

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.



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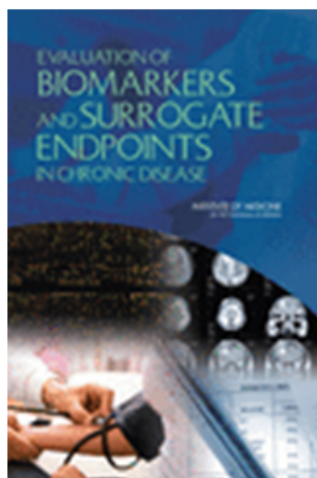
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Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease

Released: May 12, 2010

Type: Consensus Report

Topics: Biomedical and Health Research, Diseases, Quality and Patient Safety

Activity: Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease

Boards: Food and Nutrition Board, Board on Health Care Services, Board on Health Sciences Policy

From Pilot to Process at the FDA

- **Pilot Biomarker Qualification Process started in 2005.**
- **Formal Biomarker Qualification Process proposed in 2009.**
- **Draft Guidance issued in October 2010.**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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)

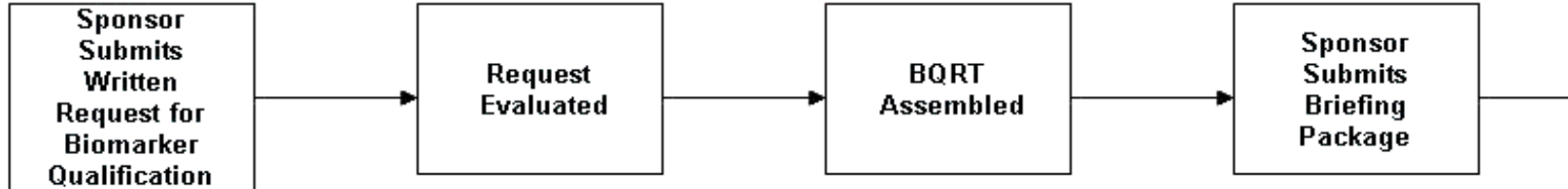
October 2010
Clinical/Medical

Qualification in the Guidance

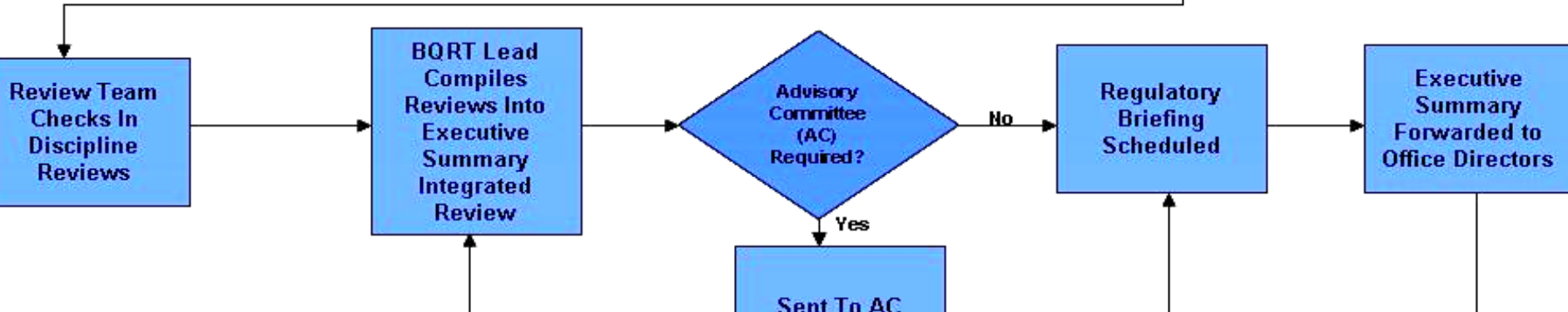
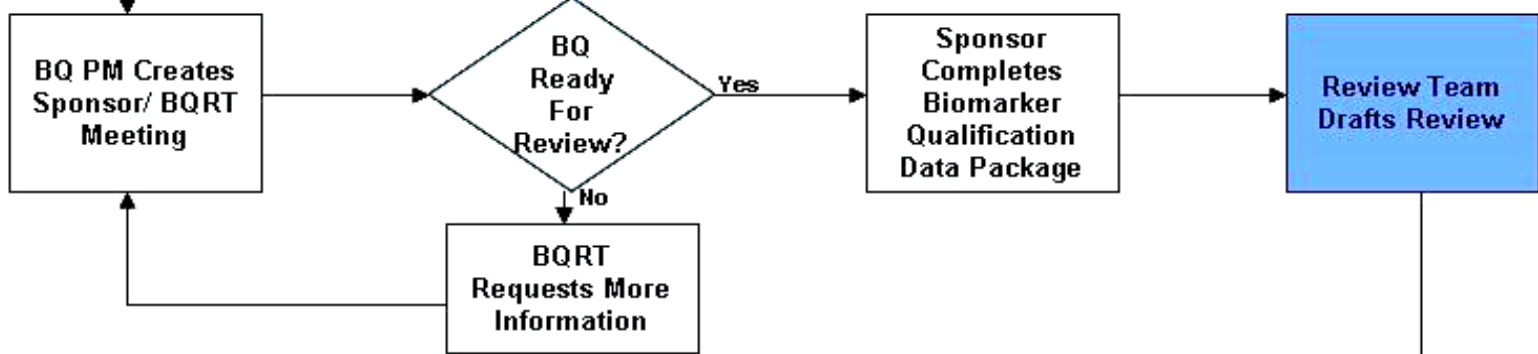
- ***Definition:*** A conclusion that within the stated *context of use*, the results of assessment can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.
- ***Regulatory implication:*** If a biomarker is qualified,
 - Analytically valid 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

