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Conference Report

AAPS Workshop on Designing the Global Chemistry, Manufacturing, and Controls (CMC) Dossier

The AAPS Workshop on Designing the Global Chemistry, Manufacturing, and Controls (CMC) Dossier was held September 14-15 in Bethesda, Maryland. The objectives of the day and a half workshop were to: 1) gain a better understanding of the various formats currently being used for the presentation of CMC information in the US, Canada, and Europe; 2) explore the importance to both industry and regulatory agencies of having a standardized format; 3) explore ways of minimizing duplication of effort in the preparation of various CMC dossiers for worldwide distribution; and 4) propose a design for a global CMC dossier.

The workshop was divided into three sessions. The first session explored the current CMC requirements in the European Union (EU), Canada, and the US and the need and/or desire for a common format from the perspective of both the regulatory agencies and the industry. The second session proposed a format for a global CMC dossier, the Basic International Registration Dossier, or B.I.R.D. This was followed by an extended breakout session for participants to discuss the proposed format. The third session updated the audience on several projects to computerize submissions and then provided a review of the changes to the global CMC format recommended by the breakout groups.

The workshop opened with remarks from representatives of the regulatory agencies of the US, Canada, and the European Union. Roger Williams, M.D., Deputy Director-designate for Pharmaceutical Sciences of the Food and Drug Administration, began by summarizing imminent changes in the Center for Drug Evaluation and Research, including the addition of three new Offices for Drug Evaluation and the creation of an Office of Pharmaceutical Sciences which will include a consolidation of all the chemists from the new drug reviewing divisions into an Office of Chemistry. Williams noted that the Health Protection Branch in Canada had recently consolidated its chemistry in a similar fashion. He noted that there are several subcommittees within the Office of Chemistry that are looking into issues relevant to the CMC dossier. In Williams' view, while creating a global format for the dossier is important, it will also be important to address the content issue for each of the components. In closing, Dr. Williams outlined the process which he saw a product of this workshop undergoing. Following the production of the workshop report and harmonization among the three participating regions (Europe, Canada, US), Williams would see the FDA issuing a draft guidance for comment by the US industry, followed by modifications, and issuance of a notice of availability. He sees this process being able to move forward quickly.

Per Helboe, Ph.D., of the Medicines Division of the National Board of Health for Denmark, spoke on behalf of the European Union. He indicated that within Europe, harmonization has been ongoing for nearly 30 years, and in particular, harmonization of the CMC technical requirements began in 1965. He believes that the outcome of this workshop is particularly timely since a revision of the notice to applicants on the CMC format is currently in process. He was, however, less optimistic about the rapidity of implementation of any workshop outcome in Europe due to the need to obtain agreement from the many different regulatory agencies involved.

Peter Jeffs, Director of the Bureau of Pharmaceutical Quality in the Drugs Directorate of Canada's Health Protection Branch (HPB), reviewed the October 1994 Drug Information Association meeting in the Netherlands in which the B.I.R.D. document was first proposed. He indicated that Canada is very anxious for there to be a global CMC dossier, and he is prepared to take the proposal resulting from this workshop back to Canada and make the changes necessary to achieve that goal. In Jeffs' view, all the regulatory agencies want the same basic information so that the key issue in harmonization is format.

The first session, entitled, "Current CMC Requirements in Canada, the European Union, and the United States and the Need for a Common Format" was moderated by Melody A. Brown of Bristol-Myers Squibb Co., co-organizer of the workshop. The session began with Charles P. Hoiberg, Ph.D., presenting the FDA's perspective. Hoiberg highlighted major differences in the drug review systems of the US and Europe, namely in the regulatory approval processes, the formatting of the documents submitted, and in the science/data requirements of those documents. He compared the structure of the core dossier and the NDA, specifically in terms of where the relevant CMC requirements were located. These differ significantly in the two regions. In particular, the NDA separates drug substance from drug product. Many data elements from the European core dossier are found in multiple locations in the NDA while others do not appear at all. The core dossier in Europe has sections for both Development Chemistry and Development Pharmaceutics, neither of which appear as distinct sections in the NDA and which do not appear to even have a comparable terminology in the US. Thus, there is a need for not only a common format, but a common language within that format. While citing some concerns about achieving agreement on a global CMC document, Hoiberg indicated that he believed the benefits of a common format clearly outweighed the difficulties and that a common format COULD be easily obtained.

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Peter Jeffs presented the perspective of Canada's HPB. He reviewed a new initiative in Canada which is a comprehensive summary of CMC data prepared by industry according to an electronic template provided by the HPB. This template consists of a series of tables to be filled in with cross-references to the actual data, either in hard copy or in an electronic database. The completed template then serves as the basis for the HPB review and the evaluation report. This template system facilitates access to the data and has resulted in improved submissions with fewer questions, improved quality and consistency of the evaluation reports, and shortened review times. The Help Guide and templates for the HPB comprehensive summary for CMC are available on-line by downloading from the Health Canada Bulletin board under Drugs Directorate/Policy Issues at Internet address http://hpb1.hwc.ca:8300/.

