Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

FINAL DOCUMENT

Title:	Guidance on Regulatory Practices for Combination Products
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1. Objectives

This document was developed by Work Group 1 of the AHWP to provide guidance for regulatory authorities and Conformity Assessment Bodies to support development of internationally harmonized combination product Guidance. This document has aims to provide insight on effective regulatory practices for combination products from the perspective of both the manufacturer and the regulator.

The information presented in this document is derived in part from the AHWP WG1's Combination Products White Paper1 issued in November 2015, where a compilation of international regulatory perspectives described both the differences and areas of harmonization in current regulatory practices for combination devices.

2. Definitions

2.1 Combination Product

Products with two or more separate medicine/biologic/medical device/diagnostic components integrally combined. Usually requires a single regulatory submission, although may be subject to review input from reviewers from multiple regulatory divisions under the leadership of a single lead reviewer from the lead authority (see below).

Examples:

- Prefilled vaccine syringe
- Insulin injector pen with prefilled cartridge
- Drug eluting stent
- Bone cement with integral antibiotic

2.2 Companion Product

Two separately supplied products which are co-dependent and cross-labelled. Usually requires separate regulatory submissions for each product, although the reviews may be cross referenced or coordinated, and the products may be cross labelled.

Examples:

- Companion Diagnostic and associated medicine
- Human fibrin vial and thrombin vial to be used together as a sealant

2.3 Kit or System

Two or more separate products which are co-packaged. May require separate regulatory submissions for each product plus a submission for the co-packaged kit or system.

Examples:

1 Available at http://www.ahwp.info/sites/default/files/ahwp-files/7_Documents/7_Final_Documents/AHWP-WG1_Regulation%20of%20Combination%20Products%20-%20a%20Review%20of%20International%20Practice_FINAL.pdf

- Hospital dressing pack containing dressing/gauze, antiseptic swabs, vial of saline, disposable dish, forceps and scissors
- Fibrinogen and Thrombin vials with their Applicator

2.4 Primary Mode of Action

The primary mode of action (PMOA) is the therapeutic or diagnostic function which is considered to be the primary purpose of the product, which should be based on the mechanism of action.

Examples:

- A drug eluting stent is generally considered to have a PMOA as a medical device which is supported in its function by the eluted medicine;

- A prefilled vaccine syringe has a PMOA as a pharmaceutical product, which is supported by the medical device for delivery.

In deciding on a regulatory pathway, most regulators consider the PMOA of a combination product and use it to determine the applicable regulations, and the specific agency division or department which bears responsibility for the products market application.

2.5 Lead Authority

The lead authority is the National Competent Agency, division or department of the relevant regulatory authority that is responsible for reviewing and processing the registration of a Combination Product. The lead authority is determined by the Combination Product's PMOA – e.g. assessment and registration of a product with a device-based PMOA will be led by the medical devices authority, assessment of a product with a medicinal PMOA will be led by the medicines authority. Note that an authority is defined widely. It can include a health department, an agency (e.g. HSA or TGA or FDA) or a Conformity Assessment Body or a Combination Products coordination Office. Thus depending on the local jurisdiction arrangements, the medicines, devices and biologics authorities may be separate organizations or different offices or divisions of a single organization.

2.6 Acronyms

AE	Adverse Event (Medical Devices)
ADR	Adverse Drug Reaction (Medicines)
STED	Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices
CAB	Conformity Assessment Body
CTD	Common Technical Dossier (Medicines)
PMOA	Primary Mode of Action

3. Current Practices

The table below is an extract from the White Paper published in November 2015 and served as reference to this guidance document. It is a summary of the information on the current regulatory requirements and practices for combination products; collated using the framework of a standard questionnaire distributed to regulatory agency representatives of a range of AHWP and IMDRF members. For a copy of the questionnaire and the full responses from each regulatory authority, please see Appendix B of the White Paper.

