



Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

FINAL DOCUMENT

Title: Regulation of Combination Products – a Review of
International Practice

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Executive Summary

This White Paper presents a summary of current international practices for regulation of Combination products in a selection of representative jurisdictions including members of both IMDRF and AHWP

The paper addresses products which *integrally combine* a medical device with a medicine or biological (E.G. drug eluting stents, devices with antimicrobial coatings). It does not include companion products which are cross labelled (e.g. companion diagnostics) or products supplied together (systems or kits).

The information gathered and presented in this white paper shows that although there are areas of consensus and similarities of practice in the regulation of combination products, there are also areas of substantial difference between regulators. Key findings were:

- No agency has a separate regulatory pathway for combination products. In almost all cases the regulatory pathway for a combination product is according to the primary mode of action. Products which have a primary action as a device (e.g. drug eluting stent) are regulated under medical device laws, and products which have a primary biologic or medicinal action (e.g. prefilled vaccine or medicine syringe) are regulated under biologic or medicine laws.
- Most agencies draw on the resources of sister divisions or agencies in regulatory assessment of the secondary modes of action.
- Many agencies had some mechanism for adjudication of borderline cases and some had arrangements for coordination of activities across divisions. These arrangements varied widely ranging from single coordinating officer to completely independent business units (e.g. the US FDA Office of Combination Products or the China FDA Administrative Service Center).
- There is wide variation in application of manufacturing regulations or guidance. Different jurisdictions may apply devices (ISO 13485 or equivalent) or pharmaceutical GMP or both. This presents a practical challenge for manufacturers in application of the relevant GMP codes to production of separate device/biologic/medicine components, and to those parts of the production process which involve the integrated components.
- Technical Dossier formats vary widely, using variants of ICH CTD, GHTF STED, local dossier formats or some combination of these. It is noted that efforts by IMDRF to develop a devices dossier format aligned with the pharmaceutical ICH CTD may provide a solution covering all product types.
- There is wide variation in approaches to regulation of clinical trials. Good Clinical practice (GCP) requirements varied with application of ICH GCP, ISO 14155 or a combination of both.
- Monitoring methods and investigational approaches to postmarket monitoring vary significantly between devices and medicines. In most jurisdictions, postmarket regulation almost always used the laws and monitoring systems applicable to the primary mode of action. For combination products, this presents risks of overlooking safety issues associated with the secondary mode of action.

CONTENTS

1	Introduction	5
2	Definitions.....	5
2.1	Product types.....	5
2.2	Primary Mode of Action.....	6
3	Current Practice	6
4	Regulatory Challenges for Combination Products	6
5	Current Practices.....	7
5.1	Regulatory pathway	9
5.2	Responsibilities and coordination.....	9
5.3	Manufacturing Controls	9
5.4	Clinical Trials	9
5.5	Technical Dossier Format.....	9
5.6	Postmarket Requirements	10
6	Summary	10
Appendix A	Questionnaire	11
Appendix B	Jurisdiction requirements	18
	Taiwan	19
	China.....	22
	Korea	25
	Thailand.....	28
	Indonesia.....	31
	Singapore.....	34
	Malaysia	37
	Saudi Arabia –.....	40
	Japan	44
	USA.....	47
	Australia	50
	Canada.....	53
	European Community	56
	Hong Kong	59

1 Introduction

Combination products present unique challenges in management of the application of different regulatory requirements and review processes and in review of multiple interacting technologies. This review has been prepared by the Combination Products working group of AHWP Study Group 1 to inform the AHWP Technical Committee as to the current regulatory practices for combination products, and to provide a background to possible future guidance preparation by AHWP. The review has considered practices in both AHWP member jurisdictions, as well as in the members of the International Medical Device Regulatory Forum (IMDRF).

2 Definitions

2.1 Product types

As a general principle a combination product is a therapeutic product which *integrally combines* features of two or more of medical device, medicine, biologic or *in vitro* diagnostic device. However there is frequent confusion about the extent of this definition, and whether other instances where medical devices are combined with drugs or diagnostics are captured within the definition of Combination Product.

In order to provide clarity we have, for the purposes of this review, adopted the following definitions.

Product type	Examples
Combination Product	
Products with two or more separate medicine/biologic/device/diagnostic components integrally combined	Prefilled vaccine syringe Insulin injector pen with prefill cartridge Drug eluting stent
Usually requires a single marketing application, although may be subject to review input from multiple regulatory divisions under a single lead determined by the Primary Mode of Action	Bone cement with integral antibiotic
Companion Product	
Two separately supplied products which are co-dependent and cross-labelled	Companion Diagnostic and associated medicine.
Usually requires separate marketing applications for each product, although the reviews may be cross referenced or coordinated and products may be cross labelled.	Human fibrin vial and Thrombin vial to be used together as a sealant

Kit or System

Two or more separate products which are co-packaged

May require a both separate regulatory submissions for each product plus a submission for the co-packaged kit or system.

Hospital dressing pack containing dressing/gauze, antiseptic swabs, vial of saline, disposable dish, forceps and scissors.

Fibrinogen and Thrombin in vials with their Applicator

Regulatory processes for Companion products are essentially the existing device, diagnostic or medicine regulations as applicable to each of the companion pair. Regulations for systems and kits are also well established within most current medical device regulatory frameworks.

