EFFICACY TOPICS

Public ICH meeting - Brussels

14th November 2008

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Topics

- Biomarkers: E15 and E16
- Overview of other ongoing ICH efficacy topics:
  - Update on E2F: development Safety Update Reports
  - E14: Question and Answer document: what's next?
  - E7: Update and next steps

Overview and Update on ICH Genomic Biomarker Guidelines E15 and E16

Lois Hinman, E16 Rapporteur, PhRMA

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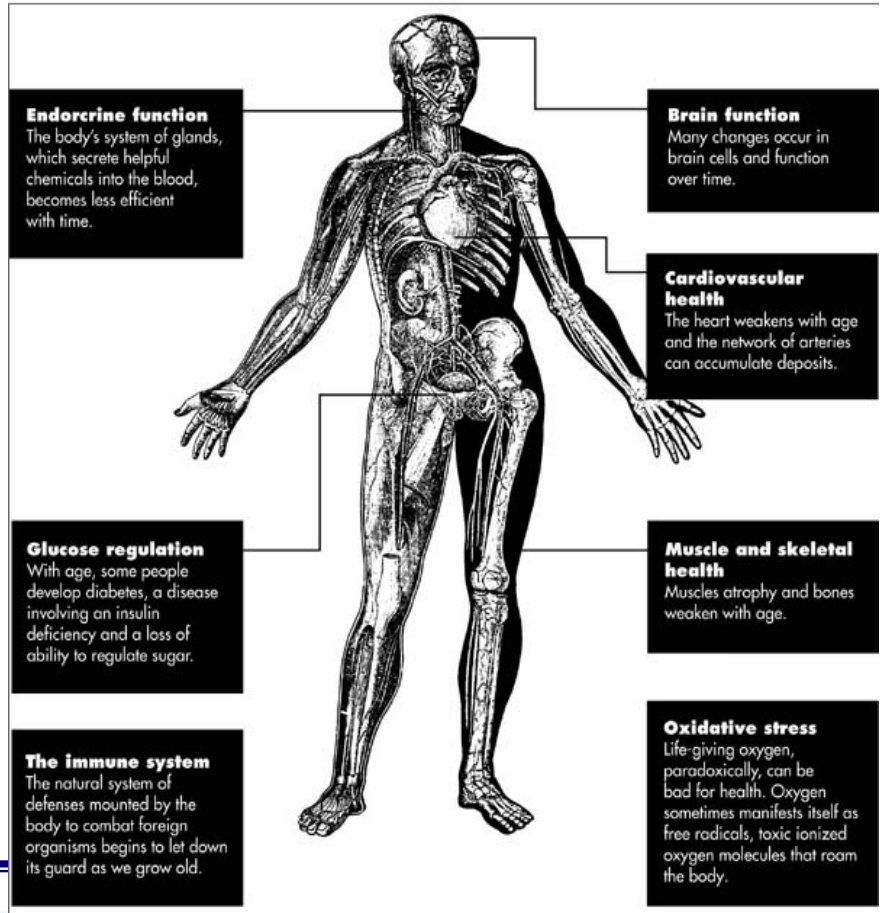
Today's Talk

- 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: Format and Data Standards

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



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*J Clin Pharmacol Therapeut 2001; 69:89-95

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.
- Personalized medicine approaches based on genomic biomarkers are generally applicable to other “omics” as well.
  - Metabolomics, Proteomics, etc.

Why Harmonize Guidance?

- Academia, 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
  - Inconsistent definitions make it difficult to achieve agreement on parameters for implementation of genomics in global pharmaceutical development, and might lead to inconsistent assessments by regulators.

First ICH Guideline on- Genomic Biomarkers: E15

- E15– reached Step 4 sign-off Yokohama, 2007
  - "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.

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

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

Draft 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	***Single Coded***	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	Double Coded	Yes	Sample can be withdrawn	Possible	General healthcare confidentiality + GCP requirements for clinical research	Possible	Yes
	Anonymzed[1]	None	None	Not possible	No potential to link genomic data to subject through key code(s)	Not possible	*Yes [with caveats to be checked with GCP inspectors]*
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

- Recent cases with global implications show a need to harmonize data to be reviewed
  - Examples in both safety and efficacy 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 necessarily for the same conclusion - but at least to look at the same data, presented in the same way.
- Currently, 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.