Table 1 Summary of Regulation of Combination Products in International Jurisdictions

	Formal Definition in Regulation	Formal Status Determination Mechanism	Separate Co-ordination body	Evaluation Process	Fees	Manufacturing Controls	Labelling	Postmarket Reporting	Clinical Trials	Clinical Data Requirements	Planned Changes
USA	Y	Y	Y	P	P	P,C	C,X	P	P	P	
EC	N	Y	N	C	C	C	C,X	P	P	P	R
AUS	N	Y	N	C	S	P,C	P,X	P	P	P	
JPN	N	N	N	P	P	P	C,X	P	P	P	R+
CAN	Y	Y	N	P	P	P,C	P,C	P	P	P	
CHN	Y	Y	Y	P	Y	C	C	Y	Y	Y	R
SGP	Y	Y	N	P	S	P	P	P	P	P	G
IDN	Y	Y	N	P	P	P	U	U	P	P	
KOR	Y	Y	N	C	P	P,C	P,X	P	P	P	
HKG	N	N	N	P	P	P	P	P	P	P	
TWN	Y*	Y*	N	P	P	C	C,X	P	P	C	G
THA	N	Y	N	P	N	U	P	P	P	P	
MYS	N	Y	N	D	D	P	U	P	C	P	R,G
KSA	Y	Y	Y	P	P	P	P	P	P	P	R

Key

Y: Yes,
N: No
P: Regulations or practice applicable to PMOA applied
C: Regulations for all components applied
L: Review coordinated by Lead agency
D: Regulations under development
S: Special Fees for combination products
X Cross labelling requirements for co-dependent products
R: Changes to Regulation
G: Changes to Guidance
U: Undefined – no regulation or guidance established

Notes

*Guidance in preparation

+ Since conduct of the survey, Japan has issued a notification *Handling of Marketing Application for Combination Products* effective on November 25, 2014, which states the scope and requirements for combination products.

4. Recommendations to Regulators:

From the table it can be seen that there is variability in regulatory practice for combination products. This guidance seeks to set out current international best practices in order to support the development of a harmonized approach to regulation of combination products

4.1 Definition

Each regulatory authority, should have an unambiguous definition of a Combination Product (whether described in legislation or appropriately issued guidance documents) based on the characteristics of the device's PMOA and secondary mode(s) of action. Where the designation is not clear, a risk based approach should be taken as described at 4.2 below.

4.2 Assignment of Lead Authority

Each regulatory authority should have some mechanism or procedure for determining the PMOA for the purpose of assigning the appropriate lead authority. For example, if the PMOA is medicinal, then the regulatory review is led by the drug division within the authority; if it is a device then the review is led by the devices division within the authority.
Nonetheless, there will be some combination products for which the designation is not clear. For such "borderline" combination products, the regulatory authority should implement a risk based assessment to place the product within the jurisdiction according to which mode of action presents the greatest risk to the patient: e.g., combination products where the device functionality presents the greatest risks should be regulated as devices, and those where the medicinal action presents the greatest risk should be regulated as medicines.

The arrangements for determination of borderline cases vary widely between jurisdictions. It may be a separate office, a determination committee, or a single coordinating officer. It is suggested that an individual, or a dedicated body, with established procedure to ensure independence throughout the process of status determinations, and the assignment of regulatory review for the combination products. Early discussion between stakeholders in borderline cases is recommended.

4.3 Communication between Authorities

Each regulatory authority should have internal mechanisms, or procedures to allow for cross-communication between the different divisions responsible for the regulatory review of a combination product. The nature of these products requires ongoing communication and collaboration of different divisions to provide effective and scientifically rigorous review. The primary responsibility for review should lie with the lead authority (as determined by the PMOA).

In order to ensure timely processing of regulatory reviews, review arrangements should include, whenever possible, parallel assessments by all participating authorities.

4.4 Manufacturer's Responsibilities

4.4.1 Clinical Trials

There is little uniformity in the current practices of regulatory authorities in regard to the application and assessment of clinical trials in the registration process for Combination Products. While, it is noted that some authorities apply a combination of devices and medicines GCP, it is suggested that the clinical practice applied (ISO 14155 or equivalent for devices, and ICH GCP for pharmaceuticals), should be based on the Combination Product's PMOA.

