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Meeting Report

International "Hands On" Dissolution and Bioequivalence Workshops

The Federation of International Pharmacists (FIP),the Indian Pharmaceutical Association (IPA) and the World Health Organization (WHO) recently sponsored two workshops on the theme of dissolution testing and bioequivalence in Bombay (23/24.01.) and Bangalore (27/28.01.),India. Both of these workshops were enthusiastically received by the participants,who numbered more than 170 at each location.International experts from regulatory authorities, Pharmacopeia,universities and the pharmaceutical industry presented the current status of dissolution testing and bioequivalence issues related to dissolution testing. Novel features of the workshops were the extensive "hands-on" demonstrations and the opportunity for participants to interact directly with the speakers in the discussion sessions. The participants made full use of the opportunity to quiz the speakers extensively about the details of dissolution testing from both a theoretical and practical standpoint and to exchange their experiences with others working in the dissolution area.

The International "Hands-On" Dissolution and Bioequivalence Workshop was based on two earlier workshops, one of which had been presented in 1999 in Melbourne, Australia (the FIP"Dissolution '99" Workshop), and the other of which was the FIP/WHO Bioequivalence Workshop, which had already been presented in Thailand, India and Korea during the last three years. The aim of the Hands-On Workshop is to bring pharmaceutical scientists in developing countries up to date with respect to the latest developments in dissolution technologies, applications of dissolution to pharmaceutical products and the relevant regulations. This should facilitate efforts in developing countries to achieve the same product quality as in the West and enable harmonization of regulations and pharmacopeial standards on a global basis.

The meeting in Bombay was kicked off by greetings from Dr. Ajit Singh, the Co-Chair of the Planning Committee and from Dr. Kokate, the President of the Indian Pharmaceutical Association (IPS) and an address from the Drug Controller General of India, Dr. Ashwini. The first session focussed on dissolution. In an overview presentation,"Design of a Dissolution Test", Dr. Vinod Shah of the FDA described the manifold possibilities for the use of dissolution testing in the quality control of pharmaceuticals. The need to have a rational basis for setting specifications of dissolution methods was emphasized, and the various dissolution Guidances and Guidelines were presented in detail.

In the second presentation "Design of Dissolution Test Equipment" Ms. Erika Stippler of LQS GmbH, Germany, described the pharmcopeial dissolution apparatus and addressed the question of which apparatus to use for which types of products. Advantages and disadvantages of the different testers were illustrated with practical examples. Slight variations in the tester design among the various pharmacopeia and their possible influence on test results was also discussed, for example the mesh size used in the reciprocating cylinder apparatus (USP, EP, JP)).

Dr. Eric Galia, Aventis Pharma Deutschland GmbH, followed with a presentation on "Calibration of Dissolution Test Equipment". Issues addressed included not only the mechanical adjustment of the dissolution test apparatus but also the USP's System Suitability Test , which can be thought of as a kind of chemical calibration. Tips and tricks for bringing out-of-calibration testers back within specifications were highly appreciated by the audience.

The morning session was brought to conclusion with a presentations on "Selection of a Dissolution Test Medium" by Prof. Jennifer Dressman of the Johann Wolfgang Goethe University in Frankfurt, Germany. Depending on the goal of the dissolution test, one could select either an aqueous buffer with or without surfactants (quality control purposes) or one of the so-called biorelevant media (IVIVC purposes). Professor Dressman further indicated the utility of the BCS (Biopharmaceutics Drug Classification Scheme) in making the initial selections of the dissolution medium for a specific drug or drug product, illustrating her choices with numerous examples.

