BIOMARKERS RELATED TO DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT: CONTEXT, STRUCTURE AND FORMAT OF QUALIFICATION SUBMISSIONS. E16.

http://www.ich.org/LOB/media/MEDIA5518.pdf

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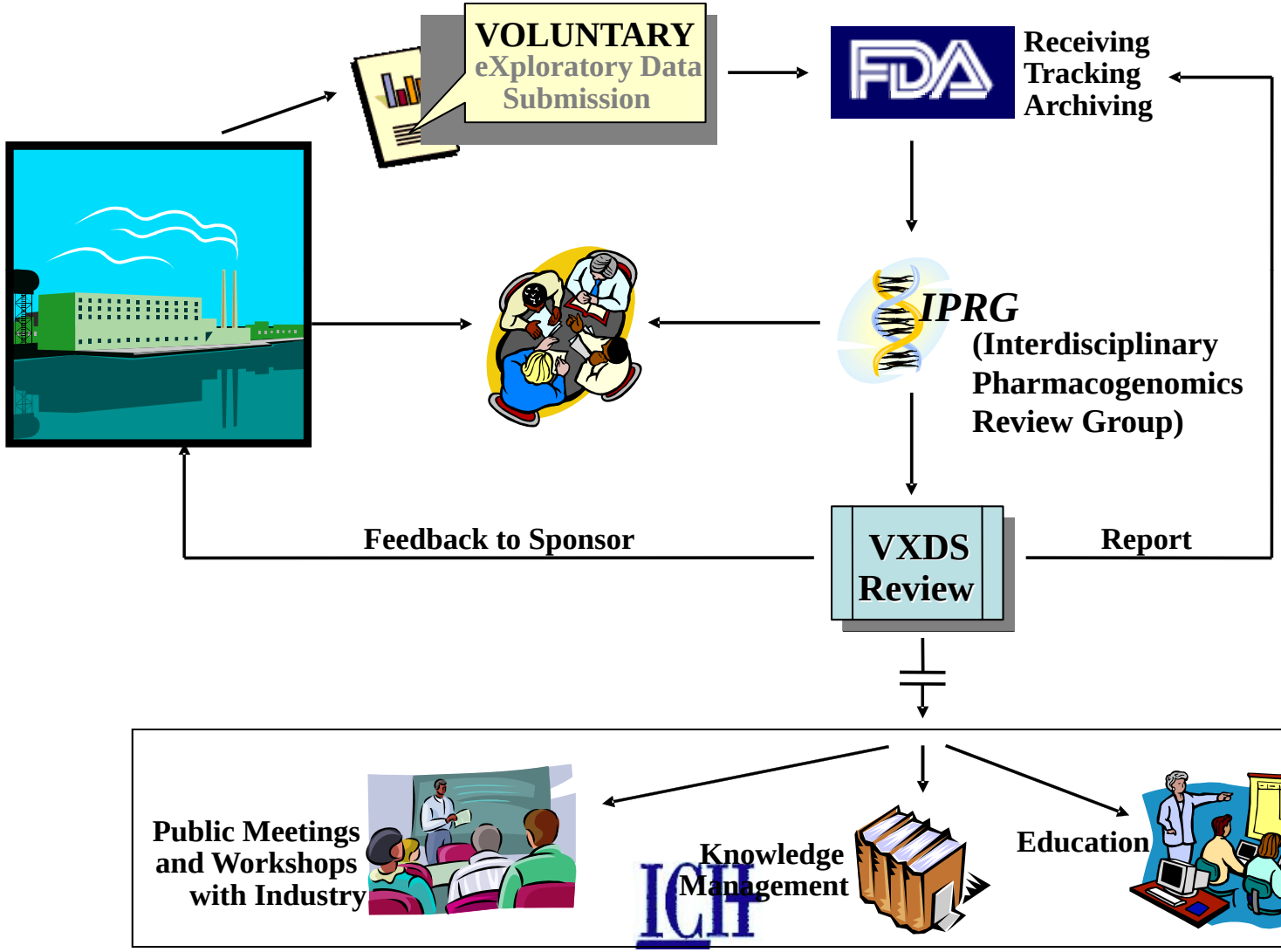
Voluntary eXploratory Data Submissions

Training reviewers in the analysis of exploratory biomarker data.
Training sponsors in the capabilities of our reviewers for the analysis and interpretation of biomarker data.



Exploratory Biomarkers
(VXDS Meetings)

A decision by a sponsor to reanalyze and submit data based on the availability of a newly qualified biomarker should be made in the context of other available nonclinical and clinical data.

