Guidelines for Registration of Combination Products

Medical Product Division
Bhutan Food and Drug Authority

Medical Product Division
Bhutan Food and Drug Authority
Ministry of Health
Royal Government of Bhutan
Post Box 1556
Thimphu, Bhutan

List of Contributors

We would like to acknowledge following officials for their contributions in developing this guideline:

1. Mr. Jigme Tenzin, Officiating Chief Regulatory Officer, MPD, BFDA
2. Mr. Jigme Dorji, Sr. Regulatory Officer, Licensing and Vigilance Section, MPD, BFDA
3. Ms. Gyelwa Kuenzom, Sr. Regulatory Officer, Licensing and Vigilance Section, MPD, BFDA
4. Mr. Sonam Chophel, Regulatory Officer, Drug Evaluation Section, MPD, BFDA
5. Ms. Sangay Choden, Regulatory Officer, Drug Evaluation Section, MPD, BFDA
6. Mr. Dorji, Regulatory Officer, Drug Evaluation Section, MPD, BFDA
7. Mr. Ugyen Tshering, Asst. Regulatory Officer, Medical Device Section, MPD, BFDA
8. Mr. Guru, Asst. Regulatory Officer, Licensing and Vigilance Section, MPD, BFDA
9. Mr. Sonam Jamtsho, Asst. Regulatory Officer, Licensing and Vigilance Section, MPD, BFDA

Compilation and Editing

1. Ms. Kinley Penjor Tshomo, Regulatory Officer, Medical Device Section, MPD, BFDA

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1. Introduction

Combination products represent a unique and dynamic category within the healthcare industry, integrating two or more different types of medical products into a single entity. The convergence of these diverse components within a single product brings forth complex regulatory challenges that necessitate comprehensive guidelines to ensure safety, efficacy, and quality.

This guidance document is intended to guide the applicant on registration of combination products, and the classification criteria of combination products to provide information on the regulatory framework for dealing with combination products submissions. This document should be read in conjunction with any relevant and applicable guidance documents. Combination products are either drug-medical device combination or medical device-drug combination.

2. Scope

2.1. This guideline shall apply to combination products of medical devices, pharmaceuticals and biologics.

3. Objectives

3.1. To guide the applicant on proper classification of combination products and the submission of appropriate documents based on the combination product category.

3.2. To provide guidance to the regulators for consistent and uniform decision-making in the regulation of combination products.

4. Normative References

4.1. The Medicines Act of the Kingdom of Bhutan 2003

4.2. Bhutan Medicines Rules and Regulation 2019

4.3. Guideline for registration of medicinal products

4.4. Guideline for registration of medical device

5. Definitions

5.1. Ancillary dossier: It refers to the dossier required by the secondary section

5.2. Authority: It refers to refers to Bhutan Food and Drug Authority

5.3. Combination product: It refers to

5.3.1. A product comprised of two or more regulated components, i.e., drug/ device, biological/device, or drug/device/biological, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

5.3.2. Two or more separate products packaged together (co-packaged) in a single package or as a unit and composed of drug and device products, device and biological products.

5.4. **Medical device-drug products**: It refers to combination products when the primary mode of action in or on the human body is not based on pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means where Medical Device section (MDS) is the primary agency of the combination product.

5.5. **Drug-medical device products**: It refers to combination products when its primary mode of action is based on pharmacological, immunological or metabolic action in/on the body where the Drug Evaluation section (DES) is the primary agency of the combination product.

5.6. **Primary dossier**: It refers to the dossier required by the primary section.

5.7. **Primary Mode of Action**: It refers to the mode of action that provides the greatest contribution to the overall therapeutic effects of the combination product

5.8. **Primary section**: It refers to the section with primary regulatory responsibility for a combination product which is determined by the primary mode of action of the product.

5.9. **Secondary section**: It refers to the section that regulates the other part(s) included in the combination product

6. Acronyms

6.1. **BFDA:** Bhutan Food and Drug Authority
6.2. **DES**: Drug Evaluation Section
6.3. **IFU**: Instruction For Use
6.4. **MDS**: Medical Device Section
6.5. **MPD**: Medical Product Division
6.6. **PMOA**: Primary Mode of Action

7. General principle

7.1. Drug-medical device/medical device-drug combination products are regulated as drug or medical devices based on the PMOA/the principal mechanism of action by which the claimed effect or purpose of the product is achieved.

