Updates

AHWP WG1 Sub-Group on Combination Products (CP)

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Nov. 8, 2011

Current CP Sub-Group Members:

- Huifen Bai / HAS, Singapore
- Meshal Alamri / Saudi Food & Drug Authority
- Chiew-Teng Chuah / 3M, Malyaysia
- Mi-Ran Han / Cook Medical, Korea
- Kitty Mao / GE Healthcare, China
- Mary Wang / J&J, China
- Jacqueline Monteiro / Medtronic, Singapore
- Ed Woo / Medtronic, USA
- Woei Jiuang Wong / CIBA Vision, Singapore
- May Ng / Biosensors International
- Ming-Che Wang / CDE, Chinese Taipei

Project Goals and Objectives

- Phase I study: Baseline establishment
- Phase II study: Comparison of similarities and differences of CP related topics between AHWP member economies
- Goal: Understand current status and provide study results to member economies for future policy making considerations
- Main focus: AHWP member economies

Updates

Nov. 8, 2011

- Phase I study: Baseline establishment
  - Study US FDA and/or EU current policy and guidelines on CP
  - GHTF Ad-Hoc working group on CP – Study current progress & accomplishments
  - Study 1-3 AHWP member economies as starting points
    - Chinese Taipei (Ming-Che Wang)
    - China (Mary Wang, Lindsay Tao)
    - Singapore (Huifen Bai)
    - Other suggestions - volunteers

US FDA
Current Policies and Guidelines (1/2)

1. Regulation:

Section 503(g) of the Federal Food, Drug, and Cosmetics Act (21 USC 353(g))
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/ucm108068.htm

2. MDUFMA Guidance:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/ucm109195.htm

- Draft Guidance for Industry and FDA Current Good Manufacturing Practice for Combination Products
- Guidance for Industry and FDA Staff: Application User Fees for Combination Products
- Definition of the Primary Mode of Action of a Combination Product
- Draft Guidance for Industry: Combination Products, Timeliness of Premarket Reviews, Dispute Resolution Guidance

US FDA
Current Policies and Guidelines (2/2)

Definition:

- A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. [21 CFR 3.2 (e)]

Premarket Review Pathways:

- Regulatory pathway determined based on primary mode of action (PMOA), previous inter-center agreements and precedents.

Registration Review:

- Office of Combination Products (OCP)– To assign an FDA center to have primary jurisdiction for review

Post market:

- OCP intends to publish a proposed regulation to clarify adverse event reporting requirements for combination products

EU EMA

Current Policies and Guidelines (1/2)

Regulation:

- Directive 93/42/EEC
- REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL – on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/200 (10 December 2007)
  http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

Classification:

- Rule 13 - combination devices that contain a medicinal substance incorporated into the device for the purpose of assisting the functioning of that device. (MEDDEV 2. 4/1 Rev. 9 June 2010)

EU EMA
Current Policies and Guidelines (2/2)

RULE 13	EXAMPLES
All devices incorporating, as an integral part[1], a substance which, if used separately, can be considered to be a medicinal product as defined in Article 1 of the Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.	- Antibiotic bone cements - Condoms with spermicide - Heparin coated catheters - Endodontic materials with antibiotics - Ophthalmic irrigation solutions principally intended for irrigation, which contain components which support the metabolism of the endothelial cells of the cornea - Dressings incorporating an antimicrobial agent where the purpose of such an agent is to provide ancillary action on the wound - Contraceptive intrauterine devices (IUDs) containing copper or silver - Drug eluting stents, *e.g.* coronary, pulmonary
All devices incorporating as an integral part, a human blood derivative are in Class III	- Surgical sealants containing human serum albumin

Note 1: "Integral part" means that the device and the medicinal substance are physically or chemically combined at the time of administration (*i.e.* use, implantation, application etc) to the patient.

Approaches of GHTF to CP

- May 2007 – Agreement by GHTF Steering Committee to establish an Ad Hoc working group (AHWG).
- October 2007 – Discussions of regulatory approaches to combination products in GHTF jurisdictions.
- May 2009 – The AHWG produced a summary table of similarities and differences between member jurisdictions.

