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PMDA Updates

June, 2015

News

1. 1st IGDRP meeting (May 25-28)

On May 25-28, the 1st International Generic Drug Regulators Programme (IGDRP) meeting was held in Pretoria, South Africa, where about 40 participants from 15 countries/regions/organizations attended. Dr. Junko Sato, International Coordination Officer and a staff member from Ministry of Health, Labour and Welfare (MHLW) participated in the steering committee meeting, and 4 staff members from Office of Generic Drugs participated in the working group meetings regarding the biowaivers and active substance master files group and the drug master files group. At both of working group meetings, updates on the activities including biowaivers were provided by participating regulatory agencies and the future action policy was discussed. The next IGDRP meeting will be held in Korea in November, 2015.

IGDRP Website
http://www.igdrp.com/

2. Japan Promoting Policy and Approval System of Innovative Drugs Symposium (May 28)

Dr. Tominaga

On May 28, Japan Promoting Policy and Approval System of Innovative Drugs Symposium was held in Beijing hosted by China Center for Food and Drug International Exchange, an affiliated organization of China Food and Drug Administration (CFDA), where Dr. Toshiyoshi Tominaga, Associate Executive Director for International Programs, Dr. Yoshiaki Uyama, Director, Office of Medical Informatics and Epidemiology, and a staff member of Office of Review Management attended.

The objective of the symposium was the introduction of Japan's regulations to China. There were presentations made by Dr. Tominaga on approaches to shorten the review period for new drugs, by Dr. Uyama on promoting global clinical trials to resolve drug lag, and by the staff of Office of Review Management on the overview of new drug approval system in Japan, as well as on PMDA's consultation system, with discussion following each presentation

3. ICH week in Fukuoka (June 5-11)

Mr. Mori (8th from the left) and Dr. Tominaga (6th from the right)

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was held in Fukuoka from June 5 to 11. Fourty staff members in total from PMDA, including Dr. Toshiyoshi Tominaga, Associate Executive Director (for International Programs) and Mr. Naoyuki Yasuda, International Coordination Officer, and also Mr. Kazuhiko Mori,Director, Evaluation and and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare (MHLW) participated in the conference. In the Steering Committee meeting, a substantial progress was achieved towards the reform of ICH to become an independent entity. Also in each working group meeting, active contributions were made, i.e.,the sign-off at Step 4 of ver.1.27 of the Change Request/Q&A document of the ICH M8 (Electronic Common Technical Document (eCTD)), and the sign-off at Step 2a/b of the ICH E6 (Addendum to Good Clinical Practice (GCP)) .

The next ICH will be held in Jacksonville, Florida, U.S.A. in December 2015Will be updated.

4. Call for application to 6th PMDA Training Seminar starts (June 24)

PMDA will hold its 6th Training Seminar for officials of foreign regulatory agencies from October 19 to 23, 2015. In this seminar, there will be lectures offering an overview of drug reviews, clinical trial consultations, GCP/GLP, GMP, JP and DMF registration. Also, post-marketing safety measures and relief services for adverse health effects will be covered through lectures as well as case study group work.

For the details of the PMDA 6th Training Seminar, see following web site.
http://www.pmda.go.jp/english/symposia/0079.html

Safety Information

Pharmaceuticals and Medical Devices Safety Information No. 323, May 26, 2015

1. Utilization of New Bar Code Labeling and Termination of JAN/ITF Code Labeling on Prescription Drugs
2. Important Safety Information
   (1) Asunaprevir and daclatasvir hydrochloride
3. Revision of Precautions (No. 265)
   Duloxetine hydrochloride (and 4 others)
4. List of Products Subject to Early Post-marketing Phase Vigilance (as of April 30, 2015)

http://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0013.html

English translations of review reports

The followings are current information about English version of review reports on PMDA web site.

Pharmaceuticals
http://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0001.html

Brand Name	Generic Name	Posting date
Stribild	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	June 29

Events

Conferences/Meetings PMDA hosts or participates in:

Date	Title	Location
June 30-July 1	Pharmacopoeial Discussion Group Meeting	Tokyo
July 2	4th DIA CMC Forum in Japan	Tokyo
July14-15	Annual Thai TECT national conference	Bangkok
Aug 1	CVIT2015 HBD Session	Tokyo

August 18	The 8th Japan-China Medicine Manufacture Exchange Meeting	Beijing
August 25-28	APEC LSIF RHSC	Cebu

Reports from overseas

Our officers deliver lively reports of their activities at their stationed overseas authorities.