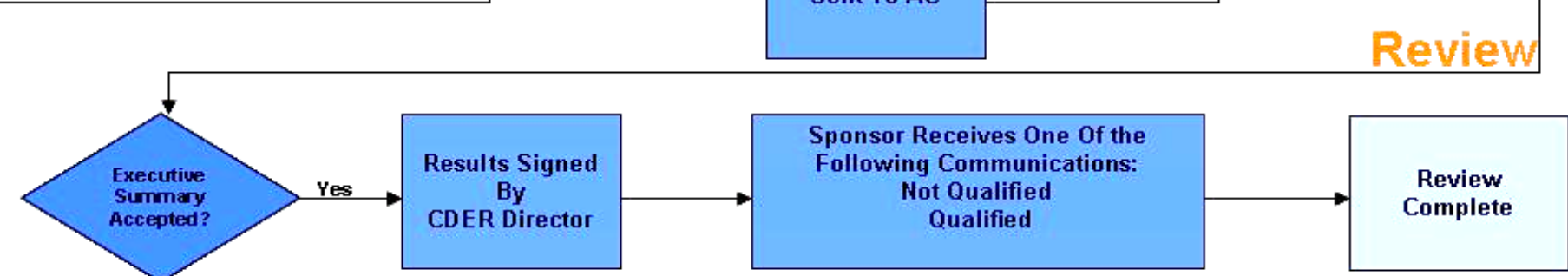
- **Comprehensive statement that:**
 - fully and clearly describes the manner and purpose of use for the biomarker
 - all important criteria regarding the circumstances under which the biomarker qualified
 - defines the boundaries within which the available data adequately justify use
 - potential value 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



Consultation and Advice



Review



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

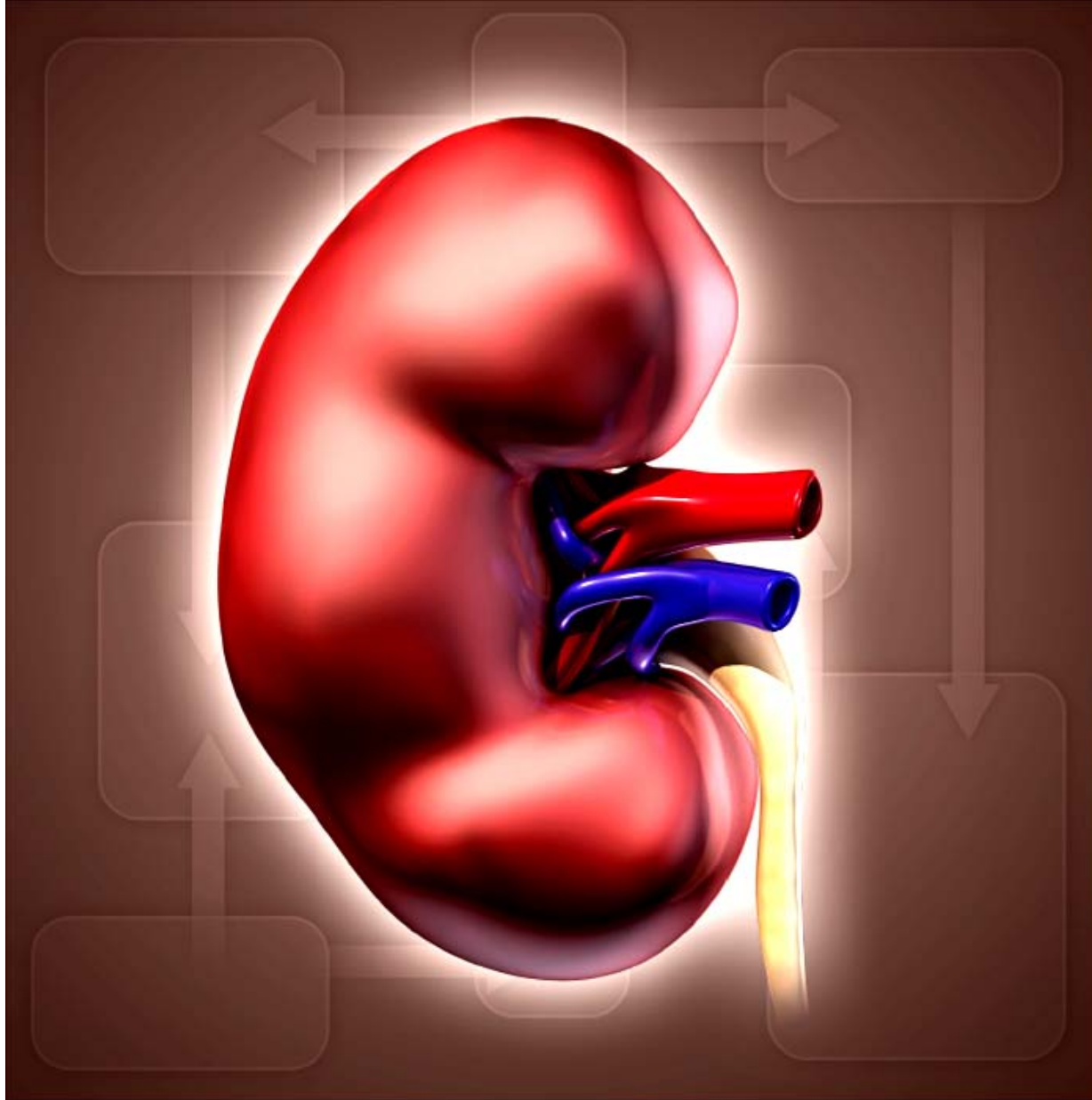


Fig. 1. New regulatory process for biomarker qualification. Biomarker qualification submissions for more sensitive and specific biomarkers of kidney toxicity have been among the first to test this process.