This white paper will focus on the regulation of Combination products.

2.2 Primary Mode of Action

In deciding on a regulatory pathway, many regulators consider the primary mode of action (PMOA) of a combination product. Typically the PMOA will be used to determine the specific agency division or department which bears responsibility for the product and the regulations applied. The primary mode of action is the therapeutic or diagnostic function which is considered to be the primary purpose of the product. For example a drug eluting stent is generally considered to have a PMOA as a medical device (a stent) which is supported in its function by the eluted medicine. A prefilled vaccine syringe has a PMOA as a biologic – the vaccine, supported by the medical device (syringe) for delivery.

3 Current Practice

Information on the current regulatory requirements and practices for combination products was collated using the framework of a standard questionnaire (Appendix A). This questionnaire was either sent to regulatory agency representatives for completion and return or used to conduct telephone interviews of agency representatives in which case the questionnaire was completed by the researcher based on interview responses. Information was gathered for a range of AHWP and IMDRF members. For some of the more well established agencies (including most IMDRF members), the questionnaire was completed by a researcher based on available published materials including regulations, guidance documents and regulatory agency websites. The information compiled was then reviewed and is described and summarised below.

4 Regulatory Challenges for Combination Products

The regulation of combination products presents a specific challenge in that the mixture of technologies and functions involved may cause ambiguity as to the application of the various regulations which may cover devices, IVDs, biologics and medicines in any given jurisdiction. In particular it is necessary to consider:

- product design and development controls;
- clinical trials requirements;
- manufacture controls;

- audit practices;
- applicability of standards, pharmacopoeia and regulatory guidance;
- technical dossier formats and content.

All of these aspects of regulation can vary widely between device, medicine and biologics. The need to assess potentially very different co-dependent technologies and their interactions with the patient or user will usually require review processes to draw on expertise of multiple technical experts from different regulatory divisions or agencies.

5 Current Practices

The current practices for regulation of combination products are summarised in

Table 1.

Detailed descriptions of requirements in individual jurisdictions are described in Appendix B.

The information gathered and presented in this white paper shows that although there are areas of consensus and similarities of practice in the regulation of combination products, there are also areas of substantial difference between regulators. The following discussion summarises the areas of consensus and of difference attempts to identify the key technical and safety challenges arising from need to manage regulatory processes in tandem.

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,X	P	P,X	
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

SAU	Y	Y	Y	P	P	P	P	P	P	P	R
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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.

5.1 Regulatory pathway

No agency surveyed had a separate regulatory pathway or regulations for combination products. This is not surprising – combination products are everywhere accommodated within existing drug and device regulations and processes. The challenges are to coordinate and apply the necessary expertise and resources to ensure that a regulatory review is effective, scientifically rigorous and efficient.

5.2 Responsibilities and coordination

In all agencies surveyed the review of a combination product is led by the agency, division or office responsible for regulating products of the same primary mode of action: if the PMOA is a medicine, then the regulatory review is led by the medicines agency or division if it is a device then the devices agency or division leads the review). Once determination is made, in almost all cases the review is led by the “Primary Mode” division, supported by other divisions as required.

The arrangements for determination of borderline cases, and for coordination of the review activities and inputs of different review divisions varied widely ranging from a separate office to a determination committee to a coordinating officer. The most well developed arrangements involved separate offices to carry out these roles, e.g. the US FDA Office of Combination Products, the China FDA Administrative Service Center. The presence of a coordinating agent provides some independence in determinations of status and for follow ups on process.

5.3 Manufacturing Controls

There is wide variation in application of manufacturing regulations or guidance. Different jurisdictions may apply devices (ISO 13485 or equivalent) or pharmaceutical GMP or both. The practical challenge for manufacturers is to apply the relevant GMP codes to production of the separate device/IVD/medicine components, and then to determine the combined requirements which apply to those parts of the production process which involve the integrated components. For example for a prefilled syringe, the syringe would typically be manufactured under devices GMP controls, the medicine under pharmaceuticals GMP and the filling operation may require GMP controls which meet both devices and pharmaceutical requirements.

5.4 Clinical Trials

There is some variation in application of clinical trials regulations or guidance. Different jurisdictions may apply devices (ISO 14155 or equivalent) or pharmaceutical (ICH) GCP or both. In most cases the applicable GMP code is that which applies to the primary mode of action of the product. However some agencies apply a combination of devices and medicines GCP.

5.5 Technical Dossier Format

The technical dossier format is a particular challenge. Product design and production information will be developed under the devices or medicines documentary arrangements applicable to the components. The component documentation must then be combined into a final dossier which in most cases but these must then be compiled according to the dossier requirements which apply to the primary mode of action: either devices Standard technical Dossier (STED) or pharmaceuticals common technical dossier (CTD).

It is notable that a current work project of the IMDRF is to develop a devices dossier format which is aligned with the pharmaceuticals CTD format. It is also important to note that this is a considerable challenge given that the pharmaceuticals CTD is not completely internationally harmonised, with local variants existing in some jurisdictions including in AHWP members.

5.6 Postmarket Requirements

Postmarket requirements almost always follow those applicable to the primary mode of action. There are significant differences in approaches to postmarket regulation between product types. Medicines postmarket tends to be focussed towards trend analysis for types of adverse reactions and consideration of pharmacological mechanisms, whereas in devices, postmarket follow up tends to apply engineering considerations to event investigations in order to determine causation and necessary corrective actions which may include product redesign.