Workshop on the therapeutic use of bacteriopharges

More than 60 participants from academia, pharmaceutical industry, and European regulators met at the EMA on June 8 to discuss the therapeutic use of bacteriophages. The "Workshop on the therapeutic use of bacteriophages" aimed at facilitating new tools for treatment of difficult-to-treat infections caused by bacteria including multi-resistant bacteria, and exploring for new anti-bacterial treatment options and their measures.

In the meeting, at first, as target diseases that bacteriophages are being used in clinical researches or are expected to be used, such as multi-resistant bacterial infection, mechanical ventilator-related pneumonia, febrile neutropenia, and burn wound skin were raised, and other target diseases including diabetic chronic ulcer in the United States were also introduced. In addition, therapeutic measures such as isolation of causative bacteria from patients prior to treatment, specification of multiple bacteriophages efficacious for the bacteria, and administration of cocktail bacteriophages to patients were explained.

What intrigued me in particular were: in terms of efficacy, comparison of efficacy between existing antibacterial drugs, opinions about study of efficacy based on range findings, and explanation of efficacy on chronic infectious diseases even if biofilm is formed; and, in terms of safety, necessity of study of bacteriophage's own proliferative ability, and opinions about importance of conducting risk management plan and post-market safety study because target patients are likely to be already in serious condition and the given treatment is based on the new technology.

The discussions at this bacteriopharge meeting were useful, with stakeholders encouraged by the comment from the co-chair, "EMA as a regulatory agency will also be able to learn a lot through honest discussion between academia and pharmaceutical industry", and had active discussions to share multiple viewpoints of efficacy and safety. Various new technologies will be applied for medical treatment from now on. As the PMDA liaison at EMA, I will continue to report on similar meetings of interest in the area of new medical technologies whenever they take place. Meeting materials and video recordings in the meeting will be available on the EMA website as shown below.

(Reference)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/05/event_detail_001155.jsp&mid=WC0b01ac058004d5c3

Mr. Yoshihiko Sano
PMDA's International Liaison Officer stationed at EMA in the United Kingdom

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Excipient Fest Americas 2015

I attended the ExcipientFest America 2015 held on April 28- 29 in Puerto Rico. ExcipientFest is an annual conference specialized in excipients. About 450 people from many excipient manufacturers, pharmaceutical manufacturing companies and academia, etc. attended this conference and actively exchanged information at Exhibitor booths. As educational sessions, industry's top-pharmaceutical experts gave presentations about new technology related to excipients and speakers from regulatory authorities also presented information on regulations for excipients. In addition, Ms. Catherine Sheehan, Senior Director of USP excipients team, gave a presentation about challenges and opportunities in developing and modernizing public standards for the National Formulary (NF) monographs. In the past, a lot of health damage were caused by diethylene glycol (DEG) adulterated in glycerin used as excipients. Therefore, there were many topics regarding measures for delivering safe medicine to patients addressed in the educational session. As one of the countermeasure against adulteration and counterfeit, stakeholders conduct various risk managements, which is called supply chain security, according to the

level of supply chain because these problems are caused by vulnerability of supply chain. I recognized again that the countermeasure against adulteration and counterfeit could be one of the primary concerns in the American pharmaceutical products industry. It seems that ExcipientFest is a relatively small conference compared to general international conferences, due to its sole focus on excipients. However, there were so many significant educational sessions in this conference, which was very helpful in obtaining important updates on excipients in a fast and intensive manner. I think this information will be useful to understand USP's position in the harmonization activities in the future.

Dr. Chie Mizumaru
PMDA's International Liaison Officer stationed at USP in the U.S.A.

How the U.S. FDA hears outside voices

In previous PMDA Update reports, I have written how outside views can help the U.S. FDA develop regulatory policy and make product-specific regulatory decisions. For example, in the December 2014 issue, I wrote about the Drug Safety and Risk Management Advisory Committee's discussion of the risk evaluation and mitigation strategy (REMS) for Soliris (eculizumab). In the May 2015 issue, I wrote about the Patient-Focused Drug Development initiative, in which the U.S.FDA convenes a series of public meetings for patients to discuss how their experience with a disease can inform drug development. A third way for the U.S. FDA to hear outside views is asking an external expert body for recommendations on specific issues. The Institute of Medicine[1)] (IOM, which will be called the National Academy of Medicine as of July 1, 2015) is an independent, nonprofit organization that provides evidence and advice to the public and to government agencies. IOM has issued two important expert opinion reports in the area of pharmacovigilance. "The Future of Drug Safety: Promoting and Protecting the Health of the Public"[2)] examined the US drug safety system and made recommendations for strengthening that system, many of which informed the Food and Drug Administration Amendments Act (FDAAA) of 2007, which gave the U.S. FDA additional authorities related to post marketing drug safety. "Ethical and Scientific Issues in Studying the Safety of Approved Drugs,"[3)] issued in 2012, provided a framework for considering the complex scientific and ethical questions that arise when studying the safety of an already marketed product. These reports, as well as other outside views, can be helpful for you to understand how the U.S.FDA develops polices and makes regulatory decisions involving post-marketing drug safety.