Towards consensus practices to qualify safety biomarkers for use in early drug development

Frank D Sistare¹, Frank Dieterle², Sean Troth¹, Daniel J Holder¹, David Gerhold¹, Dina Andrews-Cleavenger³, William Baer⁴, Graham Betton⁵, Denise Bounous⁶, Kevin Carl², Nathaniel Collins⁷, Peter Goering⁸, Federico Goodsaid⁸, Yi-Zhong Gu⁷, Valerie Guilpin⁹, Ernie Harpur⁹, Alita Hassan⁴, David Jacobson-Kram⁸, Peter Kasper¹⁰, David Laurie², Beatriz Silva Lima¹¹, Romaldas Maciulaitis¹⁰, William Mattes¹², Gérard Maurer², Leslie Ann Obert¹³, Josef Ozer¹³, Marisa Papaluca-Amati¹⁰, Jonathan A Phillips¹⁴, Mark Pinches⁵, Matthew J Schipper⁴, Karol L Thompson⁸, Spiros Vamvakas¹⁰, Jean-Marc Vidal¹⁰, Jacky Vonderscher¹⁵, Elizabeth Walker¹², Craig Webb⁴ & Yan Yu¹

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 Ozer^{2,28}, Craig P Webb^{5,6}, William Baer^{5,7}, Anthony Senagore^{5,8}, Matthew J Schipper^{5,9}, 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 Gu^{17,29}, Karol L Thompson³, Peter L Goering³, Jean-Marc Vidal⁴, Eric Abadie⁴, Romaldas Maciulaitis^{4,18}, 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 Pasanen^{4,19}, 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 Collins^{17,29}, 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

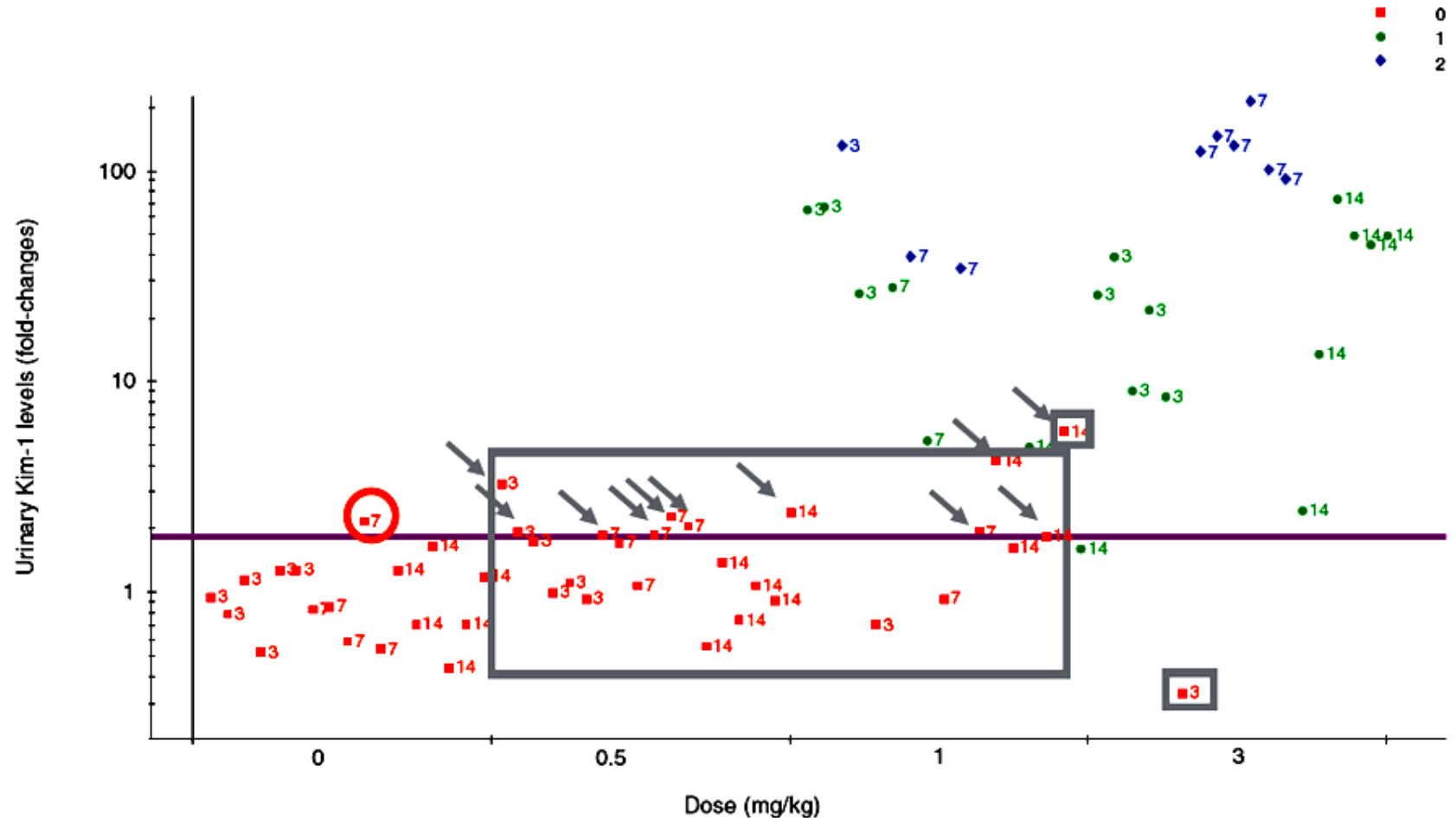


Figure 1 Urinary Kim-1 levels after cisplatin treatment¹⁶. Termination time point is labeled for each animal. The symbol and color represent the histopathology grading for proximal tubular injury. The magenta line represents the Kim-1 threshold for 95% specificity based on ~200 control animals. One animal 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 1 Summary of claims submitted by the PSTC to the FDA and EMEA on seven biomarkers associated with nephrotoxicity