Per Helboe, Ph.D., presented the perspective of the European Union. There are currently three different procedures for obtaining marketing authorization in Europe. In the Central procedure, one application is submitted to the European Medicines Evaluation Association (EMEA). The EMEA does not have the staff to conduct the expert reviews itself and must use the expert reviewers from the national agencies. The end result of an application submitted to the EMEA is one marketing authorization for the entire EU. This procedure is mandatory for biotechnology products but optional for new chemical entities. The Mutual Recognition procedure is a decentralized procedure that is also used for marketing a drug in more than one member state. It has been an option for companies since January 1995 but will become mandatory for those companies not using the Central procedure after January 1998. The National procedure can be used until January 1998 for marketing in multiple member states, but after that date can be used only if the company wishes to market in one member state only. All three types of marketing authorization procedures require a renewal process every 5 years. Helboe enumerated the major differences between the formats of the CMC portion of the core dossier and the NDA. The key difference seems to be the expert report which in Europe is prepared by the sponsor with independent experts and forms the basis of the assessment report. The assessment report is the basis for the marketing authorization decision under all three procedures outlined previously. Helboe concluded his remarks by indicating that a harmonized version of the CMC dossier would be useful even if different requirements continued to exist because in addition to the economies of time and scale, it would also provide a common platform for discussing additional changes in the regulations.

The session focus then switched to the views of industry. Maria A. Geigel of Janssen Pharmaceutical Research Foundation presented the US industry perspective from two points of view—that of a US affiliate of a European company and that of the US headquarters of an international company. In the former instance, the dossier is either prepared in Europe and sent to the US for reformatting, or the NDA is prepared in parallel with the European dossier. The first approach is very time intensive, and both processes are very resource intensive. When the headquarters are located in the US, the NDA can be prepared in the US and sent to the European country for reformatting or the US prepares both the Part 2 format and the NDA. Again both processes are time and resource intensive. From the US industry view, multiple formats result in time delays and increased resource requirements. Specific factors contributing to this problem are the need to verify reformatted documents, the difficulty of ensuring that any changes are incorporated into multiple formats, the doubling of storage requirements at multiple sites, and the difficulty in finding the same information in different locations in the various formats. A harmonized CMC format would solve all of these problems. In Geigel's view the B.I.R.D. harmonizes the US and the European approach in a synergistic way, taking the best aspects of each approach.

Elizabeth Rafuse, Ph.D., of Novopharm, presented the Canadian industry's perspective on a common CMC format. The Canadian industry, according to Rafuse, firmly supports the B.I.R.D. document. Because many countries have indicated a willingness to accept the EU, FDA, or HPB report as long as it is cross-referenced to their format, she feels that the final common CMC dossier format needs to be fluid enough to accommodate changes not only in science, but in the global environment.

David J. Mazzo, Ph.D., of Rhone-Poulenc Rorer, presented the perspective of the European pharmaceutical industry, represented in general by the European parents or affiliates of global pharmaceutical companies. Given the truly global nature of the pharmaceutical industry, Mazzo's view was that it would be surprising to find a dramatic difference in positions among the US, Canadian, and European industries. Such differences as exist arise from the fact that global companies function in local environments. In general, however, the European industry supports harmonization to standardize and improve the quality of submissions and review, to reduce complexity and costs, and to accelerate review and approval. Mazzo did an informal survey of several European companies to get their view on a harmonized CMC dossier. According to the responses, it would cost about 0.2 - 3 man years per NDA/MA to convert from the EU format to the US format, not taking into account translation time. In the respondent's view, there are four parts of the US format that are unnecessary. The environmental assessment and the drug substance synthesis, raw materials, and intermediates information are too detailed. However, the chemistry summary from the environmental assessment should be added to the EU dossier. Both the manufacturing and packaging batch records and the facility information is unnecessary. Commenting specifically on the B.I.R.D. document, Mazzo felt it is consistent with the harmonization efforts ongoing in the companies, the order of presentation is logical, there is a good distinction between the regulatory and scientific aspects, and with some fine-tuning, it should be generally acceptable. Other considerations included whether evidence of GMP compliance was truly needed in the CMC dossier, whether content could actually be separated from format, whether harmonization can be achieved without an increase in unnecessary requirements, and finally, that scientific rationale should supersede any local customs.

The afternoon session of the first day, entitled "Design-

ing the Global CMC Dossier," was moderated by Dhiren N. Shah, Ph.D., of Marion Merrell Dow Inc., a co-organizer of the workshop. Dr. Shah presented an overhead showing the time to prepare a submission for the US and the additional 250 to 350 person hours required above and beyond the US submission time to submit to Canada and Europe. Dr. Shah then introduced Manuel Zahn, Ph.D., of Knoll AG in Germany and author of the B.I.R.D. document. Dr. Zahn emphasized that the B.I.R.D. consists of more than the CMC section even though that was the portion under discussion at this workshop. In addition, he expressed his skepticism that a discussion of format could be separated from one on content. Nevertheless, he emphasized that a universal format should be user-friendly from the reviewing chemist's point of view, independent of the source of the agent (chemical/biological/herbal), independent of the target of the submission (US/Canada/EU), and independent of the purpose of the submission (IND/NDA/ANDA/MA/DMF). Two key features of the harmonized format are the separation of drug substance from drug product and the inclusions of a Development Pharmaceutics section. In addition, the proposed format attempts to separate the routine data required for inspections from the scientific data and to avoid duplication of data without good reason.

