in drug development.
  – The qualification process is expected to expedite development of successful marketing applications.
  – If qualified for a specific context of use,
    • industry can use the biomarker for the qualified purpose during drug development
    • CDER reviewers can be confident in applying the DDT for the qualified use without the need to reconfirm the DDT’s utility.
Context of Use

• Comprehensive statement that:
  – fully and clearly describes the manner and purpose of use for the biomarker
  – all important criteria regarding the circumstances under which the biomarker qualified
  – defines the boundaries within which the available data adequately justify use
  – potential value outside these boundaries
    • data from additional studies obtained over time may be submitted to expand the qualified context of use

• May include range of:
  – clinical disorders
  – drug classes
  – species
  – procedures and criteria for how samples are obtained
  – interpretation of results
Biomarker Qualification Process at CDER

Sponsor Submits Written Request for Biomarker Qualification → Request Evaluated → BQRT Assembled → Sponsor Submits Briefing Package

Consultation and Advice

BQ PM Creates Sponsor/BQRT Meeting

BQ Ready For Review?

Yes → Sponsor Completes Biomarker Qualification Data Package → Review Team Drafts Review

No → BQRT Requests More Information

Review Team Checks In Discipline Reviews

BQRT Lead Compiles Reviews Into Executive Summary Integrated Review

Advisory Committee (AC) Required?

Yes → Sent To AC → Results Signed By CDER Director → Review Complete

No → Regulatory Briefing Scheduled → Executive Summary Forwarded to Office Directors

What would a submission look like?

Section 1: Administrative Information
1.1 Cover letter
1.2 Names of the principal investigators and working group members (if applicable)
1.3 Any appropriate FDA forms
1.4 Specific questions the submitter has for CDER

Section 2: Summaries
2.1 Introduction
2.2 Context of Use
   (i) general area
   (ii) specific biomarker use
   (iii) the critical parameters that define when and how the biomarker should be used. The context of use can be limited to use in drug development.
2.3 Methodology and Results
2.4 Knowledge Gaps and Development Plan
2.5 Measurement Methodology

Appendix
Biomarker Qualification and the Predictive Safety Testing Consortium
Fig. 1. New regulatory process for biomarker qualification. Biomarker qualification submissions for more sensitive and specific biomarkers of kidney toxicity have been among the first to test this process.
Towards consensus practices to qualify safety biomarkers for use in early drug development


Nature Biotechnology volume 28 number 5 may 2010, pp 446-454.
Renal biomarker qualification submission: a dialog between the FDA-EMEA and Predictive Safety Testing Consortium

Frank Dieterle¹, Frank Sistare², Federico Goodsaid³, Marisa Papaluca⁴, Josef S Ozer²,²⁸, Craig P Webb⁵,⁶, William Baer⁵,⁷, Anthony Senagore⁵,⁸, Matthew J Schipper⁵,⁹, Jacky Vonderscher¹⁰, Stefan Sultana⁵, David L Gerhold², Jonathan A Phillips¹¹, Gérard Maurer¹, Kevin Carl¹, David Laurie¹, Ernie Harpur¹², Manisha Sonee¹³, Daniela Ennulat¹⁴, Dan Holder¹⁵, Dina Andrews-Cleavenger¹⁶, Yi-Zhong Gu¹⁷,²⁹, Karol L Thompson³, Peter L Goering³, Jean-Marc Vidal⁴, Eric Abadie⁴, Romaldas Maciulaitis⁴,¹⁸, David Jacobson-Kram³, Albert F Defelice³, Elizabeth A Hausner³, Melanie Blank³, Aliza Thompson³, Patricia Harlow³, Douglas Throckmorton³, Shen Xiao³, Nancy Xu³, William Taylor³, Spiros Vamvakas⁴, Bruno Flamion⁴, Beatriz Silva Lima⁴, Peter Kasper⁴, Markku Pasanen⁴,¹⁹, Krishna Prasad⁴, Sean Troth²⁰, Denise Bounous²¹, Denise Robinson-Gravatt²², Graham Betton²³, Myrtle A Davis²⁴, Jackie Akunda²⁵, James Eric McDuffie¹³, Laura Suter¹⁰, Leslie Obert²², Magalie Guffroy¹², Mark Pinches²³, Supriya Jayadev¹¹, Eric A Blomme²⁶, Sven A Beushausen²², Valérie G Barlow¹², Nathaniel Collins¹⁷,²⁹, Jeff Waring²⁶, David Honor²⁶, Sandra Snook¹³, Jinhe Lee²⁶, Phil Rossi²⁷, Elizabeth Walker²⁷ & William Mattes²⁷

