

Overview and Update on ICH Genomic Biomarker Guidelines E15 and E16

Lois Hinman, E16 Rapportuer, PhRMA
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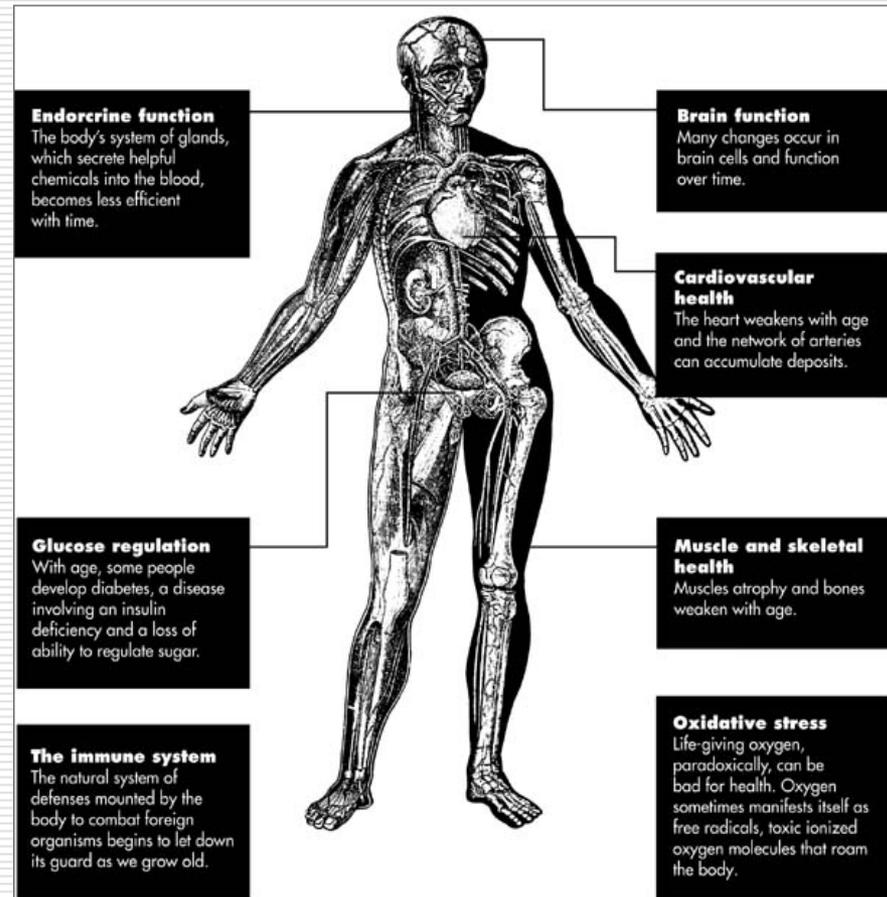
Today's Talk

- Why harmonize guidance in this field?
 - Need for harmonized terms/process
 - Goals and accomplishments of E15
 - Genomic Terminology –Step 4 Fall 2006
 - Objectives and Progress with E16
 - Biomarker Qualification: Context, Format and Data Standards
 - Where do we go from here?
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Biomarkers: Increasingly Important in Drug Development

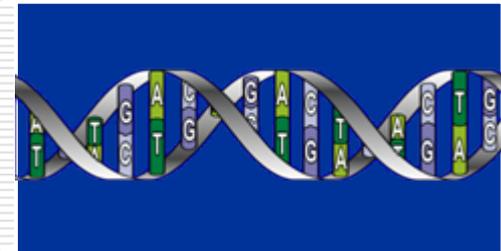
Biomarker: A characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or a pharmacological response to a therapeutic intervention*

- Used in clinical practice to:
 - identify risk for disease
 - make a diagnosis
 - assess severity
 - identify the organs involved
 - guide treatment



Scientific advances being made globally in drug and disease specific biomarkers with genomic biomarkers leading the way.