Following a question and answer session, the participants broke up into four groups, broken down into drug substance and drug product, to discuss the CMC portion of the B.I.R.D. document and to come up with proposals for modifying the format to make it more acceptable to both the industry and the regulatory agencies. Dr. Shah encouraged the participants to focus on the format, rather than the content of the CMC portion of the B.I.R.D. in order to have an achievable goal.

The second morning began with a session entitled "Review of the CMC Design Proposal," moderated by David N. Ridge, Ph.D., of Hoffman-La Roche, Inc. He began by summarizing the three points of consensus achieved the first day—there is a universal need and desire for a consistent format, significant benefits will accrue to both the industry and the agencies from such a consistent format, and a consistent format is achievable within a reasonable time frame. The resounding bottom line from the industry was that there was much less concern over what was required in the dossier than over the need to "just do it."

Following Ridge's summary, overviews of ongoing projects to facilitate electronic submissions were presented. Robert Kapitany, Ph.D., of the HPB gave the first public presentation of the Multiagency Electronic Review Submission (MERS) pilot project. This project, a joint effort of the regulatory agencies of the US, Sweden, Canada, the Netherlands, and Australia, arose out of the recognition that confusion would result from multiple computerized submission reports and of the need to increase efficiency in times of increasing demand and decreasing resources. The key principle upon which MERS is based is that implementation options are determined by user needs and not by the proprietary nature of the electronic submission. Therefore, MERS uses standard generalized markup language (SGML) which has the benefit of allowing context sensitive searching, the use of multiple software formats without conversion, independence from any particular database management software, multiple authoring and editing on a single source file, and importability from multiple software sources into a single file. The key feature is the Document Type Definition (DTD). The DTD format is hierarchical and as the user moves through the various levels, eventually permits the user to interact with the DTD just as if using a word processor. Everything one would need for any of the three regions would be entered into the DTD. Because of the use of SGML, any relational database can be used and multiple types of SGML-based software can be used to produce agency-specific documents.

Ubrani Venkataram, Ph.D., of the FDA, spoke about FDA's electronic submission standardization efforts. The FDA has formed an Information Technology Technical Committee under Dr. Venkataram. This committee has five subcommittees addressing technology evaluation, format and content of the CMC, glossary for the CMC, the CMC data base, and the computer-assisted chemistry review. Each of these subcommittees are looking into aspects of electronic submission that will eventually impact on the CMC dossier.

Following these two talks, reports from the break-out sessions were presented. These reports addressed recommendations from the breakout groups for specific changes in the drug substance and drug product sections of the CMC portion of the B.I.R.D. Part S of the B.I.R.D. deals with drug substance. Section S 1, originally called Description and Nomenclature, was renamed Nomenclature and Characterization to better define what was included. While more appropriately a content issue, certain of the illustrative examples were moved from one category of the document to another for ease of reading. Under the section titled "Manufacture," a separate subsection on Manufacturing Site was added to make it easier to find the name and address of the manufacturer or facility for each operation. A new subsection for Quality Control of Isolated Intermediates was also added to the section on Manufacture. Under the section titled "Control Tests on Drug Substance", a new subsection, Justification of Specifications, was added immediately following the section on Specifications. Under the section on stability, a new subsection on Production Stability Protocol was added to address how the first three production batches would be studied. The terms "scientific data" and "regulatory data" in the stability section were dropped and the section formerly called Stability (Regulatory data) was renamed Stability Conclusions to more accurately reflect its derivation from the Stability Data section preceding it.

Many of the changes recommended for drug product paralleled those for drug substance for consistency. In Part P, Drug Product, "Development Pharmaceutics" was made a separate section from "Composition." Subsections on "Justification of Specifications" were added to the section on "Control Test on Excipients," and the section on "Control Tests on Drug Product." The section titled "Control Tests on Container" was renamed "Container/Closure" and separate subsections were added for "Description," "Composition," "Source," "Specifications," "Qualification of Container/Closure System," "Test Methods," and "Validation." Under the stability section, the subsection for regulatory data was renamed "Stability Conclusions," similar to what was

done for drug substance, and a subsection of "Production Stability Protocol" was added to accommodate the commitment and protocol for future planned stability studies. A section on "Other Information" not applicable to all regions was added with subsections addressing "Bioavailability/Bioequivalence," "Environmental Assessment," "Microbiology," and "Method Validation Package."

In closing, regulators from Canada, the US, and the EU all made the commitment to take the revised B.I.R.D. back to their agencies (or in the case of Europe to multiple agencies) for internal discussion, subsequent harmonization among the regions, and, hopefully, implementation in the not-too-distant future.

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