7.2. Other criteria that need to be considered while classifying the combination products are the statutory definitions and the proposed indication/claim.

7.3. Combination products regulated as drugs/medicines are based on pharmacological, immunological or metabolic action in/on the body and will be registered in accordance with the Guideline for registration of medicinal products.

7.4. Combination products regulated as medical devices do not achieve its primary mode of action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such

means and will be registered in accordance with the Guideline for registration of medical devices.

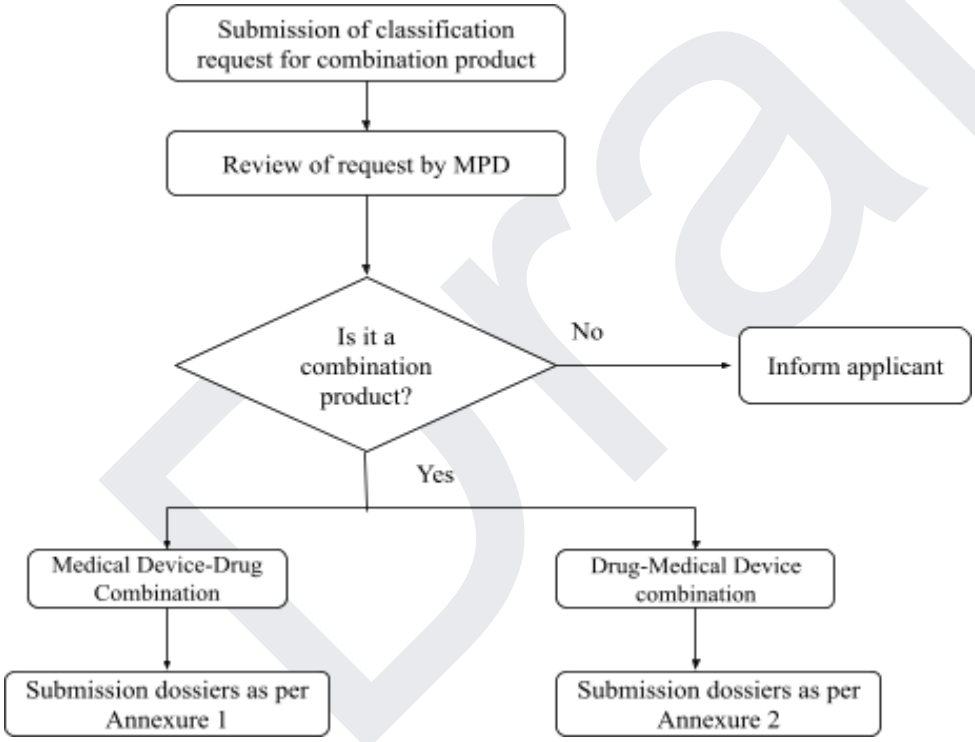
7.5. There are two routes of registration for combination products:

7.5.1. Full route of registration: Combination product that is not eligible under Abridged route of registration.

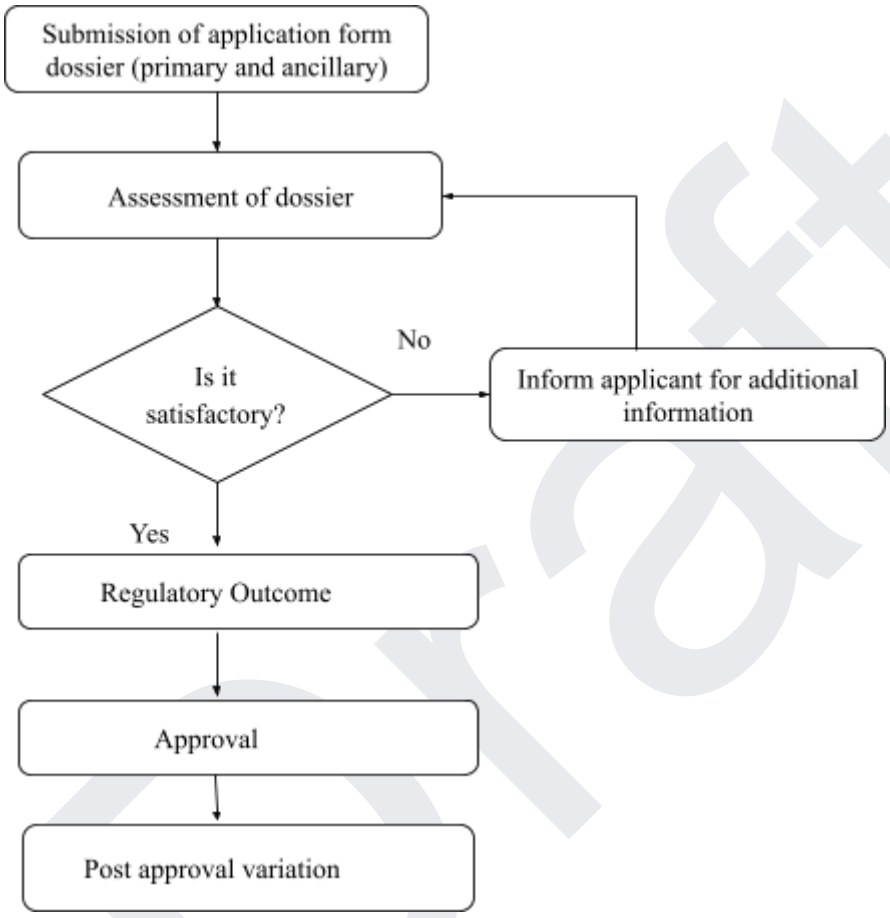
7.5.2. Abridged route of registration: Combination product that is WHO prequalified or is registered in any one of the WHO listed Authorities (WLA)

8. Process flow chart

8.1. Preliminary assessment for combination product



8.2. Registration of combination products



9. Procedure

9.1. Preliminary assessment for combination product

9.1.1. The applicant should submit the request for classification of combination product as per Annexure 5 along with supporting documents

9.1.2. The request for classification of combination products should be reviewed to identify whether the product is a combination product or not, based on the statutory definitions, the proposed indication/claim and PMOA.

9.1.3. In case of combination products, the applicant will be guided to submit application forms and dossiers.

9.1.4. The primary and secondary section responsible for the review of the product will also be identified.

9.2. Registration of combination products

9.2.1. The applicant shall submit the application form as per Annexure 3 or 4 based on the route of registration with the dossiers (primary and

ancillary dossiers as per Annexure 1 and 2 respectively) along with application fee

9.2.2. The dossier submitted should be assessed and evaluation queries may be issued to the applicant if clarification or additional information is required. The maximum number of queries from the Authority will be capped at two.

9.2.3. The product registration certificate is issued within a TAT of 60 calendar days considering the stop clock principle

9.2.4. The product registration certificate is valid for three years

9.2.5. The renewal process is as per the relevant guideline for registration of medicinal products and medical devices respectively.

10. Reference

10.1. Guideline for Drug-Medical Device and Medical Device-Drug combination product, Ministry of Health, Malaysia, 2023

10.2. Guidance for Combination Products Classification, Saudi Food and Drug Authority, 2020

11. Annexure 1: Document requirement for Medical Device-Drug combination

Sl. No.	Documents required	Full route /Standard Route	ABR route
	For primary dossier		
1	As per Guideline for registration of medical devices	Yes	Yes
	For ancillary dossier		
	Part I: General Information 1. Generic or International Nonproprietary name (INN) 2. Brand name or trade name (if applicable) 3. Dosage form 4. Strength 5. Compendial/ In-house specifications 6. List of all the ingredients in the dosage form and their amount on a per unit basis, as per the label claim and batch quantities 7. Description of the organoleptic characteristics 8. Commercial presentation of packaging and pack size 9. The therapeutic category/pharmacological classification to which the pharmaceutical product belongs 10. Indication 11. Dose and directions for use for each indication 12. Mechanism of Action(s) for the claimed indication 13. List of all the major and common side effects. Side effects specific to the particular drug including newly recognized side effects should be identified. 14. Information on use in pregnancy, breastfeeding and other special group of patients including known contraindications and compatibility of use of the finished product during pregnancy and breastfeeding. 15. Withdrawal Period for food producing animals (For Veterinary Medicines)	Yes	Yes