Qualified Biomarkers
(Biomarker Qualification Process)

Regulatory Applications

…any additional data required to support qualification for regulatory use will be expected to depend on what data may already be publicly available, data that may lie within regulatory repositories, data that lie with individual sponsors, or data available from consortia and institutions.

How do exploratory biomarkers become qualified biomarkers?

- Evidentiary Standards
- Incremental Qualification Context
- Biomarker Qualification Process

Background for E16

- ICH guideline on genomic biomarkers (E15) 2007: http://www.ich.org/LOB/media/MEDIA3383.pdf
  - "Definitions of genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories"
- ICH E16 2008
  - First Meeting of E16 EWG: June 2008
  - Document for Consultation: June 2009
  - Step 4: August 2010

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Definition of Qualification in E16

- *…a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through post-approval.*

Objective of E16

- Create a harmonized recommended structure for biomarker qualification applications that will foster consistency of applications across regions and facilitate discussions with and among regulatory authorities.
- Reduce the burden on sponsors as a harmonized format will be recommended for use across all ICH regulatory regions.
- Facilitate incorporation of biomarker data into specific product-related applications.

Scope of E16

- Context, structure, and format of qualification submissions
  - clinical and nonclinical genomic biomarkers
  - development of drug or biotechnology products
    - Translational medicine approaches
    - Pharmacokinetics
    - Pharmacodynamics
    - Efficacy
    - Safety

E16 – General Content

- Focus on genomic biomarkers but principles are applicable to other biomarker categories.
- Submission for a combination of biomarkers (e.g., genomic together with non-genomic biomarkers) is also possible.
- Aim of guideline is to facilitate submission of a harmonized package for qualification of biomarkers.
- Not intended to establish global *evidentiary standards* or global *regulatory process* for biomarker qualification.
- Also provides general guidance for submission of biomarker data using CTD structure where applicable.

Data Descriptors in Biomarker Qualification

Context → Structure → Format

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General Principles in E16

- context of use
  - corresponds to the data supporting its qualification
  - clearly detailed in the submission package
  - specific use of the biomarker in drug or biotechnology product development
  - narrow or broad: the biomarker(s) might be useful for only a single drug or biotechnology product, or for several drug or biotechnology products in a drug class, or even across several drug classes.

- structure
  - consistent regardless of the context proposed
  - flexible enough to deal with the specific attributes of each submission
  - facilitate submission and review of future biomarker qualification submissions expanding the use of the biomarker to new contexts e.g., if a nonclinical context of use expands to a clinical context of use.

- format of the data
  - varies significantly depending on the context
  - only possible to provide general guidelines
  - should support an evaluation of the data and can include reports, tabulations, and raw data (if requested by regulatory authorities according to the relevant practices in place)
  - should be consistent with the methodology and platform used for analyzing the biomarker in question.
  - reference to standards and / or accepted methods used should be described as applicable.

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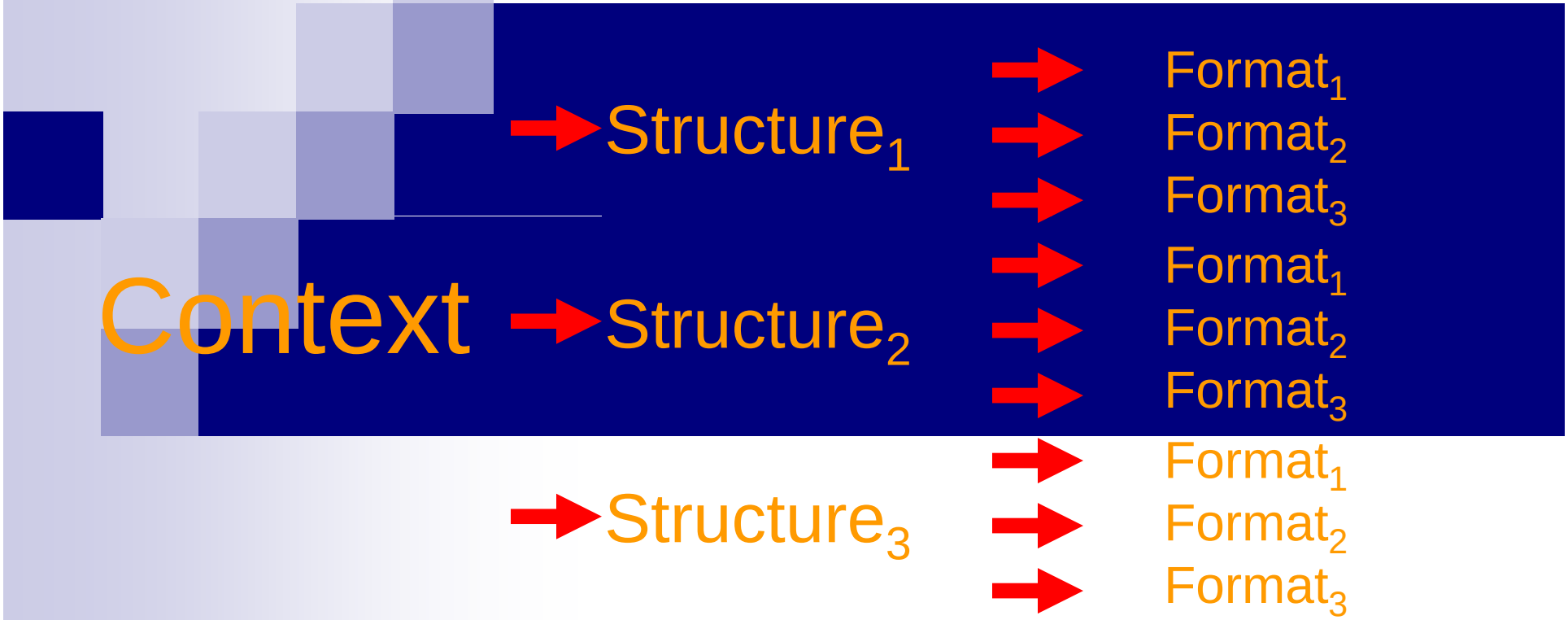
Data Descriptors in Biomarker Qualification