Biomarker	Qualified preclinically	Adds information to SCr and BUN ^{a,b}	Outperforms SCr and/or BUN ^{a-d}	Analytically validated assay	Widely available assay	Qualified for clinical use ^e
KIM-1	Yes	Yes ^a	Yes ^a	Yes	Pending	Yes
Albumin	Yes	Yes ^a	Yes ^a	Yes	Yes	Yes
CLU	Yes	Yes ^a	Yes ^a	Yes	Yes	Pending
TFF3	Yes	Yes ^a	No	Yes	Pending	Pending
Total protein	Yes	Yes ^b	Yes ^{b,c}	Yes	Yes	Yes
Cystatin C	Yes	Yes ^b	Yes ^{b,c}	Yes	Yes	Yes
β 2-microglobulin	Yes	Yes ^b	Yes ^{b,c}	Yes	Yes	Yes

^aAcute tubular alterations. ^bAcute glomerular injury with acute tubular reabsorption impairment. ^cBiomarker outperformed SCr. ^dIf an inclusion ROC analysis is considered, instead of an exclusion ROC analysis, cystatin C and β 2-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). ^eQualified for clinical use refers to a 'case-by-case' context and not to a broad general qualification.

Clinical application of tubular markers

Tubular toxicity confirmed by histopathology in one or several species including rat.
BUN and SCr levels in control range

Measure BUN, SCr, KIM-1 and albumin in urine samples of GLP study in animal species showing tubular toxicity to demonstrate reversibility, interim urine samplings and periodic histopathological assessments

Yes
KIM-1, albumin diagnostic?*

No

Phase 1/2 clinical trial:
monitor KIM-1, albumin, BUN, SCr. Base decisions on best preclinical marker among KIM-1, albumin**

Nonmonitorable kidney toxicity:
clinical trial delayed unless mechanistic understanding can be developed to address human irrelevance

- * Sponsor can voluntarily measure albumin or Kim-1 alone or both markers together.
** Preclinical best marker means marker with the best diagnostic performance compared to histopathology.

Clinical application of glomerular markers

Glomerular toxicity confirmed by histopathology in one or several species including rat.
BUN and SCr levels in control range

Measure BUN, SCr, β 2-microglobulin, cystatin C and total protein in urine samples of GLP study in animal species showing glomerular toxicity to demonstrate reversibility, interim urine samplings and periodic histopathological assessments

Yes
Cystatin C, β 2-microglobulin, total protein diagnostic?*

No

Phase 1/2 clinical trial:
monitor cystatin C, β 2-microglobulin, total protein, BUN, SCr. Base decisions on best preclinical marker among β 2-microglobulin, cystatin C, total protein**

Nonmonitorable kidney toxicity:
clinical trial delayed unless mechanistic understanding can be developed to address human irrelevance

- * Sponsor can voluntarily measure cystatin C, β 2-microglobulin, total protein alone or several of these markers.
** Preclinical best marker means marker with the best diagnostic performance compared to histopathology.

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^{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

	Industry and academic consortium member input	Regulatory BQRT member input	Other regulatory research scientist contributor input
1. Set expectations and core principles, and precisely define the goals, objectives and limited new biomarker qualification claims.	Yes	Yes	Yes
2. Evaluate candidate safety biomarkers against strength-of-evidence criteria (Table 2).	Yes	No	Yes
3. Assess the utility of any existing available data, study samples and assays.	Yes	No	Yes
4. Complete gap analysis: prioritize biomarker candidates specify analytical assay validation needs set general design of new studies identify new biomarkers to be measured in existing samples	Yes	No	Yes
5. Define research plan to address gaps: define fit-for-purpose assay validation plans define study protocols and specific studies to test biomarker performance claims align on processes, procedures, lexicons for collection of gold standard measurements align on the statistical analysis plan	Yes	Yes	Yes
6. Resolve unforeseen issues in ongoing manner.	Yes	Yes	Yes
7. Execute research plan and submit results and conclusions for BQRT review.	Yes	No	Yes

Table 3 Hierarchical organization and binning of PSTC kidney histologic injury lexicon

Category	Description	PSTC lexicon		
		Primary designation	Secondary lesion	Tertiary segments
Tubular necrosis and degeneration	Degeneration/necrosis of tubular epithelium	Tubular cell degeneration/necrosis	Degeneration Necrosis	No precise location possible Proximal convoluted tubule Thick descending tubule Loop of Henle Distal convoluted tubule
Tubular cell regeneration	Tubular basophilia Tubular regeneration, epithelial	Tubular cell regeneration	Basophilia Mitosis increased	No precise location possible Proximal convoluted tubule Thick descending tubule Loop of Henle Distal convoluted tubule
Glomerulopathy	Glomerulopathy	Glomerular alteration	Bowman's space decr. Bowman's space incr. Mesangial prolif./expansion Glomerular vacuolation	Glomerulus
Other renal injury	Tubular dilatation Fibrosis	Tubular dilation Fibrosis		Cortex Medulla Papilla
Other	Pelvis dilation Nephropathy Mineralization Inflammation Infiltration Cast	Pelvis dilation Nephropathy Mineralization Inflammation Infiltration Intratubular cast	Acute, chronic Crystalline, hyaline, granular	Cortex Medulla Papilla Pelvis
Nonrenal tissues	Liver damage composite score Quadriceps damage composite score Soleus damage composite score Heart damage composite score			

