Guidance document on definitions and information for applications submitted under Borderline Product category

This guidance document provides relevant definitions and information need to complete/assess the documents submitted to the National Medicines Regulatory Authority (NMRA) related to products which are believed to be "Borderline products".

Definitions and interpretations of terms

1. **Active PHARMACEUTICAL ingredient (API)**

   Any substance or combination of substances used in a finished product, intended to furnish pharmacological activity or to otherwise have an effect in the prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (1).

   Note: When it comes to products those will be determined as Borderline will have one or more active ingredients and not pharmaceutical ingredients

2. **Active ingredient:** The ingredient(s) which the therapeutic claims that the manufacturer makes about the product (claims to treat or prevent disease or to interfere with the normal operation of a physiological function of the human body)
3. **Application Number:** The number issued by the Authority after submission of the application for the registration/classification of a borderline product
4. **Name and address of the Applicant:**

   Details of Applicant

   Name and the addresses (both business and postal)
5. **Applicant**: Future Product license holder
6. **Date of Application submitted to the NMRA:**

   Date the complete application was submitted to the NMRA office/uploaded to the website
7. **Date of Evaluation:**

   First date the evaluation was commenced by the Pharmacist
8. **Classification Report Number:**

   Online submission: Number is generated automatically by the eNMRA system

   Manual submission: Assigned according to the Classification application accepting register '' by the NMRA handling staff (by a Document Accepting Pharmacist)
9. **Sample Import Licence (Only for foreign manufactures):**

   For the samples of borderline products to be evaluated for registration, foreign manufacturers require a sample import licence as per the NMRA act Section 102(4)

10. Finished borderline product

A finished dosage form of a borderline product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

11. Manufacturer

A company that produces, packages, repackages, labels and/or re-labels borderline products.

i. Local manufacturer: Manufacturer of borderline products at a manufacturing facility within Sri Lanka

ii. Foreign Manufacturer: Manufacturer of borderline products at a manufacturing outside Sri Lanka

12. Manufacturer name:

Company name and address of the Manufacturer

13. Site address:

Address of the borderline product manufacturing site

14. Formulation Approval Number and approval issuing date (only for local manufacturers):

In case of local manufacturers, once receiving the classification report, the manufacturer concerned have to obtain the approval for the formulation from the NMRA. Number for the application is assigned according to the ''Formulation approval register'' available in the manufacturing division of the NMRA. The date of the formulation approval is as per the date mentioned in the '' Formulation approval letter'' issued by the NMRA.

15. Sample Import License (Only for foreign manufactures):

In case of foreign manufacturers, once receiving the classification report, the manufacturer/agent concerned have to obtain sample import license from the NMRA. This is to import the sample to be submitted with the dossier when submitting the application for registration.

16. Whole Sale License: License issued by the NMRA for the wholesale of borderline products

17. Authorization letter:

Letter given by the manufacturer to the applicant (marketing authorization holder in Sri Lanka) stating that the specific company in Sri Lanka will be given the authority to import the respective product.

(More than one authorization holder can be present in some occasions)

18. Brand name:

Name given to a pharmaceutical product (therapeutic good or cosmetic) by the manufacturer: The use of this name is reserved exclusively to its owner as opposed to the generic name (if available) for a borderline product.

19. Product name:

The trademark or brand name of the borderline product

20. Country of manufacture:

The country where the borderline product manufacturing/exporting occurs

21. COPP/CPPs-Certificate of Pharmaceutical Product (Issuing body, number, validity, date of issue, valid at the point of submission)

The CoPP establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only. CPPs conform to the format established by the World Health Organization (WHO) found in the link below: https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/modelcertificate/en/

22. FSC-Free Sale Certificate Issuing body, number, validity, date of issue, valid at the point of submission)

A Certificate from the health authorities of the country in which it is produced confirming that the borderline product is in use there and the period of use and if not, reasons for not marketing it in the country of the manufacture. An original or copy of a free sale certificate which is attested by a Drugs Regulatory Agency / Medical Device Control Agency / Food Safety Authority / Any government regulatory body in country of origin with manufacturing licence and ISO Certificate/ GMP Certificate is accepted (for cosmetics come under borderline product category- Acceptable FSC is required which is original attested by Sri Lankan embassy or foreign ministry).