Nature Biotechnology volume 28 number 5 may 2010, pp 455-462.
Better Biomarkers of Nephrotoxicity

Figure 1 Urinary Kim-1 levels after cisplatin treatment\textsuperscript{16}. Termination time point is labeled for each animal. The symbol and color represent the histopathology grading for proximal tubular injury. The magenta line represents the Kim-1 threshold for 95\% specificity based on ~200 control animals. One animal in this study represents a false positive (encircled). Animals within the gray boxes are removed for the exclusion analysis in contrast to the inclusion analysis. A number of animals in this box show significantly higher urinary Kim-1 levels (marked with arrows) than control animals.
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Qualified preclinically</th>
<th>Adds information to SCr and BUN(^{a,b})</th>
<th>Outperforms SCr and/or BUN(^{a-d})</th>
<th>Analytically validated assay</th>
<th>Widely available assay</th>
<th>Qualified for clinical use(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1</td>
<td>Yes</td>
<td>Yes(^a)</td>
<td>Yes(^a)</td>
<td>Yes</td>
<td>Pending</td>
<td>Yes</td>
</tr>
<tr>
<td>Albumin</td>
<td>Yes</td>
<td>Yes(^a)</td>
<td>Yes(^a)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CLU</td>
<td>Yes</td>
<td>Yes(^a)</td>
<td>Yes(^a)</td>
<td>Yes</td>
<td>Yes</td>
<td>Pending</td>
</tr>
<tr>
<td>TFF3</td>
<td>Yes</td>
<td>Yes(^a)</td>
<td>No</td>
<td>Yes</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>Total protein</td>
<td>Yes</td>
<td>Yes(^b)</td>
<td>Yes(^b,c)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>Yes</td>
<td>Yes(^b)</td>
<td>Yes(^b,c)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>Yes</td>
<td>Yes(^b)</td>
<td>Yes(^b,c)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

\(^a\) Acute tubular alterations. \(^b\) Acute glomerular injury with acute tubular reabsorption impairment. \(^c\) Biomarker outperformed SCr. \(^d\) If an inclusion ROC analysis is considered, instead of an exclusion ROC analysis, cystatin C and β2-microglobulin outperform not only SCr but also blood urea nitrogen with respect to the prediction of histopathologically confirmed kidney injury (see text for further details of the ROC analysis). \(^e\) Qualified for clinical use refers to a 'case-by-case' context and not to a broad general qualification.
Figure 1 Flow charts explaining the proposed limited clinical translational use of the new renal biomarkers. This is in the context of permitting the progression of a compound into human testing, which requires the demonstration of reversibility upon drug cessation in an animal study. It is not uncommon for a compound to be associated with histopathological evidence of drug-induced glomerular or proximal tubular injury in animal toxicology studies without an observed change in BUN and Scr.
Box 1  Strength-of-evidence criteria for evaluating biomarkers

In line with previous work carried out elsewhere\textsuperscript{10,24}, the PSTC considered several criteria in initial selection of renal biomarkers for investigation. These criteria are outlined below.

- **Availability of a sufficiently validated analytical assay**
- Biological plausibility of the association of the biomarkers with injury to the organ of interest
- Understanding of the molecular mechanism of the biomarker response
- Strong association of changes in biomarker levels to pathological outcomes and superior performance relative to currently accepted biomarkers
- Consistent response across mechanistically diverse toxicants, sexes, strains and species
- Both dose-response and temporal relationships relating the magnitude of biomarker alterations to the severity of injury, and the onset of and recovery from injury
- Adequate specificity to ensure that the biomarker does not respond to injury of other organs or to benign activation of physiological processes in the organ of interest
Table 1  Steps in the regulatory qualification of new safety biomarkers for PSTC