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.

E16 – General Principles

- The guideline will describe the context, structure and format of regulatory submissions for genomic biomarker qualification
- Aim of guideline is to facilitate submission and review of biomarker qualification data among regions
  - Not to establish global *evidentiary standards* or global *regulatory process* for biomarker qualification
- Focus on genomic biomarkers but principles are applicable to other biomarker categories
- Overall structure will facilitate incorporation of biomarker data into product-related regulatory filing
  - General principles of CTD structure retained

EWG Work Progress: June to Nov 2008

- 2 work streams identified to work on
  - context
  - structure and format
- Full Team Web Conferences:
  - July 08 to discuss initial contributions of work streams
  - Sept 08 to agree on key elements of a preliminary step 1 document, establish a writing team.
- Writing Team prepared first draft for discussion and finalization of step 1 document Brussels 08

Key Elements of Guideline

Part I. Introduction

- Objective of Guideline
- Background
- Scope of the Guideline
- General Principles

Part II. Structure of Genomic Biomarker Qualification Submissions

Appendix to Guideline:

- Examples of biomarker context

Part II: Structure of Biomarker Qualification Submissions: Organizational Analogy to CTD

- Section 1: Regional Administrative Information
- Section 2: Overview
  - Introduction
  - Context
  - Methodology and Results
    - Integrated Summary
    - Individual Study Report Synopses
- Section 3: Study Reports
  - General principles
  - Specific recommendations for reports containing genomic data
- Section 4: Other Supportive Documents and References

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Next Steps for E16

- Step 1 Draft – Brussels 08
- Collect and consolidate preliminary comments on Step 1 Guideline - by March 2009
- Notify other interest groups
- Report progress to ICH SC Spring 09
- Prepare Step 2 document in Yokohama, June 2009 for public consultation.
- Propose Step 4 sign off 2010

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ICH E2F Development Safety Update Reports

Spiros Vamvakas

EMEA Technical Coordinator for ICH

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Public consultation

- Deadline in December 2008
- Monthly teleconferences since August, 2008 to discuss model reports for both commercial and non-commercial sponsors
- The EWG considers breaking up into smaller groups to discuss the comments and prepare answers before coming back to the guideline

Communication plan

- DIA webinar (already delivered)
- Article in Pharmaceutical Medicine (planned)
- Session at 45th Annual DIA meeting
- Series of presentations at various meetings
- In the EU, the guideline was distributed to
  - representatives of Ethics Committees to actively solicit their feedback
  - the EMEA Working Group with Healthcare Professionals Organisations

Timetable

- January 2009 – process the comments
- During 2009 work on the step 4 document
- Based on the comments received, the finalisation may be 2009 - 2010

ICH E14 QT prolongation Q&A document

Solange Rohou - EFPIA IWG

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Background information

- **Guideline (step 4) approved in May 2005**
  - Implemented in EU (Nov.05) and in the US
  - Implementation still pending in Japan
  - http://www.emea.europa.eu/pdfs/human/ich/000204en.pdf
- **ICH E14 Q&A document initiated in 2005**
  - 11 questions - 7 answered, 4 were duplicates or considered inappropriate
  - Recently finalised in June 2008
  - http://www.emea.europa.eu/pdfs/human/ich/31013308en.pdf

NEXT STEPS FOR IWG

- Rapid progress in this scientific domain has been acknowledged
- To have regular TCs to discuss the need to address outstanding questions; endorsed last June by the ICH Steering Committee
- Two new Questions are currently under assessment

ICH E7 Elderly Q&A document

Status November 2008

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Current status

- Discussion have started to update the existing guideline (June 1993 – Step 5)
  - http://www.emea.europa.eu/pdfs/human/ich/037995en.pdf
- Focus is on
  - Optimising number of expected elderly participants in a given indication
  - Charactering the safety profile, as part of RMP and PMS
- Concept Paper recently endorsed by the ICH Steering Committee

Timetable

- Establishment of an Implementation Working Group to create a Q&A document
- Q&A should be discussed in 2 face-to-face meetings
- Discussion of the draft would require one year timeframe

QUESTIONS?