23. Route of Administration:

The route of the borderline product is administered in e.g parenteral (intravenous, intramuscular, and subcutaneous), oral, nasal, ocular, transmucosal (buccal, vaginal, and rectal), and transdermal.

24. Manufacturing site approval by the NMRA:

NMRA had to approve the manufacturing site (both local and overseas) prior the product registration (this will become applicable in future)

25. GMP certificate from the country of origin:

Good Manufacturing Practices certificate is requested by importers, exporters, procurement agencies and regulatory authorities. According to WHO standards it is valid for a period of 2 years from the date of issue, but not exceeding 3 years after the inspection was carried out. The WHO model certificate of GMP can be found at the following link:

https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelCertificateGMPTRS908Annex5.pdf?ua=1

26. Status of Manufacturer: Actual Manufacturer, License holder, other

Actual/Physical Manufacturer: the applicant is responsible for manufacture of the borderline product

License Holder: License holder to manufacture the borderline product who will not be the actual manufacturer all the times

Note: in some instances, though the product ownership lies with the manufacturer who is the legal license holder with NMRA, another manufacturer might physically manufacture the product. In such instances, the manufacturer is called as physical manufacturer/actual manufacturer

Other: An applicant not (contract manufacturer/ loan license holder)

The NMRA requires the address of both license holder and physical manufacturer (if applicable)

27. Product registered at the country of Manufacture:

Products with registration for manufacture at the country of manufacture by the relevant countries regulatory authority.

28. Product marketed at the country of manufacture:

Product has the marketing authorization by the regulatory authority of the country of manufacture evidence given in the COPP or the Free sale certificate

29. Address tally with authorization letter:

The address of manufacturing site and the address given in items tally

30. GMP certificate is available (if applicable)

The applicant must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Registrar of Sri Lanka, and whose manufacturing facility has been approved for the compliance for the GMP by the NMRA. For manufacturers from borderline product manufacturing countries outside of Sri Lanka, a GMP certificate must be obtained from

A model GMP certificate as given by the WHO is available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelCertificateGMPTRS908Annex5.pdf?ua=1

The following items must be available for the NMRA to accept the GMP certificate provided with the product

- Name & address of issuing body (GMP)
- ISO certificate (if applicable): ISO 9001:2015
- Valid at the point of submission
- Manufacturer name & address are present
- Manufacturer name and address tally with authorization letter

- Manufacturer name and address tally with address in COPP/ Free Sale Certificate
- Product name is included in the approved product list (if applicable)

31. Manufacturing license is available

An (Statement of Licensing Status of Pharmaceutical Product) SLSPP is issued by the competent authority of the exporting country and is intended for use by importing agents when considering bids in an international tender. It is requested by the importing agent as a condition for bidding. The following items must be available for the NMRA to accept the Manufacturing Licence:

- Name & address of the issuing body
- Valid at the point of submission
- Manufacturer name & address are present
- Manufacturer name and address tally with authorization letter
- List of products is attached
- Brand name/Product name is available including dosage form

32. Master formula is given (per unit dose)

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls. The guidance on the components and characteristics of a master formula as given by the WHO can be obtain from the following link: (https://www.who.int/immunization_standards/vaccine_quality/guide_to_master_formulae _final_2012.pdf)

33. Batch Manufacturing formula is given

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product. The guidance on the components and characteristics of a batch manufacturing formula as given by the WHO can be obtained from the following link: (https://www.who.int/immunization_standards/vaccine_quality/guide_to_master_formulae_final _2012.pdf)

34. Specifications are given for API/ Active ingredients and all ingredients

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which substance or new borderline product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and / or product, when tested according to the listed analytical

procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

The note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances given by the EMA can be found at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-6-test-procedures-acceptance-criteria-new-drug-substances-new-drug-products- chemical_en.pdf).