<table>
<thead>
<tr>
<th>Step</th>
<th>Industry and academic consortium member input</th>
<th>Regulatory BQRT member input</th>
<th>Other regulatory research scientist contributor input</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Set expectations and core principles, and precisely define the goals, objectives and limited new biomarker qualification claims.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Evaluate candidate safety biomarkers against strength-of-evidence criteria (Table 2).</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Assess the utility of any existing available data, study samples and assays.</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Complete gap analysis:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>prioritize biomarker candidates</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>specify analytical assay validation needs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>set general design of new studies</td>
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<tr>
<td>identify new biomarkers to be measured in existing samples</td>
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<tr>
<td>5. Define research plan to address gaps:</td>
<td></td>
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<tr>
<td>define fit-for-purpose assay validation plans</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>define study protocols and specific studies to test biomarker performance claims</td>
<td></td>
<td></td>
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<tr>
<td>align on processes, procedures, lexicons for collection of gold standard measurements</td>
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<tr>
<td>align on the statistical analysis plan</td>
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<tr>
<td>6. Resolve unforeseen issues in ongoing manner.</td>
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<tr>
<td>7. Execute research plan and submit results and conclusions for BQRT review.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Description</td>
<td>Primary designation</td>
<td>Secondary lesion</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Tubular necrosis and degeneration</td>
<td>Degeneration/necrosis of tubular epithelium</td>
<td>Tubular cell degeneration/necrosis</td>
<td>Degeneration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No precise location possible</td>
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<tr>
<td>Tubular cell regeneration</td>
<td>Tubular basophilia</td>
<td>Tubular cell regeneration</td>
<td>Basophilia</td>
</tr>
<tr>
<td></td>
<td>Tubular regeneration, epithelial</td>
<td></td>
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<tr>
<td>Glomerulopathy</td>
<td>Glomerulopathy</td>
<td>Glomerular alteration</td>
<td>Bowman’s space decr.</td>
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<tr>
<td></td>
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<td>Bowman’s space incr.</td>
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<td></td>
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<td></td>
<td>Mesangial prolif./expansion</td>
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<tr>
<td></td>
<td></td>
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<td>Glomerular vacuolation</td>
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<tr>
<td>Other renal injury</td>
<td>Tubular dilatation</td>
<td>Tubular dilation</td>
<td>Fibrosis</td>
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<td></td>
<td>Fibrosis</td>
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<td></td>
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<tr>
<td>Other</td>
<td>Pelvis dilation</td>
<td>Pelvis dilation</td>
<td>Acute, chronic</td>
</tr>
<tr>
<td></td>
<td>Nephropathy</td>
<td>Nephropathy</td>
<td>Crystalline, hyaline, granular</td>
</tr>
<tr>
<td></td>
<td>Mineralization</td>
<td>Mineralization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
<td>Inflammation</td>
<td></td>
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<tr>
<td></td>
<td>Infiltration</td>
<td>Infiltration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cast</td>
<td>Intratubular cast</td>
<td></td>
</tr>
<tr>
<td>Nonrenal tissues</td>
<td>Liver damage composite score</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Quadriceps damage composite score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Soleus damage composite score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart damage composite score</td>
<td></td>
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</tr>
</tbody>
</table>

Diverse descriptors of kidney histology were given hierarchical designations to conform to a standardized, hierarchical PSTC Renal Lexicon. Each type of kidney injury was then binned into one of four categories: tubular necrosis/degeneration, tubular cell regeneration, glomerulopathy or other renal injury. ‘Other renal injury’ comprised two histological findings that are generally treatment related, whereas ‘Other’ histological changes are occasionally observed in untreated animals and may thus be unrelated to treatment. The scores in each of the four categories are then summed in a composite score as the largest grade for any row in that category.
What is the most effective path for regulatory acceptance of biomarkers?
How are biomarkers accepted today in regulatory agencies?

- Accepted over time

- Drug-dependent context of use
  - Original Submission
  - Labeling Updates
  - Codevelopment of drug and test

- Biomarker Qualification Process
ICH HARMONISED TRIPARTITE GUIDELINE

Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions

E16

Description: The harmonised tripartite Guideline was finalised under Step 4 in August 2010. The Guideline describes recommendations regarding context, structure, and format of regulatory submissions for qualification of genomic biomarkers, as defined in ICH E15.

Implementation: Step 5
EU: Adopted by CHMP, September 2010, issued as EMA/CHMP/ICH/380636/2009
MHLW: Adopted 20 January 2011, PFSB/ELD Notification No. 0120-1/ PFSB/SD Notification No. 0120-1
FDA: Published in the Federal Register, 11 August 2011, Vol. 76, No. 155, p. 49773-4

Current Step 4 version
dated 20 August 2010
Qualification of novel methodologies for drug development: guidance to applicants

09 January 2012
EMA/CHMP/SAWP/72894/2008 Rev.1
Scientific Advice Working Party of CHMP

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<table>
<thead>
<tr>
<th>Agreed by SAWP</th>
<th>27 February 2008</th>
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</thead>
<tbody>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>24 April 2008</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>30 June 2008</td>
</tr>
<tr>
<td>Final Agreed by CHMP</td>
<td>22 January 2009</td>
</tr>
</tbody>
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Keywords

