ICH

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

Final Concept Paper
E16: Genomic Biomarkers Related to Drug Response:
Context, Structure and Format of Qualification Submissions[*]
17 April 2008
Endorsed by the Steering Committee on 11 April 2008[**]

Type of Harmonization Action Proposed

This concept paper supports a proposal for a new harmonized ICH guideline on important aspects for the qualification of PG biomarkers. In particular, this new guideline will provide recommendations on the collection of data to support the qualification of PG biomarkers, including

- how to define the qualification context and the claims for intended use,
- standard methods for data collection,
- formats for submission of data to regulatory authorities.

Statement of Perceived Problem

ICH E15 harmonized on terminology for pharmacogenomics and pharmacogenetics, sample and data coding and PG biomarkers[1], thereby setting the stage for harmonization on the use of such data in drug development and regulatory settings. One important issue when using PG biomarkers[2] is understanding the types of data that can support the qualification of PG biomarkers and how such data should be collected and reported to regulatory authorities. Formal recommendations in this area are not available, despite the dramatic rise in exploratory PG research in drug development and submissions to regulatory agencies. Also, different formats of PG data being submitted to regulatory agencies in different ICH regions have made it difficult for regulatory agencies to have discussions between them about qualifying biomarkers for an intended use. The ability to do so is of extreme importance to the industry involved with global drug development. Through the ICH process, harmonized recommendations on these issues can be provided that could be of use to facilitate global medical product development.

Issues to be Resolved

The FDA, EMEA/CHMP, and MHLW individually and together have started to review submissions for qualification of PG biomarkers for specific purposes proposed by industry. However, there are no harmonized recommendations on the collection of data to support the qualification of PG biomarkers, including recommendations on the types of data submissions

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[*] In June 2008, the E16 name was changed from "Pharmaco Genomic (PG) Biomarker Qualification : Format and data standards" to "Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions".

[**] Endorsed by the Steering Committee on 11 April 2008, subject to amendments which have been included in this version dated 17 April 2008.

[1] http://www.fda.gov/cder/guidance/7619dft.htm

[2] A PG biomarker is defined as a measurable DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other intervention.

that might support qualification, standard methods for their collection, and recommended formats for submission of data to regulatory authorities. By achieving harmonization before regional, domestic guidances or polices are established, we have the opportunity to facilitate the incorporation of novel PG biomarkers into the development and regulation of new medical products.

Background to the Proposal

Based on the deliberations of the E15 expert working group, common ground and mutual interest between industry and regulatory authorities in the three major ICH regions have been established to harmonize on key issues in pharmacogenomics. A crucial and timely opportunity exists now for companies and regulatory agencies to advance this field around the world by providing recommendations on the collection of data to support the qualification of PG biomarkers, including recommendations on the types of data that might support qualification, recommendations on standard methods for their collection, and recommended formats for submission of data to regulatory authorities. Such harmonized recommendations would assist in the simultaneous development and regulatory appraisal of the use of PG biomarkers in decision-making and reduce uncertainty from the industry viewpoint.

There are three considerations for qualifying a PG biomarker for a specific purpose:

(1) the types of data defining the R&D context and the specific use;
(2) the scientific standards and formats for data submission needed to assist in timely submissions and efficient reviews; and
(3) the regulatory standards applied to analyze and qualify PG biomarkers.

Before the last consideration can be addressed, more experience in the qualification of biomarkers is needed worldwide, and therefore this would not be the focus of the proposed document, but possibly a later initiative.

ICH E-15, by design, focused on definitions for PG biomarkers, pharmacogenomics, pharmacogenetics, and PG data and sample coding categories. ICH E-15 therefore intended to establish a starting point that would serve as the basis for these types of markers to become integral to medicinal products development. The present proposal is to develop a new ICH guidance discussing recommended standards and formats for submission of data to regulatory authorities. There are increasing numbers of PG biomarkers and many potential applications for these markers in medical product development and regulatory decision-making.

We propose that the scope for an Expert Working Group would be on the harmonization of recommendations on types of data to be collected and on format and standards of PG biomarker data submissions to regulatory authorities.

The work of the group would include a general discussion about the extent and nature of clinical biological rationale (causal basis) that would support "fitness for purpose", and considerations of best practices for biomarker qualification such as analytical and clinical validation procedures, and principles for clinical utility.

There are two broad classes of PG biomarkers: those associated with the development of a specific drug (e.g. PG biomarkers used to support dosing decisions, to select targeted therapies, etc.) and PG biomarkers associated with e.g. disease states, disease progression,

physiological changes or risk of toxicity, etc. It is felt that to facilitate the development of a harmonized qualification process, the Expert Working Group would select a number of well-established and scientifically accepted PG biomarker examples in each class that would serve as case studies. An example would be a cytochrome P450 enzyme such as CYP2C9. These examples would serve to create easy templates and to describe scientific standards that would represent common ground for harmonization of PG biomarkers data submission in various other, more complex settings. The advantage of using examples to illustrate the qualification process, format and content is that details are more easily communicated as opposed to describing general concepts that may not translate well between regions.

It is important to also stipulate what is not in the scope of this new proposal. Issues that **will not** be addressed in the proposed guideline include:

- The regulatory process to be applied to accept PG biomarkers (e.g., for use as diagnostic tests);
- Use of qualified PG biomarkers in Marketing Authorization regulatory decisions (e.g., use as surrogates for clinical efficacy);
- Qualification and content/format for submission of non-PG biomarkers.

Relevant Experience in the ICH Regions

Since 2004, the FDA has reviewed approximately 40 voluntary PG data submissions (VGDS) which often contain PG biomarker data. Through this process considerable experience has been gained with respect to the submission format and content, as well as the analysis of such biomarker data. Furthermore, many of these submissions either directly or indirectly addressed the issue of PG biomarker qualification.

Similarly, in Europe the EMEA has held more than 20 meetings of a similar type with industry. In Japan, the PMDA has recently formed a Pharmacogenomics Discussion Group to accomplish the same tasks. The latter group has held approximately 10 informal meetings with industry sponsors on the use of PG information in the context of conducting clinical trials in Japan. Thus, the experience in the areas of pharmacogenomics proposed for harmonization in this concept paper is considerable between all ICH regions.

In addition, FDA and EMEA have held four bilateral VGDS/briefing meetings so far. The last joint meeting was held in July 2007 (with the participation of PMDA as an observer) and it specifically addressed the qualification of safety biomarkers. These data were jointly reviewed by the FDA and EMEA. Thus, there is groundwork established in inter-region communication to lead us into new harmonization efforts for an ICH Expert Working Group on PG biomarkers.

Type of Expert Working Group

It is proposed that an ICH Expert Working Group be established and mandated to draft an ICH guideline on PG Biomarker Qualification, Content and Format of a Submission. The new group could consist of all or many of the same members as in the E15 Working Group.

Timing

Approval of Concept Paper by Steering Committee	April 2008
First EWG Meeting –	June 2008 (Portland)
Second EWG Meeting –	November 2008 (Brussels)
Third (Virtual) EWG Meeting –	Spring 2009
Fourth EWG Meeting-	June 2009 (Yokohama)
Adoption of Step 2 document-	Fall 2009