For substances available in the pharmacopoeia, the components should be declared by their proper or common names, quality standards (e.g., Ph. Int .,Ph. Eur., BP, USP, JP, In-House) and, if applicable, their grades (e.g., Microcrystalline Cellulose NF (PH 102)) and special technical characteristics (e.g., lyophilized, micronized, solubilized, emulsified).

35. Functions of all ingredients

Weather active ingredient or excipient needs to be identified with type of excipient eg: preservative, antioxidant, flavoring agent, coloring agent, humectant etc.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g., capsule shells, coloring blends, imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g., summary of product characteristics, labeling, and package leaflet).

36. Are the units/values within authorized concentration or limits? The strength of the active ingredient/s must be within the safe limits for human use.

Note 1: Expected amount of active ingredient(s) intake by a person depends not only on unit strength, but also on daily intake and duration of intake given in the product information leaflet

Note 2: If the borderline product is formulated using an active moiety, then the composition for the active moiety (portion of which represents the pharmacologically active moiety) should be clearly indicated. The Active moiety can be either a molecule or ion. The appended portions of the molecule such as salts, chelates and esteres should be excluded. The exact mass of such substances must be calculated on the basis of the quantity of the pharmacological moiety. (e.g., 1 g of active moiety base = 1.25 g active moiety hydrochloride). All overages should be clearly indicated (e.g., Contains 5 kg (corresponding to 2%) overage of the active moiety to compensate for manufacturing losses).

Note 3: NMRA has given guidance on safe limits for most of the ingredients. You can access them in www.nmra.gov.lk

A. Guideline on Product Categorization Reference Details Vitamins & Elements given under the borderline product category

B. Guideline of Amino Acid Requirements

C. Guideline on Dietary recommendations of Iodine

37. COA /s of all active ingredients:

A CoA lists tests performed on a particular sample with the results obtained and the acceptance criteria applied, followed by an indication of whether or not the sample complies with the specification. A CoA is usually prepared for each batch of a substance should include the information recommended in the WHO recommended model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal found in the following link: https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelCertificateAnalysisTRS902Annex10.pdf?ua=1

The following items must be available for the NMRA to accept a CoA:

• Specification is stated (BP/USP/IP/EP or In-House)

BP: British Pharmacopoeia
USP: United States Pharmacopoeia
IP: Indian Pharmacopoeia
EP: European Pharmacopoeia
In-House: Criteria defined and validated by the quality control laboratory

38. The following items must be available for the NMRA to accept a CoA for active ingredients:

- Manufacture/s names mentioned in the certificates
- Test results comply with the given specification
- Conclusion is given
- Valid GMP certificates with approved product list for all active ingredients

39. COA of Excipients : See above 35 above

- The following items must be available for the NMRA to accept a CoA for excipients include:
- Specification is stated (BP/USP/IP/EP or In-House)
- Manufacture/s names mentioned in the certificates
- Test results comply with the given specification
- Conclusion is given

40. COA of Finished Products

A CoA lists tests performed on a particular sample with the results obtained and the acceptance criteria applied, followed by an indication of whether or not the sample complies with the specification. A CoA is usually prepared for each batch of a product and should include the information recommended in the WHO recommended model certificate of analysis for active pharmaceutical ingredients, excipients and medicinal found in the following link:

https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelCertificateAnalysisTRS902Annex10.pdf?ua=1

The following items must be available for the NMRA to accept a CoA for active ingredients:

- Original COA is attached
- Specification is stated (BP/USP/IP/EP or In-House)
- Assay values present (APIs or Active ingredients)
- Heavy metals test results available (If applicable): The EMA recommendations of heavy metal limits are found in the following link: https://www.ema.europa.eu/en/documents/scientific-guideline/international- conference-harmonisation-technical-requirements-registration-pharmaceuticals- human-use_en-32.pdf
- Test results comply with the given specification
- Conclusion is given
- Endorsement of authorized officers present
- For In-House specification-analytical report attached (if applicable only)