Adequate postmarket processes should bring to bear the expertise and techniques applicable to all components. Although ad hoc arrangements may exist for enlisting support of experts from other review divisions, in most cases there were no formal arrangements for coordination of postmarket activities between device/diagnostic or medicines divisions for the purposes of postmarket follow up of combination products. These differences in approach present possible risk of overlooking safety issues associated with the secondary mode of action if the necessary expertise is not available or applied to review or investigation of an adverse event.

6 Summary

The regulation of combination products is characterised in almost all jurisdictions by arrangements in which the regulatory review is led by the regulatory division responsible for the primary mode of action of the product. Combination products with a primary device or IVD mode of action are regulated as devices or IVDs, those with a primary drug action are regulated as medicines. There is a clear need in all cases for the review to be supported by expertise drawn from the appropriate review division for the secondary components. There are widely varying levels of formality for the coordination of review activities between divisions and for the determination of borderline cases.

Requirements for format of technical dossiers, for manufacturing controls for regulation of clinical trials and for postmarket activities all tend to be determined by the primary mode of action. A minority of agencies apply combined approaches. This can lead to the need to apply medicines requirements to device components and vice versa – which raises challenges both in terms of technical approaches and familiarity with practice.

There are specific areas in which greater formal coordination provides a potential for improvement in the effectiveness of regulation, particularly in the area of postmarket monitoring where it is essential that appropriate expertise is applied to investigation of adverse events.

The key issue is that the necessary expertise is brought to all stages of the regulatory process. Application of appropriate expertise ensures that important aspects of safety and performance are not overlooked. In addition it is important that lack of expertise does not result in application of unnecessarily burdensome or inappropriate regulatory requirements or review practices.

Appendix A Questionnaire

This Appendix provides a copy of the original questionnaire used for gathering the information used as input to this White Paper.

Regulation of Combination Products by AHWP members

AHWP Study Group 1 (Pre-market Regulation) is currently preparing a white paper summarising the regulation of combination products in member economies and in established non member jurisdictions (The IMDRF members).

A key part of the white paper will be a summary of the current status of regulation in member economies. We are seeking the input of the member economies as to the current practices in their regulatory systems. To compile this information we would appreciate your assistance with the following specific questions.

Please provide answers to as many questions as possible. In many cases, regulatory practice may be as important as actual legislation or regulations. Where there are important administrative practices – please identify these (e.g. it may be an administrative practice when conducting a review of an associated companion diagnostic to review the cross labelling of an associated medicine).

Helpful definition: Primary Mode of Action

In several jurisdictions, regulation of combination products is conducted according to the Primary Mode of Action (PMOA) of the product. For example a drug eluting stent is generally considered to have a PMOA as a medical device (a stent) which is supported in its function by the eluted medicine. A prefilled vaccine has a PMOA as a biologic – the vaccine, supported by the medical device (syringe) for delivery.

The definition of Primary Mode of Action is referred to in several of the questions below.

Jurisdiction

Address:

.....

Tel:.....

Email:

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

- Yes
- No

Reference(s) to regulation, guidance or practice.....

Is there a mechanism for review or designation of classification or status as combination product?

- Yes
- No

Reference(s) to regulation, guidance or practice.....

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

- Yes
- No

Comments

Is there a specific process for regulatory submissions of combination products?

- Yes
- No

Reference(s) to regulation, guidance or practice.....

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

- Separate combination products office/agency
- Agency/Division responsible for PMOA of product
- No

Details of responsible entity.....

.....
.....

Fees

What evaluation fees apply to combination products?

- Fees applicable to primary component
- Fees applicable to all components
- Special fee for combination product
- No fees
- Other

Comments/references to regulation, guidance or practice.....
.....
.....

GMP Requirements

What codes of GMP are applied to combination products?

- Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)
- Apply codes applicable to components for manufacturer of that component.
- Other
.....

Comments/references to regulation, guidance or practice.....
.....
.....

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

- Labelling regulations applicable to PMOA apply
- Labelling regulations for all components apply
- Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic)
- Other

Comments/references to regulation, guidance or practice

.....

.....

Postmarket Reporting

What arrangements apply to adverse event reporting?

- Apply the regulation applicable to primary mode of action
- Apply all regulations applicable to components for manufacturer of that component.
- Other

Comments/references to regulation, guidance or practice

.....

.....

Clinical Trials

How are combination products clinical trials regulated?

- Apply the regulation applicable to primary mode of action
- Other

Comments/references to regulation, guidance or practice

.....

.....

Clinical Data requirements

What are the clinical data requirements for combination products?

- Apply the requirements applicable to primary mode of action
- Apply all regulations applicable to components for manufacturer of that component.
- Other
.....
.....

Comments/references to regulation, guidance or practice

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Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice

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Thank you for your assistance.
Please return the completed survey to Rachel Tserng.
Rachel@brandwoodbiomedical.com
Fax : +61 2 8580 4613
Tel: +61 2 9906 2984

Appendix B Jurisdiction requirements

This Appendix presents the detailed results of the surveys made for each jurisdictions. It is important to note that the research used a range of information sources including:

1. Direct advice from regulatory agencies,
2. Information from expert advisers from within the industry.
3. Compilation by a researcher of information from published sources such as agency websites, guidances or primary regulations.