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Context

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Biomarker Qualification Context

- General Area
- Specific Biomarker Use
- Critical parameters which define when and how the biomarker should be used
- Limited to use in drug or biotechnology product development
  - A biomarker proposed for qualification would facilitate drug or biotechnology product development program(s) or drug or biotechnology product use.
  - Could offer an improvement over currently available biomarkers or safety or efficacy endpoint assessments.
- Supported by data available in the initial qualification dossier submission
  - If the reviewing authority identifies an inconsistency between the proposed context and the data, additional data can be provided during the qualification processes, if the authority agrees.

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Biomarker Qualification Context

- General Area (including, but not limited to)
  - Nonclinical / Clinical
    - Pharmacology
    - Toxicology
    - Efficacy
    - Safety
    - Disease

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Biomarker Qualification Context

- Specific Biomarker Use(s) Biomarkers can be used for a wide range of purposes, including, but not limited to, the following examples:
  - Patient / clinical trial subject selection
    - Inclusion / exclusion criteria
    - Trial enrichment or stratification
  - Assessment of disease state and / or prognosis
  - Assessment of mechanism of action
    - Mechanism of pharmacological mode of action
    - Mechanism of therapeutic effect
    - Mechanism of toxicity / adverse reaction
  - Dose optimization
    - No observed effect level (NOEL) in animal models
    - No observed adverse effect level (NOAEL) in animal models
    - Algorithm-based dose determination (quantitative algorithmic dosing)
    - Determination of likely dose range
  - Drug response monitoring
    - Monitoring drug safety
    - Monitoring drug efficacy
  - Efficacy maximization
    - Indicating / predicting drug efficacy
  - Toxicity/Adverse reactions minimization
    - Indicating / predicting toxicity / adverse reactions
    - Detecting / monitoring onset / reversibility of toxicity / adverse reactions

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Biomarker Qualification Context

- Critical Parameters of Context of Use (including, but not limited to)
  - Drug or biotechnology product-specific use/ drug class-specific use / use not linked to specific drug or biotechnology products or drug classes
  - Disease diagnosis and phenotypes, prognosis, or stage
  - Sample collection
  - Assay specifications
  - Tissue or physiological / pathological process
  - Species
  - Demographics, including ancestry and / or geographic origin
  - Environmental factors

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Biomarker Qualification Context: Examples

- Nonclinical Safety
  - Messenger RNA levels of kidney injury molecule 1 (Kim-1) and clusterin (Clu) can be included as genomic biomarkers of drug or biotechnology-induced acute renal tubular toxicity in rat toxicology studies. The context of the submission in the biomarker qualification application would be defined as follows:
    - General Area: Nonclinical safety and toxicology
    - Specific Biomarker Use: assessment of mechanism of toxicity and dose optimization (NOAEL) in animal models
    - Critical Parameters of Context of Use:
      - Drug or biotechnology product-specific use: no
      - Assay specifications: mRNA
      - Tissue or physiological / pathological process addressed: kidney
      - Species: *Rattus norvegicus*

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Biomarker Qualification Context: Examples