- **A Genomic Biomarker** is a measurable DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes and/or response to therapeutic intervention.
- Progress with techniques to measure specificity, sensitivity, and reproducibility of genomic biomarkers to qualify them for regulatory purposes is being made in all regions.
- Keep in Mind: Personalized medicine approaches based on genomic biomarkers are generally applicable to other “omics” as well.
 - Metabolomics, Proteomics, etc.



Why Harmonize Guidance?

- Both industry and regulators see biomarkers as playing an important role in drug development in the future.
 - Many studies being carried out with results that have global implications.
 - Pathways for regulatory decision making are developed independently in different regions
 - Regional specific guidances being developed
 - Inconsistent definitions make it difficult to achieve agreement on parameters for implementation of genomics in global pharmaceutical development
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First ICH Guideline on- Genomic Biomarkers: E15 – Step 4: Nov 2006

- E15: “Definitions of genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories”

 - Objective of E15
 - Timely harmonization of terminology, definitions and review process to create a common foundation upon which future guidance can be built.
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E15: Pharmacogenetics/Pharmacogenomics Terminology

- Established definitions:
 - Genomic Biomarkers
 - Pharmacogenomics
 - Pharmacogenetics

 - *Not* addressed:
 - Processes of validation or qualification
 - Evidence to validate or qualify genomic biomarkers for their intended use
 - Criteria for mutual acceptance of genomic biomarkers across regions
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E15 – Part 2:

- Definitions for Sample and Data Coding for PGx Studies
 - Define benefits and limitations of specific coding procedures
 - Agreed upon categories
 - 1. Identified
 - 2. Coded
 - 1. Single coded
 - 2. Double coded
 - 3. Anonymized
 - 3. Anonymous
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Why are Coding Procedures Important?

- Link between subject identity and genomic data
 - Extent of privacy protection
 - Actions possible
 - Sample withdrawal
 - Return of individual results
 - Clinical monitoring and follow-up
 - Data verification from GCP perspective
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E15 - Coding Summary Table

Category		Link Between Subject Identity and Genomic Data	Actions Possible if subject withdraws Consent	Return of Individual Results	Extent of Subject's Privacy protection	Patient's clinical monitoring and follow-up	Data verification from GCP perspective
Identified		Yes	Sample can be withdrawn	Possible	General healthcare confidentiality	Possible	Yes
Coded	<i>Single Coded</i>	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	<i>Double Coded</i>	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	<i>Anonymized^[1]</i>	None	None	Not possible	No potential to link genomic data to subject through key code(s)	Not possible	<i>Yes [with caveats to be checked with GCP inspectors]</i>
Anonymous		None	None	Not possible	No potential for links to genomic data	Not possible	No

^[1] Prior to anonymisation the handling of the samples and data is the same as for coded

E16 – Second Genomic Biomarker Topic, Adopted by ICH SC April, 2008

- **The Need:** there are no global standards or guidance on what and when to submit genomic biomarker data and what is expected in terms of the structure and format of the submissions.
 - Recent cases with global implications on regulatory decision making
 - Examples in both efficacy and safety markers
 - Herceptin active in Her-2 positive patients
 - CYP29 variants and implications for COX-2 inhibitor safety and warfarin dosing
 - HLA-B*1502 is a clear genetic marker for carbamazepine induced SJS.
 - *not necessary to make the same conclusion/label - but at least look at the same data, in the same way.*
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Aim of E16

- To harmonise the **structure** and **format** of submissions for genomic biomarker qualification with the understanding that this will facilitate discussion within and across regions.
 - This is in the spirit of previous successful ICH experience with the harmonized CTD.
 - This guideline will not address evidentiary standards
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First Meeting of E16 Expert Working - Portland (June 2008)

- Agreements from first meeting
 - Key Elements of Guideline
 - Context
 - Structure
 - Format
 - Guideline will elaborate on the concept of context and intended use, which will drive specifics of structural elements and formats.
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EWG Work Plan – June to Nov 2008

- 2 work streams identified to work on
 - Context and Structure/Format
 - Each group has met several times
 - Webinar – full team July, Sept and Oct discuss progress from subteams
 - Writing Group formed Sept 08 to draft outline for discussion in Brussels
 - Aim for finalization of step 1 document Brussels 08
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Structure of Biomarker Submission (under discussion): Analogy to CTD Structure

A. Introduction section of the guideline

1 Objective

2 Scope

B. Guideline content

Section 1 *Analogy to CTD Module 1*: Regional administrative details

Section 2 *Analogy to CTD Module 2*:

Overall summary and Context of proposed (pre)clinical biomarker(s)-safety/efficacy, pharm/tox, intended use: predict response, tec.