This allowed the compilation of as comprehensive a range of information across as wide a range of AHWP member economies as feasible.

However although we are confident that the information presented is current and as accurate as possible, none of the information presented should be considered to be a formal position or policy of any regulatory authority.

Taiwan

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Guidance for request of resignation of combination products is in preparation.

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Guidance for request of resignation of combination products is in preparation.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

If PMOA is of the drug, the combination product is regulated as a drug. If PMOA is of a device, the combination product is regulated as a device.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

not applicable

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

If the PMOA is that of a drug, the responsible entity in TFDA is Division of Medicinal Products. If the PMOA is that of a device, the responsible entity is Division of Medical Devices and Cosmetics.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

There are no special user fees for combination products. Combination products are subject to the user fees associated with their submission type.

GMP Requirements

What codes of GMP are applied to combination products?

- Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)
- Apply codes applicable to components for manufacturer of that component.
- Other

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

- Labelling regulations applicable to PMOA apply Labelling regulations for all components apply
- Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No comments or references

Postmarket Reporting

What arrangements apply to adverse event reporting?

- Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments or references

Clinical Trials

How are combination products clinical trials regulated?

- Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No comments or references

Clinical Data Requirements

What are the clinical data requirements for combination products?

- Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments or references

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

TFDA is in the process of developing a guidance document titled “Guidance for Request of Designation of Combination Products” and will continue to develop guidance documents as necessary to facilitate classification and approval of combination products

China

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Clause 1 in CFDA announcement No.16 in 2009 only formulates the definition of drug-device combination. But we are aware of combination product doesn't limit to this type, some of else combinations like drug/biologic/device, biologic/device maybe available as well. "Guideline on Writing the Registration Application of Drug-Containing Medical Device" issued by CMDE also give out the definition of drug-device combinations.

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Clause 4 in CFDA announcement No.16 in 2009 gives out CFDA acceptance office, CMDE and CDE will work together as the expert panel to review the classification application within 20 work-days and determine the product jurisdiction; however the actual timescale is always longer than the proposed one.

Evaluation Process

Are combination products regulated on the principle of "primary mode of action" (PMOA)?

Yes No

Comments:

Clause 2 in CFDA announcement No.16 in 2009 specifies two PMOA, one is device, and the other is drug.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance, or practice:

Clause 7 in CFDA announcement No.16 in 2009, during CFDA submission, if primary device product, we are requested to indicate that in the registration application form.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product
No

Details of responsible entity:

CFDA acceptance office is responsible for receipt of submission, CMDE will be the lead center to review primary device product whilst an intercenter (CMDE & CDE) review will be proceeded, that means CMDE

transfers the complete registration dossiers to CDE for the review comments, then CMDE consolidate the comments and send off the written supplemental notification to the applicant.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

No comments

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No specific requirement is applied to combinations; however ISO 13485 Certs for primary device product along with GMP cert for drug part are required for CFDA submission.

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

Per Guideline on Writing the Registration Application of Drug-Containing Medical Device, in Chinese version IFU, we are requested to further provide relevant information of drug contained in the device including drug name (general name), composition, and content, anticipated function etc apart from general request applicable to device

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

Current understating is that there is no specific requirements.

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No specific requirement on how to perform the clinical trial on drug-device combination product and we have yet conducted clinical trial on this kind product in China yet, only provide the clinical evaluations in CFDA imported product registration. Our current understanding is it shall be apply the regulation applicable to PMOA (Device).

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

same as above about clinical trials.

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

It seems there is no significant change made to regulatory management on combination products since CFDA No. 16 in 2009; we can track down that there is a draft version named 《药械结合产品审批程序（草案）》 compiled by CMDE in 2008 maybe still in discussion, till now not go public.

Korea

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

MFDS Established Rule No. 31 – Established Rules on Combination and Composite Medical Products (tentative)

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

MFDS Established Rule No. 31 - Rules on Combination and Composite Medical Products (tentative, herein after the Established Rule No. 31)

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

Article 4.1 of the MFDS Established Rule No. 31 (the Classification of a combination product shall be based on its PMOA and with reference to the following examples under the subparagraphs).

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

Article 5 (Determination of the appropriate Regulatory Bureau/Division) and the Article 6 (Handling product approval applications) of the MFDS Established Rule No. 31

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

Article 5.1(Determination of the appropriate Regulatory Bureau/Division) of the MFDS Established Rule No. 31 states that the personnel in the Support Centre shall sort out submitted applications in accordance with the Article 4.1 and those for combination products shall be designated to its responsible Division.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

No Comment

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

MFDS classifies applications into either medical products or pharmaceutical products according to PMOA before designating the application to its regulatory division for appropriate approval process. Combination Product is dealt by POMA Division under the MFDS where proceeds its simultaneous review on medical products and pharmaceutical product of combination products.

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

If the product is classified as a medical device, it is regulated by the Medical products Act by the Korea MFDS, particularly pertinent with the Article 20 or 23 of the Labelling Requirements.

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

MFDS classifies applications into either medical products or pharmaceutical products according to PMOA before designating the application to its regulatory division for appropriate approval process. Combination Product is dealt by POMA Division under the MFDS where proceeds its simultaneous review on medical products and pharmaceutical product of combination products.