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**

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E16/Step4/E16_Step_4.pdf

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022bb0

09 January 2012
EMA/CHMP/SAWP/72894/2008 Rev.1¹
Scientific Advice Working Party of CHMP

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

Qualification of novel methodologies for drug development: guidance to applicants

http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004207.doc

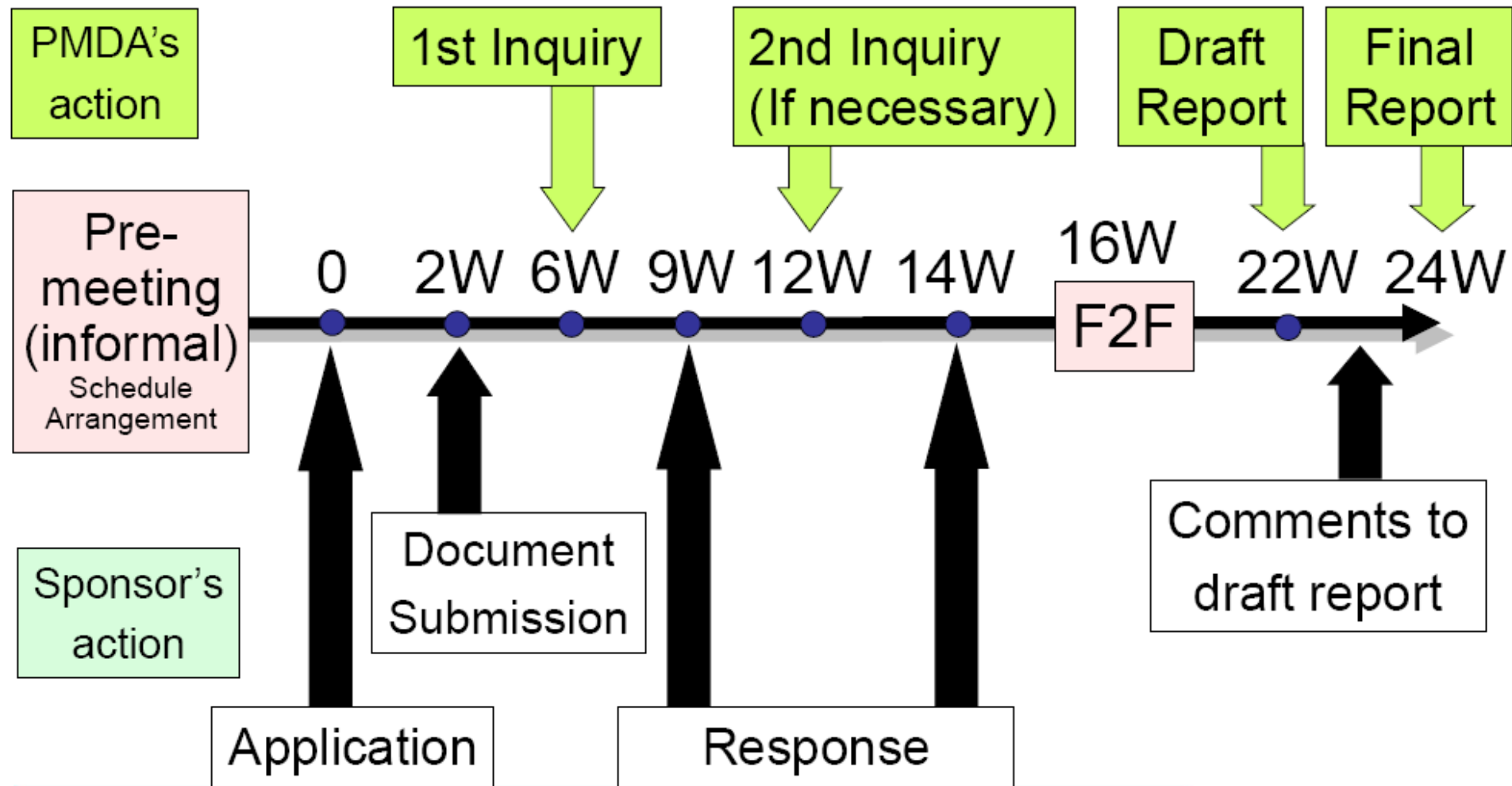
Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	<i>EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.</i>
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PMDA: Special Consultation on Biomarker Qualification

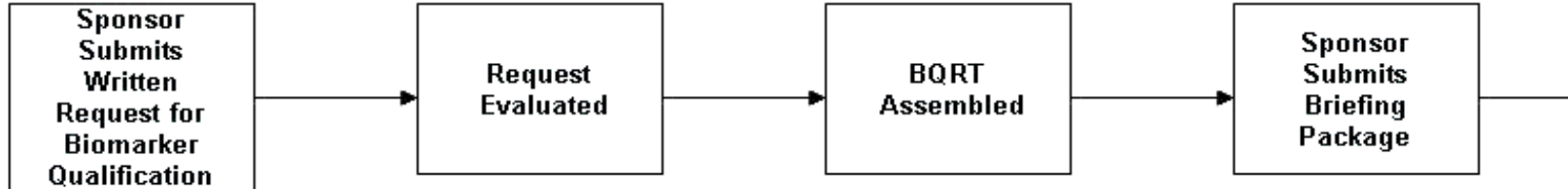
- **PMDA Scientific Consultation regarding Biomarker Qualification**
- **Similar to FDA/EMA Biomarker Qualification Meeting**
- **Focus on general strategy for Biomarker Qualification**
 - **Individual issues related to a individual drug are covered by Existing Consultation**
- **PMDA provides an assessment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