1) http://www.iom.edu/
2) http://www.iom.edu/reports/2006/the-future-of-drug-safety-promoting-and-protecting-the-health-of-the-public.aspx
3) http://www.iom.edu/reports/2012/ethical-and-scientific-issues-in-studying-the-safety-of-approved-drugs.aspx

Ms. Shohko Sekine
PMDA's Officer at CDER, U.S. FDA in the U.S.A.

Introduction of the review case utilizing physiologically based pharmacokinetic modeling and simulation-Evaluation of the effect of genetic polymorphism and co-medication on drug exposure

I have been referring to the utility of physiologically based pharmacokinetic (PBPK) modeling and simulation for quantitative evaluation of drug-drug interactions (DDIs) in my previous reports. Substrate PBPK model, in which quantitative information on absorption, distribution, metabolism, excretion and drug-protein interaction are incorporated and which is established to be able to describe drug disposition in human, is sometimes used for the prediction of complex DDIs such as co -administration of multiple enzyme inhibitors and DDIs in patients with genetic polymorphism. I would like to introduce a recent review case in FDA evaluating the effect of genetic polymorphism and co-medication on drug exposure.

U.S. FDA approved Cerdelga (eliglustat) for the long-term treatment of adult patients with the Type 1 form of Gaucher disease in August, 20141). Eliglustat is extensively metabolized by CYP2D6 and to a lesser extent, CYP3A4. As part of the New Drug Application review, sponsor's PBPK reports were reviewed to evaluate the effect of CYP2D6 polymorphism and co-medication, either alone or in combination on eliglustat exposure. Sponsor built the eliglustat PBPK model that can describe the observed exposure data in different CYP2D6 phenotype population and capture the effect of paroxetine, a strong CYP2D6 inhibitor and ketoconazole, a strong CYP3A inhibitor in CYP2D6 extensive metabolizers (EMs). Multiple scenarios were simulated using this eliglustat PBPK model in subjects with different CYP2D6 phenotypes, taking eliglustat in combination with CYP inhibitors. For example, simulation using

this PBPK model suggested that concomitant use of eliglustat with paroxetine and ketoconazole may increase the AUC of eliglustat about 24-fold in CYP2D6 EMs and ketoconazole may increase the AUC of eliglustat about 6-fold in CYP2D6 PMs. These prediction results were described and also provided as tables in the drug product label2), providing dose recommendation to the patients taking eliglustat in the presence of various CYP inhibitors in CYP2D6 different phenotypes.

In order to apply the prediction results based on PBPK modeling and simulation in new drug review, it is necessary that PBPK model can predict reasonably human PK in some situations with accuracy. In the review case of eliglustat described above, eliglustat PBPK model was built using the results of in vitro ADME experiments and several clinical PK studies and was able to predict reasonably observed eliglustat human PK in some situations such as PK in different CYP2D6 phenotypes and DDIs with strong inhibitors. Therefore, the eliglustat PBPK model is considered sufficient in providing dose recommendation in subjects taking eliglustat with various CYP inhibitors in different CYP2D6 phenotypes. I think it is important to accumulate knowledge on PBPK modeling and simulation methodology through understanding issues general to all cases as well as unique problems specific for individual review cases. I am going to learn those continuously during my training and hope my experiences in FDA are very useful for the new drug review in PMDA.

1) Cerdelga (eliglustat) Capsules Clinical Pharmacology Biopharmaceutics Review(s)
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf
2) Cerdelga label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

Dr. Masanobu Sato
PMDA's Officer at CDER, U.S. FDA in the U.S.A.