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

MFDS classifies applications into either medical products or pharmaceutical products according to PMOA before designating the application to its regulatory division for appropriate approval process. Combination Product is dealt by POMA Division under the MFDS where proceeds its simultaneous review on medical products and pharmaceutical product of combination products.

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice

No comments.

Thailand

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

No Comment

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

To set a meeting among involved divisions, Medical Device Act 2008 has the principles of the primary mode of action for the classification criteria to be a medical devices.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

No comments

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

No comments

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

If the combination products POA is a medical devices, and submission is going to Medical Devices Division.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

Currently no fees apply.

GMP Requirements

What codes of GMP are applied to combination products?

- Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)
- Apply codes applicable to components for manufacturer of that component.
- Other

Comments/references to regulation, guidance or practice:

Pending decision making on whether both GMP require for Drug or Medical Devices or not. None on case basis.

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

- Labelling regulations applicable to PMOA apply Labelling regulations for all components apply
- Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

If classify as a drug – following the drug labelling requirement. If classify as a medical devices – following the medical devices requirements

Postmarket Reporting

What arrangements apply to adverse event reporting?

- Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

- Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

It depends on the products. For example, if using new design, new chemical, clinical total requirements applies.

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

Currently, we have not yet established specific GMP for medical devices to accept ICH GMP for Medical Devices. We have not yet set decision relating to clinical data requirements. We plan to establish GMP for Medical Devices in the future.

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice N.A.

Indonesia

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Currently US FDA guidance included combination product. Next in 2015 will refer to AMDD (ASEAN Medical Devices Directive)

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

At the practice the "expert team" review the combination products data to determine the product classification to medical devices or drugs.

Evaluation Process

Are combination products regulated on the principle of "primary mode of action" (PMOA)?

Yes No

Comments:

No comments

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

At the practice, we ask for the product's regulatory marketing status from the country of origin and from GHTF country to be a basic reference, than we form an expert team to review the product's document.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

if the combination product goes to medical device it will be regulated by Directorate of Medical Device Production and Distribution Development, if it is drug it will be regulated by NA-DFC (National Agency of Drug and Food Control)

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

According to the risk classification of the product.

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

according to Ministry of Health regulation No. 1189 year 2010

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No specific labelling, only written substance or parts shall appear on the label

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice

No comments

Singapore

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

No comments

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Medical Device Combination products are designated as such based on the risk classification rule 14, both in legislation (Health Products (Medical Device) Regulations, Third Schedule) and per published guidelines (GN-13, Guidance to Risk Classification).

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

No comments

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

The submission process is similar to non-combination medical devices, but the drug substance documentation requirements are not published. Companies are encouraged to write in to enquire on the relevant submission requirements specifically for the drug substance

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

Medical Device Branch – Medical Device Combination (drug as ancillary) Therapeutic Products Branch – Drug Combination

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

Health Products (Medical Device) Regulations, Fourth Schedule (Fees) – Combination abridged evaluation fee (\$\$10,000) compared to Class D abridged evaluation fee (\$\$5,700).

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No comments

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No comments

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

Guidelines on Combination Medical Devices are currently lacking, and there are plans to look into the development of published guidelines. However, with the recent initiatives on restructuring the medical device pre-market submission framework, this has been put on hold at the moment.

Malaysia

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

No comments

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

we have meetings such as technical meeting and

Steering Committee meetings for combination products (6 times per year and 2 times per year respectively) between Pharmacy department (inclusive of cosmetics) and Medical Device

Authority.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

Mainly looking at intended purpose and mode of action.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

In the process of developing the evaluation route for combination products.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

I am the person in charge to handle all product classification in Medical Devices Authority. If there is a product assumed to be combination product, we will discuss in the technical meeting of combination products. Members of the committee are both from MDA and Pharmaceutical bureau of Malaysia.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

No decision has been made as regards to the fees.

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No comments

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

At the moment there is no guidance on this.

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

In the process of developing proper route of evaluation for combination product. The application for the evaluation of combination product will be based on the mode of action and its primary intended purpose and it will be via online system. Several relevant guidelines also will be produced accordingly by the committee

Saudi Arabia –

Note: The following answers are based on a draft requirement for the combination products which is currently under review, once it's approved it will be implemented and published through SFDA website.

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Therapeutic product that combine medical device with drug either physically on single entity or they separate but they are packaged on single package ,or both of them they package separate but they are used together to achieve the intended use.

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

The combination products committee is responsible to receive all submissions related to combination product or products with unclear regulatory classification.

The combination product committee will work as a coordination center between all sectors to monitor and simplify the process for pre-market approval of combination product.

The combination Products committee will ensure timely and effective pre-market review and follow up with the post-market issues with different sectors.

The combination product committee will decide whether a product is considered as a medical device or a drug product for the product that regulatory classification is not clear.

A combination product will be subject to either the Medical Devices Regulations or the Drug Regulations after the principal intended action is achieved.

If the Primary mode of action of the combination product meet the definition of the pharmacological and is achieved by pharmacological action, the combination product will be subject to the Drug Regulations.

If the Primary mode of action of the combination product meet the definition of medical device and it does not have a biological product, and it does not achieve its intended action through chemical action within or on the body and is not dependent on being metabolized for the achievement of intended action. The combination product will be subject to the medical device Regulations.