4.4.2 Manufacturing Controls

There is a significant practical challenge faced by the manufacturer in the application of the relevant Good Manufacturing Practice (GMP) Code, regulation or standard to production of separate device, diagnostic or medicinal components of a Combination Product, and then further in the determination of the combined requirements which apply to those parts of the production process that involve the integrated components.

There should not be a need for manufacturers to maintain separate quality systems. It would be sufficient for the manufacturer to maintain a quality system compliant to either a medical device (e.g. ISO 13485) or medicine (e.g. ICH GMP) quality system standard, but with additional elements added to address the requirements for the mode(s) of action not covered by the primary quality system standard used. For example, if a manufacturer of a device/medicine combination product is certified to ISO 13485, they should also ensure that applicable elements of pharmaceutical GMP not addressed by ISO 13485 are addressed by the quality system with inclusion of additional operating procedures and requirements.

The audit practices of the regulatory authorities should ensure that manufacturers are compliant with the relevant sections of all of the applicable manufacturing standards. It is the responsibility of the manufacturer to ensure the completion and maintenance of fundamental documentation, such as gap analyses and risk management reports to justify the approach taken to achieve quality systems compliance.

4.4.3 Technical Dossier

Manufacturers of Combination Products should need to compile only one set of documentation for submission to the relevant health authority. Product design and production information will necessarily be developed for both the device and medicinal components of the product, however the format of the dossier in which this information is presented, be it the STED for devices or CTD for pharmaceuticals, will be dependent on the Combination Product's PMOA.

The information relevant to the secondary mode(s) of action should be clearly identified, and preferably arranged at a single location in the submission dossier (irrespective of the format chosen) in order to facilitate ease of review by other participating authorities assessing the secondary mode(s) of action.

This single dossier is then submitted to, and reviewed by the lead authority, with input and correspondence where necessary from the other participating authorities related to the secondary mode(s) of action. In this way, the Lead Authority is able to act as a single point of contact with the manufacturer, and minimize the burden of documentation and communication for all parties.