PMDA: Special Consultation on Biomarker Qualification

- PMDA Scientific Consultation regarding Biomarker Qualification
- Similar to FDA/EMEA Biomarker Qualification Meeting
- Focus on general strategy for Biomarker Qualification
  - Individual issues related to a individual drug are covered by Existing Consultation
- PMDA provides an assessment report for this consultation

Timeline of Special Consultation on PGx/Biomarker Qualification for *Pilot*

- **PMDA’s action**
  - Pre-meeting (informal)
    - Schedule Arrangement
- **Sponsor’s action**
  - Application
  - Document Submission
  - Response

1. **1st Inquiry**
2. **2nd Inquiry (If necessary)**
3. **Draft Report**
4. **Final Report**

Key Dates:
- Week 0: Pre-meeting (informal)
- Week 2: Schedule Arrangement
- Week 6: Document Submission
- Week 9: Application
- Week 12: Response
- Week 14: F2F
- Week 16: Draft Report
- Week 22: Comments to draft report
- Week 24: Final Report
Which is the best path?

- Biomarkers of nephrotoxicity
  - Qualified in the context in which they can be used to better interpret other nonclinical safety assessment results in regulatory submissions.
  - Context of use may be incrementally expanded in the future for clinical applications as qualification data become available for these biomarkers.

- Biomarkers used to select patients in clinical studies are not usually qualified independently of the clinical studies they are reported with.
Biomarker Qualification Program

The Biomarker Qualification Program was established to support CDER's work with external scientists and clinicians in developing biomarkers. As an inter-Office collaborative endeavor within CDER, the Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process.

The goals of the CDER Biomarker Qualification Program are to:

- Provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development
- Facilitate integration of qualified biomarkers in the regulatory review process
- Encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making
- Support outreach to relevant external stakeholders to foster biomarker development

Biomarkers being considered for qualification are conceptually independent of the specific test performing the measurement. A biomarker cannot become qualified without a reliable means to measure it. However, FDA clearance of a testing device for marketing does not imply that the biomarker it measures has been demonstrated to have a qualified use in drug development and evaluation. Additionally, qualification of a biomarker does not automatically imply that a specific test device used in the qualification process for a biomarker has been reviewed by FDA and cleared or approved for use in patient care.

The biomarker may also have potential value outside the boundaries of the qualified context of use. As data from additional studies are obtained over time, submitters of biomarkers will be able to continue working with the Biomarker Qualification Program to submit additional data and expand the qualified context of use.

Qualified DDT:

<table>
<thead>
<tr>
<th>DDT Type</th>
<th>Name</th>
<th>Submitter</th>
<th>Qualification Date</th>
<th>Link to Supporting Information</th>
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</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>Seven Biomarkers of Drug-Induced Nephrotoxicity in Rats</td>
<td>Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)</td>
<td>4/14/2008</td>
<td>Predictive Safety Testing Consortium (PDF - 163KB)</td>
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<tr>
<td>Biomarker</td>
<td>Nonclinical Qualification of Urinary Biomarkers of Nephrotoxicity</td>
<td>International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group</td>
<td>9/22/2010</td>
<td>HESI Nephrotoxicity Qualification (PDF - 234KB)</td>
</tr>
</tbody>
</table>
Total Biomarker Qualification Process Timeline Length at FDA

• Time from submission to Center Director letter for initial 2007 PSTC Nephrotoxicity submission: 12 months.
  – baseline of 3+ years

• Process shares similar scheduling uncertainties with NDA reviews
  – not yet at an equal level of review resource priorities as NDAs.
Distribution of submissions throughout the Biomarker Qualification Process at the FDA

Consultation and Advice: 74%
Qualified: 13%
Review: 13%
Challenges for a Biomarker Qualification Process

Timeline to Biomarker Qualification

1) Resubmission into BQP of biomarkers previously reviewed by a Clinical Division
2) Surrogates
Challenges for a Biomarker Qualification Process

Timeline to Biomarker Qualification
Should additional biomarker qualification acceptance paths be developed?

• Yes.

• What do we know it should be?
  – Universal
    • follow ICH E16
    • potential for interagency review process
  – Independent of drug review
    • reviewers have exclusive task of biomarker qualification submission reviews
  – Suitable for conditional approval pathway
  – Aware of potential for a biomarker qualification process gap.