41. Manufacturing process validation Summery

Section 3.1.P.3.3, 3.1.P.3.4 and 3.1.P.3.5 on the guideline for registration of medicines should be followed

42. The following items must be available for the NMRA to accept a manufacturing process validation summary for active ingredients include:

- Valid batch size (commercial batch size) used for validation
- Three commercial/ consecutive batches used
- Manufacturing Equipment
- Critical Process step & Parameters
- (Tablet/Capsule/ Cream/ Other)
- Tabulation of the test result
- Batch Analysis
- Evaluation of data & where applicable, statistical process control analysis
- Conclusion & Recommendation

43. Evaluation of analytical validation (Only for in house specification)

For analytical methods used to quantify active ingredients, excipients and finished borderline products using analytical methodologies such as HPLC. Analytical method validation proves if the test system is suitable for its intended purpose. Method validation report should be given in the dossier if the quantification method of any active ingredient, excipient or a finished product parameter is done by an in-house method or if a validated method or a method given in the pharmacopoeia conditions are changed (e.g., use of different instrument with different characteristics or changing the matrix of the samples. The method validation report should contain the following details (items 48-58):

44. Chromatographic or other analytical mode provided:

This includes the instrumentation, the steps of sample preparation, analytical conditions such as column specifications in chromatography, temperatures, flow rates of mobile phases, composition of mobile phase, matrices of samples etc.

45. Specificity

The specificity of an analytical method demonstrate that the method was capable of selectively quantifying the analyte of interest in the presence other interfering components such as impurities, degrades, matrix, etc.

Specificity of a chromatographic method can be demonstrated by the resolution of the two components which elute closest to each other. But in assays such as titrations which are termed non-specific assays multiple tests must confirm specificity. Even for chromatographic methods tests such as peak purity tests may be used to eliminate the possibility of chromatographic peaks arising due to several compounds where specificity is proven by more than one method.

46. Linearity

A linear relationship should be proven through the lower limit of quantification to the upper limit of quantification of the analytical method. Linearity is evaluated by visual inspection of a plot of signals of the instrument as a function of analyte concentration or content. The correlation coefficient, y-intercept, slope of the regression line and residual sum of squares should be submitted. For the establishment of linearity, a minimum of 5 concentrations is recommended. The coefficient of determination/R2 value above 0.995 is generally recommended to prove linearity.

47. Range

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides

an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. The range contains the lower limit of quantification and the upper limit of quantification. The following minimum specified ranges should be considered:

- for the assay of an active substance or a finished product: linearity should be proven normally from 80% to 120 % of the test concentration;
- for content uniformity testing linearity must be proven covering a minimum of 70% to 130% percent of the test concentration, unless a wider more appropriate range, based on the nature of the dosage is justified;
- for dissolution testing: linearity of +/-20 % over the specified range;
- for the determination of an impurity: from the reporting level of an impurity 1 to 120% of the specification; for impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the detection/ quantitation limit should be commensurate with the level at which the impurities must be controlled. Note: for validation of impurity test procedures carried out during development, it may be necessary to consider the range around a suggested (probable) limit;

if assay and purity are performed together as one test and only a 100% standard is used, linearity should cover the range from the reporting level of the impurities1 to 120% of the assay specification;

48. Accuracy

Accuracy is the closeness of test results obtained from the analytical method to the true value. This is sometimes termed trueness, which is stated quantitatively in terms of bias. Several methods of determining accuracy are available:

i. application of an analytical procedure to an analyte of known purity (e.g. reference material);

ii. comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined (independent procedure,

Accuracy may be inferred once precision, linearity and specificity have been established.