	PART II: QUALITY DATA OF DRUG COMPONENT **As per:** ICH M4Q: COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE QUALITY OVERALL SUMMARY OF MODULE 2 AND MODULE 3: QUALITY OR THE ASEAN COMMON TECHNICAL DOSSIER (ACTD) FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE Part II: QUALITY	Yes	No
	PART III: NON CLINICAL DOCUMENT 1. Non Clinical Overview 2. Tabular Listing of Non Clinical Study 3. Non Clinical/ Biocompatibility Study Reports	Yes (*only for New chemical entities*)	No
	PART IV: CLINICAL DOCUMENT 1. Product Development Rationale 2. Tabular Listing of Clinical Study 3. Clinical document pertaining to the medical device with ancillary component (i.e.: Clinical Evaluation Report (CER), in-house clinical report, published clinical paper (if any))	Yes (*only for New chemical entities*)	No

12. Annexure 2: Document requirement for Drug-Medical Device combination

Sl.No.	Documents required	Full route	Abridged route
For primary dossier			
1	As per Guideline for registration of medicinal products 2020	Yes	Yes
For ancillary dossier			
1	Device description including Instruction of use (IFU) / Product Catalog /Brochure	Yes	Yes
2	Relevant essential principle and evidence of conformity (for Risk Class C and D)	Yes	No
3	Performance data/Report or Certificate of Analysis	Yes	Yes
4	Clinical Evidence (for Risk Class C and D)	Yes	No
5	Risk analysis	Yes	No

Annexure 3:

Application form for Combination products

APPLICATION FOR REGISTRATION OF COMBINATION PRODUCT (Abridged route)

M/s.....hereby applies for registration of the combination product specified below for sale/distribution in Bhutan.

Combination product (tick whichever applicable)

□ Drug-Medical Device combination
□ Medical Device-Drug combination

Basis for Abridge registration (tick whichever applicable

□ The product is WHO prequalified
□ The product has obtained regulatory approval from WHO Listed Authority

Name of the WLA where the product is approved: .....

Sl. no	Product name	Composition (With Strength)	Manufacturer	Pack size	Risk classification

Declaration (please tick the boxes):

□ I hereby declare that the documents and information submitted is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading

□ I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravene the provision(s) of the act and regulations made there under.

□If my application is granted, I shall abide by the Medicines Act and Regulations and any other standards set by the Authority.

Dated Signature of applicant with name and contact No.

Annexure 4:

APPLICATION FOR REGISTRATION OF COMBINATION PRODUCT (Full route)

M/s.....hereby applies for registration of the combination product specified below for sale/distribution in Bhutan.

Combination product (tick whichever applicable)

□ Drug-Medical Device combination
□ Medical Device-Drug combination

Sl. no	Product name	Composition (With Strength)	Manufacturer	Pack size	Risk classification

Declaration (please tick the boxes):

□ I hereby declare that the documents and information submitted is true to my knowledge and will be liable for any consequences if any information provided is proved to be false or misleading.

□I declare that I have read the regulation and I am fully aware that my application may be rejected if I do not fulfill the conditions or contravene the provision(s) of the act and regulations made there under.

□If my application is granted, I shall abide by the Medicines Act and Regulations and any other standards set by the Authority.

Dated Signature of applicant with name and contact No.

Annexure 5:
Template for classification request for combination products

Date: (DD/MM/YYYY)

To
The Medical Product Division
Bhutan Food and Drug Authority

Subject: Request for Classification of Combination Product

Dear Sir/Madam,

We, (Firm Name) would like to submit this request for the classification of a combination product.

Details of products:
Generic name:
Brand name:
Manufacturer:
Intended use/indication:
Mode of action:

Supporting Documents:
-Product insert/IFU/Manual
-Packaging specimen

We hereby declare that all the information provided in this submission is true, complete, and accurate to the best of our knowledge

Yours Faithfully,

(Signature of applicant)
(Name and address)

Quality Policy of Medical Product Division

"We commit to provide consistent regulatory operations with risk based planning and continual improvement in compliance with the recognized standards to meet our consumers' satisfaction and confidence"

Bhutan Food and Drug Authority
Royal Government of Bhutan

P.O. 1556

Phone: 337074.337075, Fax: 33580
Email: bfda@gov.bt Website: www.bfda.gov.bt