Discussion of the various aspects of dissolution test design both among the participants and with the speakers was already in full swing during

Workshop faculty with the local organizing committee and some participants at the Banalore Workshop.

lunch, and was then framed into a more formal setting during the afternoon sessions. Participants were divided into four groups, two of which attended the "hands-on" demonstrations first, and two of which joined forces to pose questions to the discussion panel. The practical sessions consisted of an Operational Qualification/Performance Qualification (OQ/PQ) demonstration, run concurrently on two different partly automated testers by Dr. Galia and Ms. Stippler with the participants free to watch, help with the calibration and/or jump in with questions about OQ and PQ. The informal atmosphere led to a rich exchange of experiences among the participants as well as with the experts. The dissolution testers were kindly provided for the workshops by Erweka GmbH (Germany), which was represented at the meetings by the owner, Werner Mueller and the laboratory manager, Frank Wucher.

The panel for the discussion round consisted of Dr. Roger Williams (CEO, USP), Dr. Vinod Shah, Prof. Jennifer Dressman and Prof. Kamal Midha (University of Saskatchewan, Canada). Questions included everything from selection of test apparatus for controlled release dosage forms, through de-aeration of media and how to accomplish this in a reproducible way, to the use of surfactants for poorly soluble compounds in comparison to 4 L vessels or use of the flow through tester. After the first sessions, there was a short tea break before the groups swapped activities.

The lectures on the second day addressed the topic of "Dissolution & Bioequivalence". In the first presentation "Dissolution-A Quality Control vs. Bioequivalence Test" Dr. Vinod Shah described the circumstances under which biowaivers can be considered. Cases where a biowaiver may be allowed are described in the FDA"BCS-Guidance". In the content of the BCS, Dr. Shah defined the circumstances in which a dissolution test may be regarded as sufficient to show bioequivalence of two products. The next presentation, "In vitro/in vivo Correlations and Mapping Concept" was given by Prof. Jennifer Dressman, who described the various levels of correlation between in vivo and in vitro results, as well as how to set up the in vivo and in vitro studies to facilitate the correlation and illustration of the correlation techniques themselves. Practical examples of Level A, B and C correlations achieved with deconvolution and for the use of convolution techniques were shown.

Dr. Roger Williams then gave a presentation on

"Hands On" meeting report … *continued*

"Product Quality: International Perspectives", including the viewpoint of the USP on issues like bioequivalence, CMC (Chemistry, Manufacturing and Controls), and the International Conference on Harmonization (ICH). In addition, he talked briefly about the history and organizational structure of the USP and how new chapters and monographs are generated.

The last lecture of the workshop, "Current Developments in BA/BE Requirements for Highly Variable Drugs & Drug Products: Issues & Options" was presented by Professor Kamal Midha. He discussed the advantages of replicate and four-period studies, with special reference to bioequivalence testing of highly variable products. Using various examples, he illustrated the importance of the replicate design for assessing (intra- as well as inter-subject) variablity and gave some thoughts about bioequivalence criteria for such products, including weighting for the product specific variability.

After the lectures, there was another panel discussion, this time with all participants attending at the same time. Questions primarily addressed bioequivalence issues and showed the strong interest among the pharmaceutical scientists in India with respect to correct design of bioequivalence studies. Other areas that were clarified included the criteria for biowaivers, IVIVC procedures and curve comparison using the f2 factor and other statistical parameters.

The very active level of participation as well as the strong attendance reflected the ambition on the part of the Indian pharmaceutical companies to become important players on the world market, and their recognition of the need to harmonize local standards to the international level. In addition, one has to bear in mind that as of 2005, India will comply with the GATT treaty, which among other issues, will require that international patent law is respected in all treaty signing nations. Because of the enormous changes that this will require, the Indian pharmaceutical industry is committed to making itself fit for the future in the most efficient manner possible.

The FIP would like to specially thank the local organizers of the workshop (in Bombay by Prof. H.L. Bhalla (University of Bombay) and A. Singh (Chairman, Associated Capsules Group); in Bangalore by Prof. S.Suresh (University of Bangalore) and Dr. Radha Shekar (Eros PharmaCts.) and their colleagues, for the immense effort that they put into the planning and organization of the two events.