New Draft Guidance for Patient Preference Information at FDA

U.S.FDA (CDRH /CBER) released the draft guidance on "Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling" on May 18, 2015[1]. U.S.FDA believes that patients' insights and perspectives can help the Agency evaluate the benefit-risk profile of certain devices. This guidance document is following upon the "Benefit-Risk Guidance" issued on March 28, 2012[2] and "FDA's current policy on balancing premarket and postmarket data collection during U.S.FDA review of PMAs"[3] and "Expedited Access Pathway Guidance"[4] both issued on April 13, 2015 as part of U.S.FDA's regulatory decision-making information.

The overview and scope of the document are as stated below;

- "This draft guidance document explains the principal concepts that sponsors and other stakeholders should consider when choosing to collect patient preference information, which may inform FDA's benefit-risk determinations in the premarket review of PMAs, HDE applications, and *de novo* requests."
- "Notably, this draft guidance does not change any review standards for safety or effectiveness (refer to Section 3.6), or create any extra burden on sponsors of premarket submissions."
- "Rather, it provides recommendations relating to the voluntary collection of patient preference information that may be submitted for consideration as valid scientific evidence as part of FDA's benefit-risk assessment during its review of PMAs, HDE applications, and de novo requests."
- "Patient preference information may not be relevant or appropriate for all device types. Furthermore, not all benefit-risk scenarios are "preference-sensitive."

Fortunately, I had the opportunity to talk with the person responsible for managing the Benefit/Risk policy in the Office of Device Evaluation in CDRH during this dispatch program and was able to gain a better understanding of the series of the issued guidance and draft documents. I assume that this document has been produced as a result of CDRH's sincere consideration of how 'Patient Preference Information' could be integrated into benefit-risk determinations in the premarket reviews for medical devices. Although the implementations of this concept will be only valid for limited certain situations, I believe that the concept closely aligns with patients' needs. At the same time, I find that the nature of the document echoes one of the principles from PMDA's philosophy: "We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices." Moreover, U.S.FDA's decisions and directions have huge influences on the world, thus we need a continued focus and close relationship with U.S.FDA to follow its changes and advances.

1) Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

2) Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm
3) Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393994.pdf
4) Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions
http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393978.pdf

Ms. Rie Fukaya
Visiting Reviewer at CDRH, U.S. FDA in the U.S.A.

Participation in the Ear, Nose, and Throat Devices Panel

Currently I am learning the review process and organization of The Division of Ophthalmic and Ear, Nose, and Throat (ENT) devices at the U.S.FDA. An advisory panel meeting of the Ear, Nose, and Throat Devices Panel of the Medical Devices Advisory Committee was held on April 30, 2015. The purpose of this panel meeting was not to discuss the approval of an individual medical device, but for the panelists to make recommendations regarding the appropriate regulatory classification of certain ENT medical devices and to make a decision regarding whether a premarket to postmarket shift in clinical data requirements would be appropriate for modifications to cochlear implants in pediatric patients. I attended this panel with great interest because the PMDA has discussed the evaluation of medical devices in pediatric use in the Science Board.

Cochlear implants from three companies for pediatric patients have been approved with premarket pediatric clinical data in the U.S. On the other hand, The U.S.FDA has been encouraging industry to develop medical devices for pediatric patients and has included "Strike the Right Balance Between Premarket and Postmarket Data Collection" in the CDRH's Strategic Priorities for 2014-2015. Cochlear implants are among the products reviewed under this priority. The U.S.FDA concluded that cochlear implants would continue to require PMAs to provide reasonable assurance of their safety and effectiveness.

With these considerations, the U.S.FDA proposed a shift in some clinical data requirements from premarket assessment to postmarket collection (e.g, it is difficult to evaluate the clinical outcomes in prelingual pediatric patients such as the performance of the speech recognition tests and there had been no serious safety concerns related to the fitting approved advanced speech coding strategies in pediatric patients in the published studies). The outside experts discussed the propositions with the observation of industry. As a result the panel agreed the shift in clinical data requirements in pediatric patients from premarket to postmarket of the approved adult indications. The U.S.FDA will discuss the guidance for cochlear implants for pediatric patients with industry.

The situation in Japan is different from that of U.S. because the neither adult nor pediatric patients are identified explicitly in the indications for use of cochlear implants. I think we need to be aware of issues of indications medical devices in pediatric patients and solve them as the PMDA continues the discussion in the Science Board. The discussions in the above panel were very meaningful for me and helped me a lot.

Panel materials are available at following web site.
http://www.fda.gov/advisorycommittees/calendar/ucm438065.htm

Mr. Takehiro Ichikawa
PMDA's International Officer at CDRH, U.S. FDA in the U.S.A