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

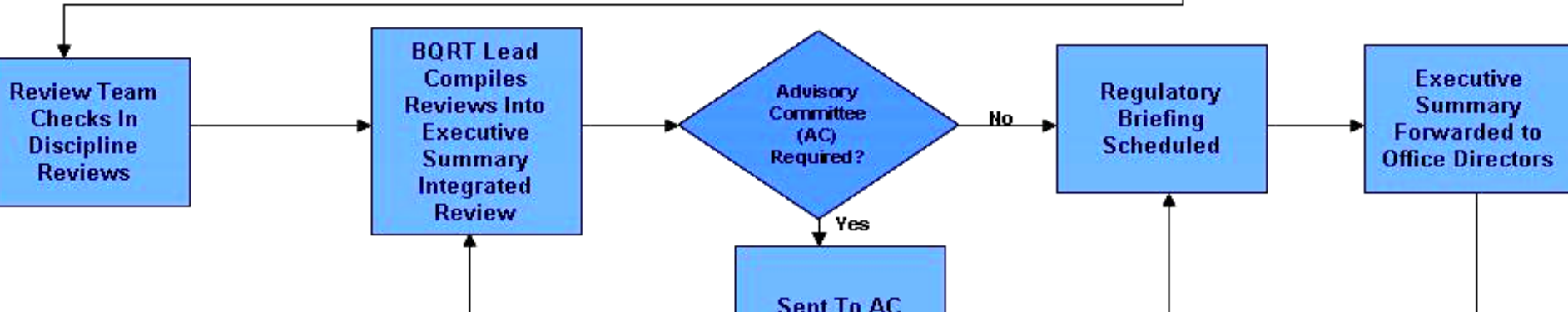
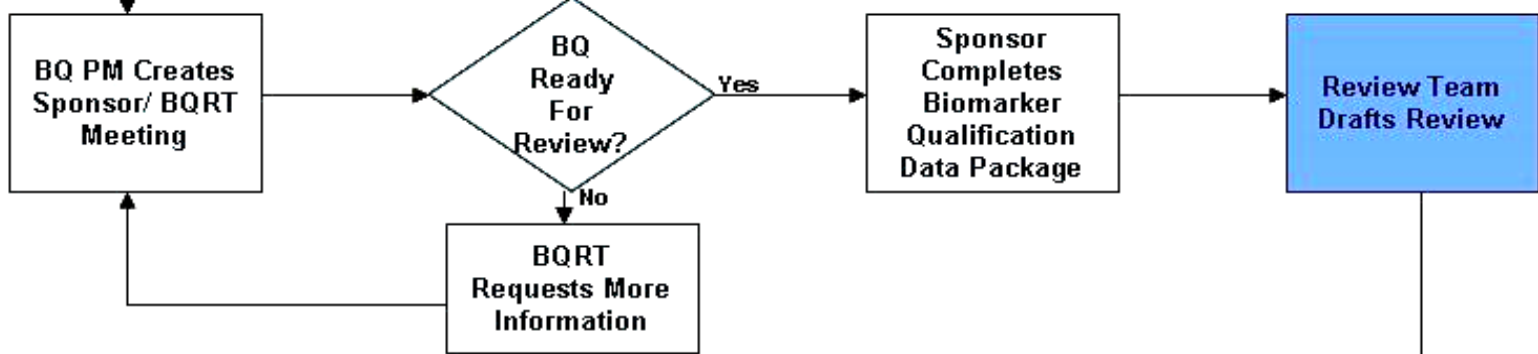


Which is the best path?

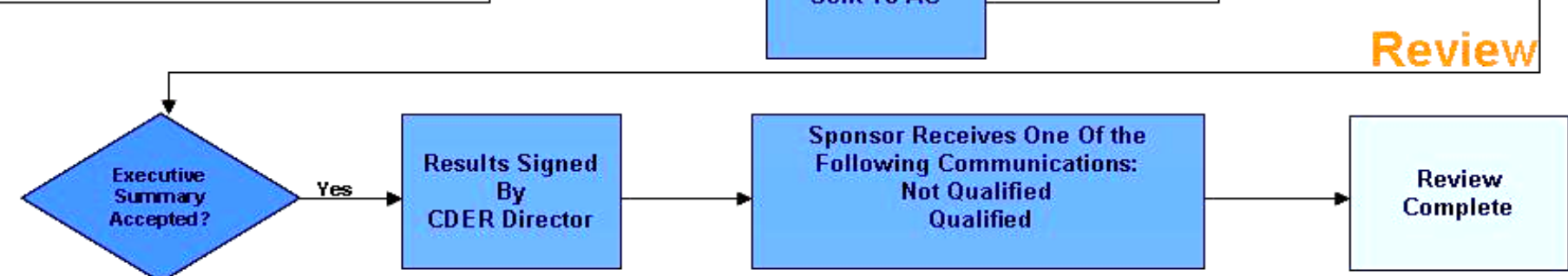
- **Biomarkers of nephrotoxicity**
 - **Qualified in the context in which they can be used to better interpret other nonclinical safety assessment results in regulatory submissions.**
 - **Context of use may be incrementally expanded in the future for clinical applications as qualification data become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



Consultation and Advice



Review



Biomarker Qualification Process Webpage at the FDA

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm>

Drugs

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Development & Approval Process (Drugs)

[Drug Development Tools Qualification Program](#)

[Animal Model Qualification Program](#)

[Biomarker Qualification Program](#)

[Clinical Outcome Assessment Qualification Program](#)

Resources for You

- [Biomarker Qualification Context of Use](#)
- [Biomarker Qualification Process](#)
- [Biomarker Qualification FAQ](#)
- [Biomarker Qualification Submissions](#)
- [Biomarker Qualification Templates](#)

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.