Methodology and results (summaries and tabulations) – format recommended.

Section 3 *Analogy to CTD Module 4/5*:

Table of content

Study reports (and raw data)

References

C. Appendixes to the guideline (case studies to provide examples of BM context)

Next Steps

- Reach Step 1 for E16 – Nov. 2008
 - Aim for Step 2 in Spring '09 & Step 4 in 2010
 - A few thoughts on where to go next:
 - Field is advancing quickly – regulatory decisions mostly on a case by case basis.
 - Harmonized Guidance on Biomarker Qualification - framework being developed through private/public partnerships
 - Guidance on Co-development ? (important for companion products)
 - Expand from Genomics Biomarker to other “omics” – when and how ?
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ICH E16 Expert Working Group

Industry:

PhRMA

- ❑ Lois Hinman, Novartis, (rapporteur)
- ❑ Amelia Warner, Schering Plough

EFPIA

- ❑ Duncan McHale, Astra Zenaca
- ❑ Klaus Lindpainter, Roche

JPMA

- ❑ Sanae Yasuda, Esai
- ❑ Yosuhiko Imai, Bristol Myers KK
- ❑ Tomoko Ichihara, Chugai
- ❑ Makoto Suzuki, Pfizer

FDA:

Federico Goodsaid & Lawrence Lesko
(CDER)
Jennifer Catalano Raj Puri (CBER)

EMA:

Marisa Papuluca-Amati and Guiseppe
Novelli

MHLW:

Yoshodai Uyama, Akihuro Ishigura,
Katsuhiko Mishime

Observers:

Agnes Klein-Canada, Margaretha
Bindshedeler-Switzerland, Lambit
Rago-WHO;

Back ups

Definitions from E15

- **A genomic biomarker is defined as a DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other intervention.**
 - **Pharmacogenomics (PGx) is defined as the investigation of variations of DNA and RNA characteristics as related to drug response.**
 - **Pharmacogenetics (PGt) is a subset of PGx and is defined as the influence of variations in DNA sequence on drug response.**
 - PGx and PGt are applicable to activities such as drug discovery, drug development, and clinical practice.
 - Drug response includes drug disposition (PK) and drug effect (PD).
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Biomarker Context

Level 1

Non-Clinical

Clinical

Level 2

Pharmacology

Toxicology

Efficacy

Safety

Level 3

Non-comprehensive list

Response prediction
Mechanism of effect
Dose optimization
Response monitoring
Toxicity detection
Patient selection

Proposed structure of the BM qualification dossier

Executive Summary

- i. The objectives of your request
- ii. The need and impact of proposed biomarker(s)
- iii. Briefly summarize sources of Data and Major Findings
- iv. If applicable present remaining gaps and a brief overview of how these will be addressed
- v. Conclusion

1. Statement of need and impact of proposed preclinical biomarker(s)

- a) Background information on the disease/setting associated with the biomarker(s):
- b) Background information on the currently available tools
- c) Background information on the proposed biomarker(s)
- d) Intended application of the biomarker(s)

2. Objectives (detailed intended purpose/claim and scientific rationale for it)

3. Methodology and Results.

- a) Evidence from primary data
- b) Evidence from published literature (including metadata)

4. (As applicable) Future studies and methods for further method development towards qualification

5. Conclusions

6. References and Appendixes

Proposed timelines E16

- Step 1 signoff – Brussels 08
 - Report progress to ICH SC Spring 09
 - Step 2 document sign off 2009
 - Step 4 sign off 2010
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