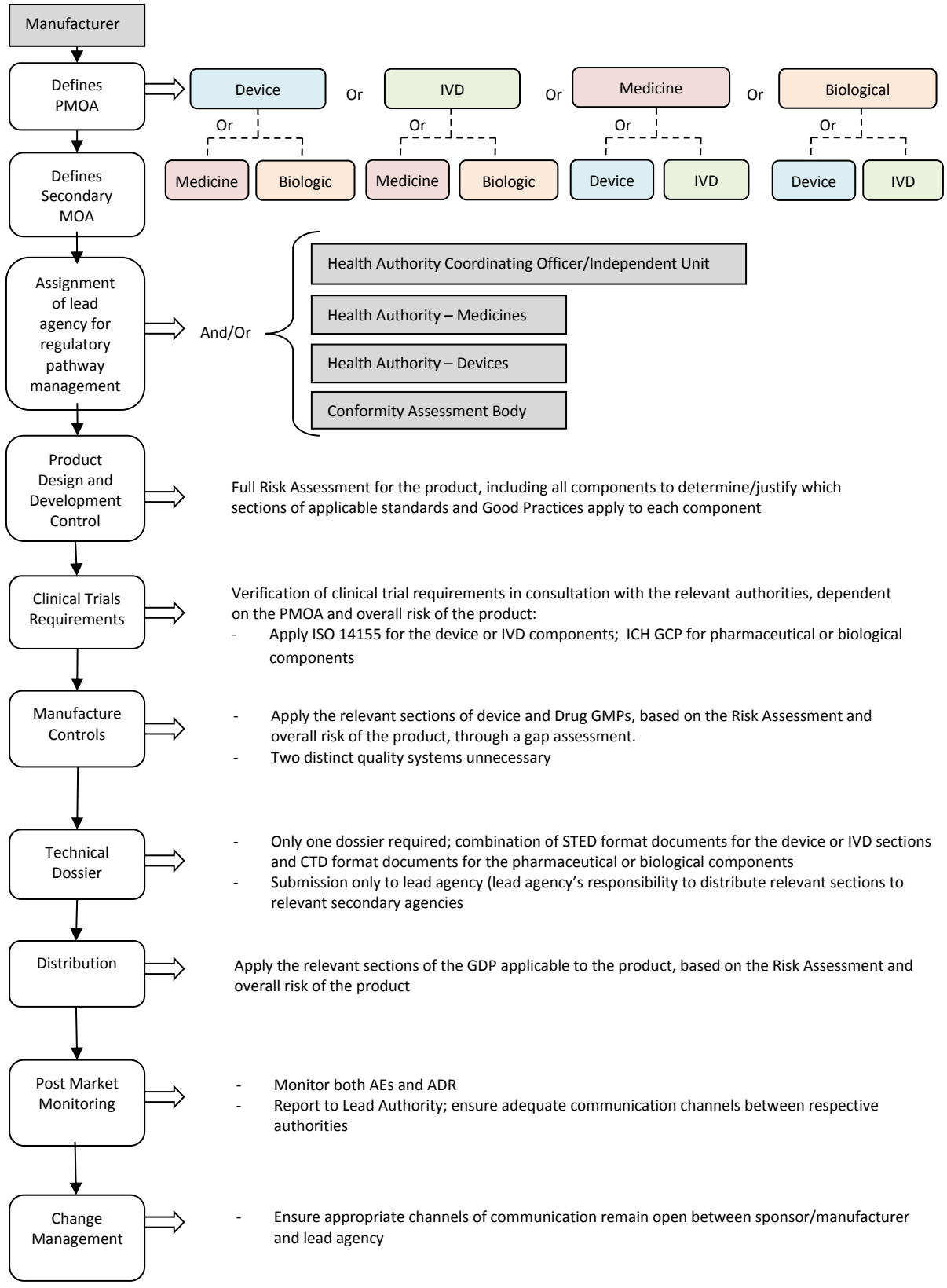
The current work of the IMDRF to develop a common Table of Contents for a regulatory dossier is noted. This may provide a future opportunity to integrate regulatory dossier formats for medical devices, medicines and combination products.

4.5 Post-market Requirements

The reporting of postmarket events by the authorized representative or manufacturer will reflect the current procedures related to the product's PMOA. However, because the nature of the assessment of such events differs (medicines tends to be focused towards trend analysis and consideration of pharmacological mechanisms; whereas device activities tends to investigate with engineering considerations to determine causation and necessary corrective actions). Communication between authorities is necessary to ensure a effective review of every post-market event. Therefore, the regulatory authorities should have adequate communication pathways to facilitate the exchange of information between device, and pharmaceutical authorities, to allow for the visibility, and

assessment of reportable postmarket events. The efficient communication of information between both authorities is essential to ensure effective operation of post-market regulatory control of combination products.

4.6 Process flow for handling the registration of Combination Products



5. Conclusion

The regulation of Combination Products, by necessity, requires the combined experience and expertise of a number of individuals and authorities. The key step in the regulation of such products is the initial identification of the PMOA which enables the appointment of lead authority, determination of regulatory pathway, formats of technical dossiers, requirements of manufacturing controls and clinical trials and the designation of post market activities.

The recommended practice for the regulation of Combination Products involves a clear leadership role by the lead authority with supporting input from the other participating authorities. A hierarchical review structure enables each component of the product to be reviewed, and assessed by those with the most extensive expertise, whilst simultaneously streamlining the documentation and communication requirements for all parties. This ensures that all components of the product are assessed for safety and performance by qualified bodies; the manufacturers are not subject to unnecessarily burdensome, or inappropriate regulatory requirements, and there is timely access to new therapeutic products.