The combination product committee will assure that all combination products meet acceptable standards of safety, efficacy and quality before getting pre-market approval from the relevant sector.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

kindly refer to the mechanism

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

kindly refer to the mechanism

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

The combination products committee

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

If the classification committee decision is medical device then the applicant should comply with marketing authorization fees. Please refer to –

<http://www.sfda.gov.sa/en/medicaldevices/regulations/DocLib2/Fees3.pdf>.

If the classification committee decision is Drug then the applicant should comply with Drug sector Regulations & Guidelines – http://www.sfda.gov.sa/en/drug/drug_reg/Pages/drug_reg.aspx

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

Based on the committee final decision the applicant shall comply with the leader sector regulations. If the classification committee decision is medical device then the applicant should comply with implementing rule on marketing authorization fees – <http://www.sfda.gov.sa/en/medicaldevices/regulations/DocLib1/MDS-IR6.pdf>

If the classification committee decision is Drug then the applicant should comply with Drug sector Regulations & Guidelines – http://www.sfda.gov.sa/en/drug/drug_reg/Pages/drug_reg.aspx

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

- Labelling regulations applicable to PMOA apply Labelling regulations for all components apply
 Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

If the classification committee decision is medical device then the applicant should comply with marketing authorization fees. Please refer to –

<http://www.sfda.gov.sa/en/medicaldevices/regulations/DocLib2/Fees3.pdf>.

If the classification committee decision is Drug then the applicant should comply with Drug sector Regulations & Guidelines – http://www.sfda.gov.sa/en/drug/drug_reg/Pages/drug_reg.aspx

Postmarket Reporting

What arrangements apply to adverse event reporting?

- Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

If the classification committee decision is medical device then the applicant should comply with implementing rule on POST-MARKETING SURVEILLANCE –

<http://www.sfda.gov.sa/en/medicaldevices/regulations/DocLib1/MDS-IR7.pdf>

If the classification committee decision is Drug then the applicant should comply with Drug sector Regulations & Guidelines – http://www.sfda.gov.sa/en/drug/drug_reg/Pages/drug_reg.aspx

Clinical Trials

How are combination products clinical trials regulated?

- Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

Based on the committee final decision the applicant shall comply with the leader sector regulations.

Clinical Data Requirements

What are the clinical data requirements for combination products?

- Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

Based on the committee final decision the applicant shall comply with the leader sector regulations.

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

The draft regulation currently is under review, once its approved it will be implemented and published through SFDA website.

Japan

Sourced from information published by Pharmaceuticals and Medical Devices Agency (PMDA)

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

MHLW/PMDA have no independent definition for Combination Products. Generally recognized as a product that drug and medical device are physically and chemically integrated.

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Combination products are regulated under Pharmaceutical Affairs Law. MHLW/PMDA have no fixed procedure in determining the regulatory category (drug or medical devices).

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

Determine appropriate regulatory category for each application of Combination Products case by case basis, based on a primary mode of action (PMOA) of the products.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

Consultative/Collaborative review among related divisions in PMDA and HLW. There is no specific review timeline for Combination Product, however, the review timeline is set according to the application category (drug or medical devices, new or generic etc)

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

NA

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

Depends on its application category of the products as drugs or medical devices.

JPY 30m for new drug, JPY 9.4m for new and high-risk device

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

The requirement are the same as other drugs or medical devices. When combination product is regulated as Drug, it is subject to GMP inspection. When combination product is regulated as Medical Device, it is subject to QMS (ISO13485 based) inspection.

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No specific requirement for label and IFU related to Combination Products. General labelling requirements are the same as other drugs and/or Medical Devices.

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

Marketing Authorization Holders of drug or medical device have to report adverse event such as death, disorder, and infection in accordance with PAL. There is no specific requirement for Combination Products, because Combination Product is classified as either Drug or Medical Devices.

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

In general, clinical trial data in Japan is required for drugs. For medical devices, in some cases such as extrapolation could be scientifically explained by the result of foreign clinical trial, which do not require additional clinical data.

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

New J-PAL includes this category and it will be effective by the end of November 2014.

USA

Sourced from US Food and Drug Administration website

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Combination Products are defined in 21 CFR 3.2(e).

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

The Office of Combination Products (OCP) issues classification and jurisdiction assignments for medical products. The indication and configuration of a product determines the type of product (drug, device, biological products or combination products. If the product contains a combination of two or more drug, biologic or device it is considered a combination product.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

21 CFR 3.4 – the regulation regarding how FDA designates the review of combination products. Designation of lead FDA review center is based on the Primary Mode of Action (PMOA) of a product. FDA issued a final rule on August 25, 2005 for the definition of PMOA. Refer to 70FR49848 for more information.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

A combination product is assigned to an agency center that will have primary jurisdiction for its premarket review and regulation. Under section 503(g) of the Act, the assignment of a “lead center” is based upon a determination of the “primary mode of action” (PMOA) of the combination product. For example, if the PMOA of a combination product is that of a biological product, then the combination product would be assigned to the Agency component responsible for premarket review of biological products.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

Actual dossier is submitted to the Lead Center.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

No special fees, subject to the user fees associated with their submission type – MDUFMA – Medical Device User Fee and Modernization Act 2002 or PDUFA.