Accuracy should be assessed using a minimum of 9 determinations (using samples with known concentrations) over a minimum of 3 concentration levels covering the specified range

(e.g. 3 concentrations/ 3 replicates each of the total analytical procedure). Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals.

49. Precision

Precision of an analytical procedure is the closeness of agreement (degree of scatter) between a series of measurements of samples of same concentration obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. It is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

50. Robustness

Robustness tests examine the effect that the operational parameters have on the analysis results (eg. Change of temperature, change of pH, flow rate of mobile phase etc). These method parameters are varied within a realistic range, and the quantitative influence of the variables is determined. If the influence of the parameter is within a previously specified tolerance, the parameter is said to be within the method's robustness range.

51. Detection limit

The limit of detection (LOD) of an individual analytical procedure is the lowest amount of the analyte in a sample which can be detected. The LOD is not used to quantitated an exact value. For example, in chromatography, the detection limit is the injected amount that results in a peak with a height of at least two or three times as high as the baseline noise level. (Other methods of determining LOD is given in the References below)

52. Quantification Limit

The limit of quantitation (LOQ) is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy. For a chromatographic method a typical signal-to- noise ratio is 10:1 or above is required for the LOQ. (Other methods of determining LOD is given in the References below).

56. Container closure system and packaging

Section 3.1.P.7 , 3 of the guideline for registration of medicines should be followed

The following items must be available for the NMRA to accept information regarding the container, closure system and packaging of a borderline product:

- Details of the container

- Description of outer packaging
- Availability package insert
- COA s of packages
- Pack size
- Pack type

57. Product Information Leaflet

Should have the following information

- Brand Name
- Product name or Active ingredients included
- Strength (if applicable)
- Product description
- Proposed functions
- Dose(s)and directions
- Special warnings/ precautions
- Treatment for overdose
- Treatment on pregnancy and lactation
- Treatment on special conditions
- Contraindication
- Adverse effects
- Storage condition
- Overdose treatment
- Name and address of manufacturer
- Marketing authorization holder
- Date of revision of package Insert

Original PIL is attached to the dossier

58. Patient Information Leaflet

The following items must be available for the NMRA to accept a patient information leaflet of a borderline product include:

- Original PIL is attached to the dossier
- Provided in three language (English, Tamil, Sinhala)
- Brand Name
- Product name

- Active ingredients included
- Strength (if applicable)
- Product description
- Indication
- Dose and direction
- Special warnings/ precautions
- Side effects
- Storage condition
- Name and address of manufacturer
- Marketing authorization holder

Reference

https://nmra.gov.lk/images/PDF/guideline/Guideline_by_Praba/Labeling-guidelines-1.pdf

59. Product registration in other countries

Information regarding if the borderline product registered in stringent regulatory authorities is checked. The countries/territories included are:

- Australia
- Canada
- European Union(EU)
- Japan
- New Zealand
- Singapore
- UK
- USA
- Malaysia
- Thailand

60. Justification for the health benefits claimed:

If the product claims health benefits, data justifying such health benefits should be submitted for evaluation

61. Labelling

The following items must be available for the NMRA to accept a label of a borderline product:

- Brand name
- Product name
- Dosage Form
- A list of APIs or active ingredients with amount per unit dose
- Net Content/ Weight/ Volume
- The Batch number
- The Manufacturing date

- The Expiry date
- Storage Condition
- Warning Statement/ Precaution (If applicable)
- Direction for use (If applicable)
- Claims if applicable
- Name and Address of the Manufacturer
- Name and Address of the Importer
- Special labeling requirement

62. Promotional materials:

The following items must be available for the NMRA to accept promotional material of a borderline product:

- Brand Name
- Product name
- API or Active ingredients included
- Strength (if applicable)
- Product description
- Name & Address of manufacturer
- Marketing Authorization holder
- Indications/Claims

63. Other information required

- The NMRA require the following information in a product dossier of a borderline product
- Maximum retail price in LKR per unit dose
- Post market sales volumes in country of origin
- Post market sales volumes in Sri Lanka