GHTF Report (1/3)

Larry Kelly
Head, Office of Devices, Blood and Tissues
TGA (12 May 2009)

	Definition of Combination Product (CP)
AUS	**Not defined as a separate product. CPs regulated according to main function/purpose of the CP.**
Canada	**A therapeutic product that combines a drug component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive nature of the drug component and device component is integrated in a singular product.**
Japan	**No specific definition. CPs are regulated according to main function/purpose of the CP.**
US	**Product comprised of 2 or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity or co-package product, or as cross-labeled products.**
EU	**No general definition of combination product. A 'combined advanced therapy product' is defined as one that incorporates as an integral part one or more medical devices, or active implantable medical devices, and viable cells or tissues, or non-viable cells or tissues where the action on the human body of these cells or tissues is primary to the device.**

GHTF Report (2/3)

(Ref. Larry Kelly's GHTF Report)

	Components of CP
AUS	• Medical Device • Medicine (currently includes biologicals)
Canada	• Device • Drug
Japan	• Device • Drug
US	• Drug • Biological Product • Device Not CP because combined with: • Cosmetics • Foods • Dietary Supplements
EU	• Medical Device • Medicinal Product • Biologic

GHTF Report (3/3)

(Ref. Larry Kelly's GHTF Report)

	Agency Review Determinations – Who is the lead?
AUS	Consider primary intended purpose and mode of action. May be referred to an internal committee consisting of staff from relevant regulatory areas of TGA.
Canada	MDB – when classified as a Device.
Japan	PMDA leads review – Offices under PMDA will lead depending on how the CP is regarded.
US	Assignment by Office of CP to Agency Center based on "primary mode of action" of CP. If PMOA cannot otherwise be determined, assignment will be based on the following algorithm. If there is an Agency Center that regulates other CPs presenting similar questions of safety & efficacy with regard to the CP as a whole then the CP should be assigned to that Agency Center. If not, the CP will be assigned to the Agency Center that has the most expertise related to the most significant safety & efficacy questions presented by the combination product.
EU	Consider primary mode of action. Opinions must be sought from relevant expert committees for certain CPs

Chinese Taipei

Combination Product Review Principle and Review Process

- Food and Drug Administration
- Primary Mode of Action Determination
- Considerations: Drug/device market history and use as CP

- Combination Product Regulated as Drug
  - Lead review by drug division
  - Reviewed by drug advisory committee with participation of device committee members if needed

- Combination Product Regulated as Device
  - Lead review by device division
  - Reviewed by device advisory committee with participation of drug committee members if needed

China FDA (1/2)

1. Regulation:

Notification on Matters Concerning Registration of Drug and Medical Device Combination Products: Published in Nov 2009
关于药械组合产品注册有关事宜的通告(2009年11月12日)
http://www.sda.gov.cn/WS01/CL0087/43215.html
http://eng.sfda.gov.cn/WS03/CL0757/62218.html

2. Guidance:

Guidance for registration document format for medical device containing drug
含药医疗器械产品注册申报资料撰写指导原则(2009年02月20日)
http://www.cmde.org.cn/CL0113/690.html

Guiding Principles for the Clinical Trial of Coronary Drug-eluting Stent (Draft for public comment, June 2011) 冠状动脉药物洗脱支架临床试验指导原则
http://www.cmde.org.cn/CL0013/1448.html

China FDA (2/2)

Definition:

- Combination products are composed of drug and medical device, which is manufactured as one entity per SFDA regulation. Not mentioned others, like ingredient, and etc.

Classification:

- Classification of drug or device based on which one plays the leading role
- Decision should be made prior registration and consultation with SFDA

Registration Review:

- Separate review of drug and device is required
- Leading department coordinates the review and consolidates the conclusion

Updates

Nov. 8, 2011

- Phase II study: Comparison of similarities and differences of CP related topics between AHWP member economies using surveys
  - Develop questionnaire based on phase I study results
  - Conduct CP survey in AHWP member economies
  - Collect survey results and prepare summary reports
  - WG02 involvement
  - GHTF advisory expert

Questionnaire Topics (Draft)

(Based on GHTF questionnaire)

- Definition of Combination Product
- Components of Combination Product
- Combination methods of Combination Product
- Agency review determinations - who is the lead?
- Pre-market review of applications for Combination Product
- Agency “non-primary” component consultations
- Are separate applications required for different components of investigational applications?
- Are separate applications required for different components of Combination Product applications?
- GMP/QS CP Requirements
- Adverse event/Vigilance Reporting Requirements
- Registration and Listing
- Other Combination Product Initiatives

Timelines and Major Milestones

- Proposal approval at TC meeting, July 2011 in Seoul - completed

- Annual AHWP Conference, November 2011