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

*OCP has published a draft guidance documents –
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm#curre>*

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No comments

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

OCP posted a request for comments for a concept paper about adverse event reporting for combination products. Also, OCP intended to proposed regulation to clarify adverse event reporting requirements for combination products.

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Could require clinical studies based on both constituent parts

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

Submission types are determined by the constituent part providing PMOA. The standards for marketing authorization of each constituent part must be met.

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Changes in the legislation are being considered, but this is in the early phase and the outcome is unknown.

Australia

Sourced from Therapeutic Goods Administration

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

Medical devices incorporating a medicine: means a medical device of any kind that incorporates, or is intended to incorporate, as an integral part, a substance that:

i. if used separately, would be a medicine; and

ii. is liable to act on a patient's body with action ancillary to that of the device

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Classification Rule 5.1 of Schedule 2 of the Regulations indicates that medical devices are Class III if they incorporate, or are intended to incorporate, as an integral part, a substance that:

Australian Regulatory Guidelines for Medical Devices, Section 14. Medical devices incorporating a medicine

• if used separately would be a medicine; and

• is liable to act on the patient's body with an action ancillary to that of the device.

Evaluation Process

Are combination products regulated on the principle of "primary mode of action" (PMOA)?

Yes No

Comments:

In determining how these products are regulated, TGA takes into consideration – which element (device or medicine) provides the principle therapeutic effect the principle mode of action of the product, and which element provide supporting or ancillary effect as they relate to the definition of medicine and medical devices.

TGA provide guidance and some indication of predicate decisions for combination products. A list of the products that contain both a medical devices and a medicinal components, where TGA has previously made a determination in relation to whether the type of product is to be regulated as medical device or medicine – http://www.tga.gov.au/industry/devices-guidelines-35.htm#.U6u-C_VApjo

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

No comments

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

Combination products are regulated in accordance with principal intended purpose and most of action by appropriate product regulator.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

For combination products regulated as devices, an additional special fee applies to evaluation of medicinal component

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No comments

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No comments

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

Clinical trial regulations are the same for all product types in Australia. Applicable GMP codes (ICH GCP or ISO 14155) apply according to product type.

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

N/A

Canada

Sourced from Health Canada www.hc-sc.gc.ca

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

No comments

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

- 1. A combination product will be subject to either the Medical Devices Regulations or the Food and Drug Regulations according to the principal mechanism of action by which the claimed effect or purpose is achieved.*
- 2. Where the principal mechanism of action by which the claimed effect or purpose is achieved by pharmacological, immunological, or metabolic means, the combination product will be subject to the Food and Drug Regulations, unless that action occurs in vitro, without reintroducing a modified cellular substance to the patient, in which case the product will be subject to the Medical Devices Regulations.*
- 3. Where the principal mechanism of action by which the claimed effect or purpose is not achieved by pharmacological, immunological, or metabolic means, but may be assisted in that effect or purpose by pharmacological, immunological, or metabolic means, the combination product will be subject to the Medical Devices Regulations.*
- 4. Although a combination product will be subject to either the Food and Drug Regulations or the Medical Devices Regulations, both the principal and ancillary components shall meet acceptable standards of safety, efficacy and quality. Combinations of drugs and devices to which this policy does not apply and which must comply with both the Food and Drug Regulations and the Medical Devices Regulations*

The sponsor of a submission for a combination product not previously classified may present a written request for a classification decision to the relevant Bureau Director in advance of the submission. Where possible, a decision will be rendered within 14 calendar days of receiving the request. Requests for product classifications and/or related pre-submission meetings for drug-device or drug-drug combinations should be sent in duplicate by fax or mail to either of the two relevant directorates at the addresses provided below.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

No comments

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

The sponsor is required to attest in the application or submission for a licence, Notice of Compliance, or drug identification number, as the case may be, that the ancillary component of the combination product meets acceptable standards of safety, efficacy and quality.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

The review of submissions for combination products will be undertaken according to the expertise required to assess the risk/benefit profile of the product. The review may be undertaken by one Bureau or a team of reviewers representing more than one Bureau.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

Submission for combination products classified as drugs and regulated under the Food and Drug Regulations will be subject to any fee payable for drugs under the regulations enacted for that purpose.

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No comments

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No comments

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No comments

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

N/A

European Community

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance, or practice:

MEDDEV 2.1/3 Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance, or practice:

Determination by Competent Authority following request from Notified Body.

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments:

No Comments

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

Devices with an integral medicine may require EMEA consultation. Medicines Agency consultation process is detailed in “EMEA recommendation on the procedural aspects and dossier requirements for the consultation to the EMEA by a Notified body on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device, EMEA/CHMP/401993/2005” ..

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency Agency/Division responsible for PMOA of product No

Details of responsible entity:

Combination Products in the European Union (EU) are currently regulated through 2 different arrangements

Combinations comprised solely, or

Mainly of pharmaceutical actives are controlled by medicines agencies while those consisting predominantly of devices are approved through a fragmented national-based system based on certification by an expert organization called the Notified Bodies.

Fees

What evaluation fees apply to combination products?

Fees applicable to primary component Fees applicable to all components Special fee for combination product No fees Other

Comments/references to regulation, guidance or practice:

Additional fees for EMEA consultation process for devices with integral medicine

GMP Requirements

What codes of GMP are applied to combination products?

Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)

Apply codes applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

No Comments

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

Labelling regulations applicable to PMOA apply Labelling regulations for all components apply

Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic) Other

Comments/references to regulation, guidance or practice:

No Comments

Postmarket Reporting

What arrangements apply to adverse event reporting?

Apply the regulation applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component Other

Comments/references to regulation, guidance or practice:

No Comments

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action Other

Comments/references to regulation, guidance or practice:

No Comments

Clinical Data Requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action Apply all regulations applicable to components for manufacturer of that component. Other

Comments/references to regulation, guidance or practice:

No Comments

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice:

Substantial reform of medical devices regulations is underway in Europe with draft regulations currently being considered by the European Commission

Hong Kong

Definition and Classification

Is there a definition of combination product in regulation, guidance or practice?

Yes No

Reference(s) to regulation, guidance or practice:

There is a description on the combination of a medical device (MD) and a medicinal product in Section 3.2.2 of the Overview of the Medical Device Administrative Control System (MDACS) Guidance Notes: GN-01 (http://www.mdco.gov.hk/english/mdacs/mdacs_gn/files/gn_01.pdf).

Is there a mechanism for review or designation of classification or status as combination product?

Yes No

Reference(s) to regulation, guidance or practice:

No Comments

Evaluation Process

Are combination products regulated on the principle of “primary mode of action” (PMOA)?

Yes No

Comments :

The principle is adopted in the current voluntary MD listing system.

Is there a specific process for regulatory submissions of combination products?

Yes No

Reference(s) to regulation, guidance or practice:

Combination products which fall into the definition of pharmaceutical products are evaluated and registered by the Drug Office, Department of Health. Combination products not classified as pharmaceutical products and fall into the scope of the MDACS can be listed as medical devices upon successful application.

Is there a specified person or division of the regulatory agency which is responsible for receipt of submissions and management of combination product evaluation?

Separate combination products office/agency

Agency/Division responsible for PMOA of product

No

Details of responsible entity

No Comments

Fees

What evaluation fees apply to combination products?

- Fees applicable to primary component
- Fees applicable to all components
- Special fee for combination product
- No fees
- Other

Comments/references to regulation, guidance or practice:

For listing of medical devices under the Medical Device Control office, there is no charge. However, registration fees are charged if the product is classified as a pharmaceutical product.

GMP Requirements

What codes of GMP are applied to combination products?

- Apply the code applicable to primary mode of action (e.g. ISO 13485 for primary device product, ICH GP for primary drug product?)
- Apply codes applicable to components for manufacturer of that component.
- Other

Comments/references to regulation, guidance or practice:

Combination products which fall into the definition of pharmaceutical products should follow the manufacturing requirements of drug products. Combination products not classified as pharmaceutical products and fall into the scope of the MDACS should follow the manufacturing standard of ISO 13485.

Labelling

Are there specific labelling requirements for combination products? Do any of the following apply?

- Labelling regulations applicable to PMOA apply
- Labelling regulations for all components apply
- Requirements for cross labelling of separately packaged combination products (e.g. cross labelling of medicine and companion Diagnostic)
- Other

Comments/references to regulation, guidance or practice:

Combination products which fall into the definition of pharmaceutical products should follow labelling requirements of drug products. For combination products not classified as pharmaceutical products and fall into the scope of the MDACS, reference should be made to MD labelling requirements (http://www.mdco.gov.hk/english/mdacs/mdacs_gn/files/TR005E_23apr2010.pdf).

Postmarket Reporting

What arrangements apply to adverse event reporting?

- Apply the regulation applicable to primary mode of action

Apply all regulations applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

For adverse incident reporting of pharmaceutical products, please refer to the Reporting Guidelines of Adverse Drug Reactions

(http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/adr_reporting/reporting_guideline.html) .

For adverse incident reporting of listed MD, please refer to the Guidance Notes for Adverse Incident Reporting by Local Responsible Persons (Guidance Notes: GN-03)

(http://www.mdco.gov.hk/english/mdacs/mdacs_gn/files/gn_03.pdf).

Clinical Trials

How are combination products clinical trials regulated?

Apply the regulation applicable to primary mode of action

Other

Comments/references to regulation, guidance or practice:

Currently there is no overarching legislation that regulates the clinical trial of medical devices in Hong Kong. For pharmaceutical products, a Certificate for Clinical Trial / Medicinal Test is required for the purpose of conducting a clinical trial on human beings or a medicinal test on animals, please refer to the clinical trial guidelines for details:

http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/guidelines_forms/clinicalTrial.html.

Clinical Data requirements

What are the clinical data requirements for combination products?

Apply the requirements applicable to primary mode of action

Apply all regulations applicable to components for manufacturer of that component.

Other

Comments/references to regulation, guidance or practice:

Combination products which fall into the definition of pharmaceutical products should follow clinical data requirements of drug products. For combination products not classified as pharmaceutical products and fall into the scope of the MDACS, reference should be made to the MD clinical evidence requirements (Section 7.3.2 of STED, http://www.mdco.gov.hk/english/mdacs/mdacs_gn/files/tr002).

Planned changes

Are there any other initiatives or planned regulatory changes with respect to combination products?

Comments/references to regulation, guidance or practice

No Comments