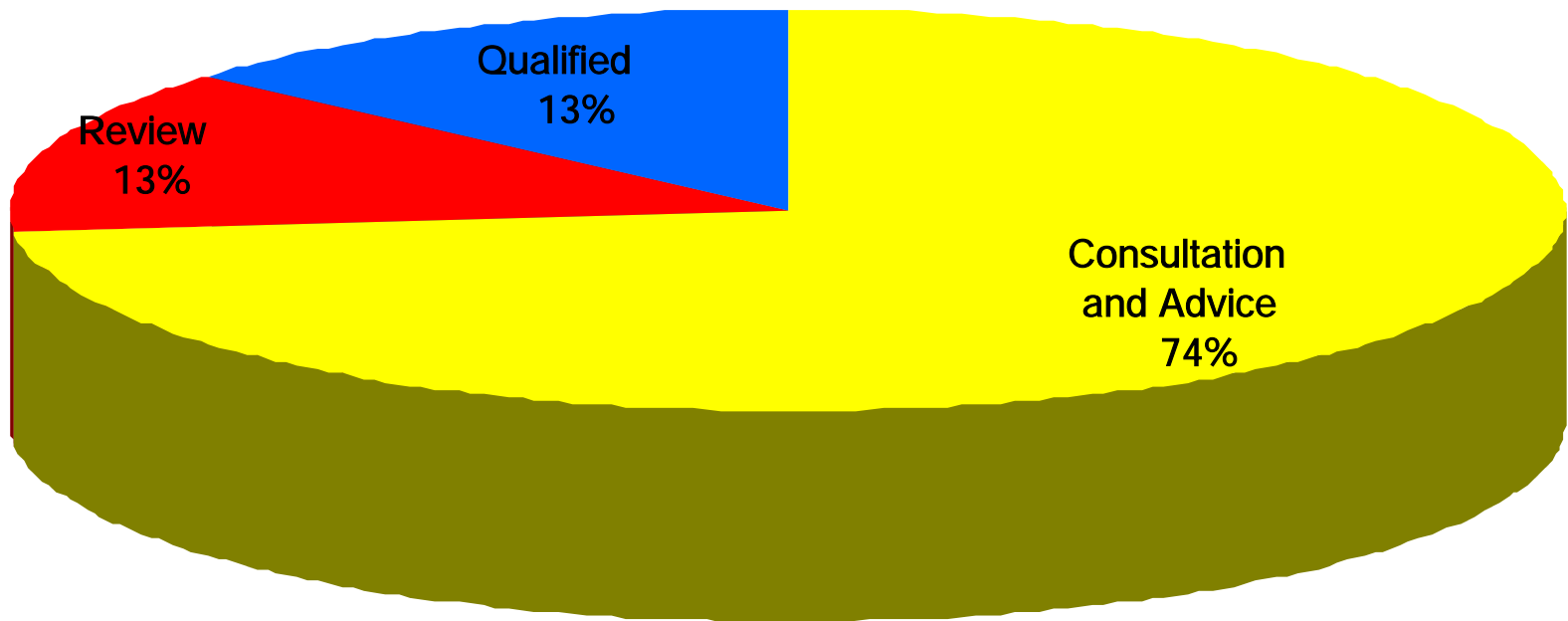
Qualified DDT:

DDT Type	Name	Submitter	Qualification Date	Link to Supporting Information
Biomarker	Seven Biomarkers of Drug-Induced Nephrotoxicity in Rats	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	4/14/2008	Predictive Safety Testing Consortium (PDF - 163KB)
Biomarker	Nonclinical Qualification of Urinary Biomarkers of Nephrotoxicity	International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	9/22/2010	HESI Nephrotoxicity Qualification (PDF - 234KB)