- Clinical Pharmacology / Drug Metabolism
  - CYP2C9 genetic polymorphism produces poor metabolizer (PM) and extensive metabolizer phenotypes and differences in drug A exposure. Plasma levels of Drug A in patients / clinical trial subjects who are known to be CYP2C9 PMs are increased due to reduced metabolic clearance. Context of the submission in the biomarker qualification application would be defined as follows:
    - General Area: Clinical Pharmacology / Drug Metabolism and Safety
    - Specific Biomarker Use: patient / clinical trial subject selection (inclusion / exclusion criteria, trial enrichment or stratification), dose optimization in individual patients and predicting adverse reactions / risk minimization
    - Critical Parameters of Context of Use:
      - Drug or biotechnology product-specific use: Drug A
      - Assay specifications: Genotyping
      - Species: *Homo sapiens*
      - Demographics including ancestry and / or geography: population-specific allele frequency

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Biomarker Qualification Context: Examples

- Clinical Safety
  - The HLA-B*1502 allele is associated with an increased risk of the development of Stevens-Johnson Syndrome following administration of Drug B in Han-Chinese.
    - General Area: clinical safety.
    - Specific Biomarker Use: patient selection (inclusion / exclusion criteria), predicted safety and mechanism of adverse reaction / toxicity
    - Critical Parameters for Context of Use:
      - Drug or biotechnology product-specific use: Drug B
      - Assay specifications: Genotyping
      - Species: *Homo sapiens*
      - Demographics including ancestry and / or geographic origin: Han-Chinese

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Structure

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Structure of Biomarker Qualification Submissions in the ICHE16 Step 4 Document

http://www.ich.org/LOB/media/MEDIA5518.pdf

- Regional Administrative Information
  - Documents specific to each region
    - application forms
    - cover letter
- Summaries
  - Introduction
  - Context
    - general area
    - specific biomarker use
    - critical parameters which define when and how the biomarker should be used
  - Methodology and results
  - Conclusion

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Structure of Biomarker Qualification Submissions in the ICHE16 Step 4 Document

http://www.ich.org/LOB/media/MEDIA5518.pdf

- Data Summaries
  - Overall approach
  - Criteria for sample suitability
  - Analytical performance characteristics
  - Results supporting context of use
  - Individual study synopses
- Quality
  - Drug quality and manufacturing data.
  - Not included in a biomarker qualification submission independent from an NDA, BLA or MAA.
- Non-clinical and Clinical Study Reports
  - Full study reports for biomarker qualification
    - raw data could be made available to the regulatory agency upon request.
    - information on compliance with Good Laboratory Practices (GLP) or Good Clinical Practices (GCP)
  - Where appropriate, the study reports can follow relevant ICH guidelines (e.g., E3, M4E, M4S) for their preparation.

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Examples of Biomarker Qualification Structure

- Study Design
- Nonclinical and Clinical Correlates
  - Individual animal or patient data.
  - Measurements for primary endpoints.
  - Measurements for other nonclinical or clinical tests.
- Sample Isolation
- Nucleic Acid Purification
- Microarray Hybridizations
- Microarray Reads
- Data Normalization
- Data Analyses
- Biological Pathway Analyses

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Format

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Examples of Biomarker Qualification Formats

- Tab-delimited files
  - Needed for spreadsheets showing microarray data.
  - Needed for spreadsheets showing individual animal or patient data.
- Text files
  - pdf
  - doc
  - others

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How do we qualify biomarkers today at the FDA?

- Case-by-case. Context of use *always* drug-dependent.
- Codevelopment of drug and test.
- Labeling Updates (for example, warfarin).
- Biomarker Qualification Process
  - *Do we need it?*

Biomarker data in regulatory submissions.

- Case-by-case. Context of use *always* drug-dependent.
  - Difficult to generate comprehensive qualification for a biomarker across multiple drugs.
  - Difficult to qualify safety biomarkers.
- Codevelopment of drug and test.
  - Limited to cases where the combination makes therapeutic and financial sense.
  - Difficult to get to a qualified biomarker status, because qualification data submitted for approval are usually from only one company.
- Labeling Updates.
  - Step-by-step process to improve therapeutic value of existing drugs.
  - Variable impact on standard of practice.
- Biomarker Qualification Process
  - Qualification across multiple drugs.
  - Focus on consensus leading to qualification.
  - Initial impact focused on drug development and regulatory review: impact on clinical practice will depend on expansion of original biomarker application context submitted for qualification.

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What about the firewall?

- Is it OK to provide advice to a sponsor on study designs throughout the qualification process?
- Do we have precedents for these?

Open Issues in Harmonization

- Process
- Evidentiary Standards
- Framework for joint submissions and review