Total Biomarker Qualification Process Timeline Length at FDA

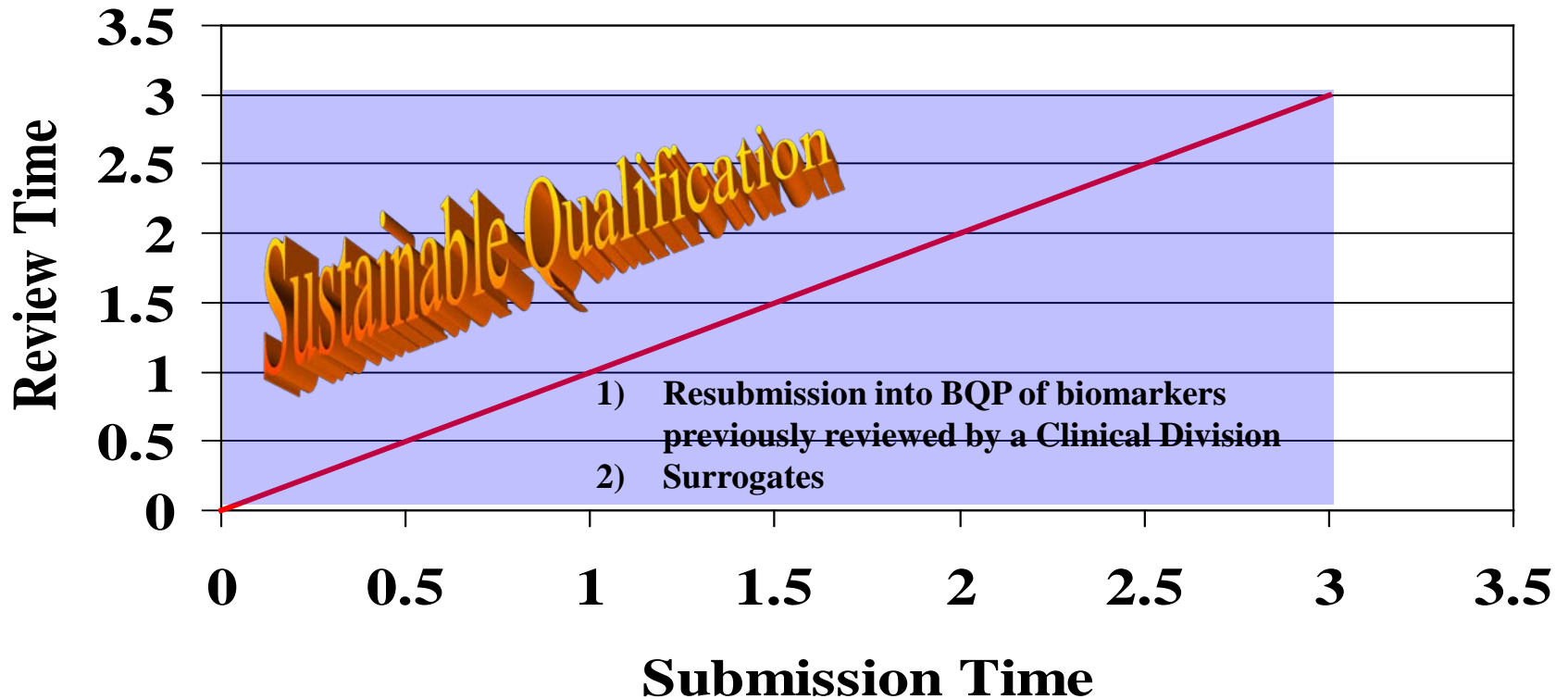
- **Time from submission to Center Director letter for initial 2007 PSTC Nephrotoxicity submission: 12 months.**
 - baseline of 3+ years
- **Process shares similar scheduling uncertainties with NDA reviews**
 - not yet at an equal level of review resource priorities as NDAs.

Distribution of submissions throughout the Biomarker Qualification Process at the FDA



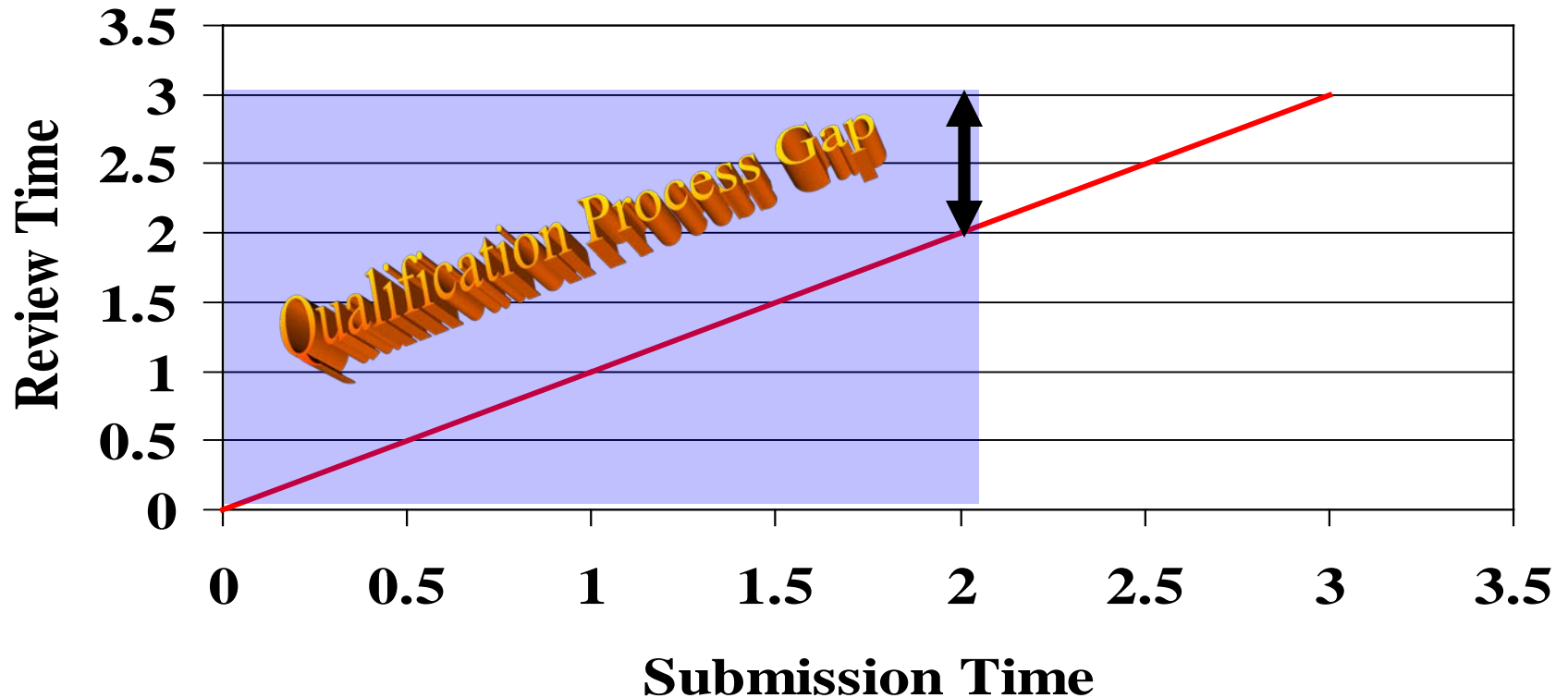
Challenges for a Biomarker Qualification Process

Timeline to Biomarker Qualification



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.**