1.0 Background:

To check the safety, efficacy and quality of the drug which are not mentioned in the pharmacopoeias recognized by Drug Act 2035, and establish the method of analysis for the analysis of such drug products, DDA can take advice from the drug advisory committee (DAC) as per Drug Act 2035. For this provision of Drug Act, DDA has formed a committee to assist DDA in establishment of analytical method, product (quality control) specification for non pharmacopoeial product. The committee has so far prepared SOP for study of documents on non pharmacopoeial products for regulatory approval, guidelines for analytical method validation, check lists for analytical method validation for submission of application for registration, check list for evaluation of document submitted by the industry and protocol for the establishment of some of methods of non pharmacopoeial products and quality control specifications. This step will help in development of Nepal Pharmacopoeia too. The standard of drugs then will be as per Nepal Pharmacopoeia. DDA has not been able to prepare Nepal Pharmacopoeia till now therefore the standard of drug will be as per the quality control specifications and analytical methods suggested by the committee after the method is approved by DDA/ DAC for non pharmacopoeial drug products. This will be the baseline for further development of standards for new molecules which are not come out in pharmacopoeia for future WHO activity.

2.0 Objective:

1. To provide the documented evidence that whether the analytical method submitted by pharmaceutical industry is suitable for the analytical operation.
2. To develop the documents required during the submission of non-pharmacopoeial product.
3. To select the most appropriate method from the available different non-pharmacopoeial methods and develop the product (quality control) specification and standard analytical method for non pharmacopoeial drug product.

3.0 Scope:

3.1 Define the **procedure,** documentation, reference and acceptance criteria to be used for the evaluation of documents of non pharmacopoeial product.

3.2 The product specification (Quality control) and analytical methods suggested by the committee would be approved by DDA/DAC will be the standard for those non pharmacopoeial drug products until and unless published in the monograph of any of the pharmacopoeia recognised by Drug Standard Regulation, 2043.

4.0 CATEGORY OF THE NON PHARMACOPOEIAL DRUG

Based upon the study of the documents submitted by the domestic and foreign pharmaceutical industry, seven categories of non pharmacopoeial products have been identified. The subcategory of the products, analytical method requirement and recommendation is mentioned in Table 1.

Category 1: The monograph of the active product ingredient (API) and dosage form is not available in the pharmacopoeia.

Category 2: The monograph of the API is available in pharmacopoeia but dosage form is not available in the pharmacopoeia.

Category 3: The monograph of the API and dosage form (e.g. tablet) is available but the dosage form (e.g. capsule etc.), type of tablet dosage form (e.g. chewable tablet etc.) submitted by the pharmaceutical industry is not available in pharmacopoeia.

Note: If the monograph of API and dosage form (e.g. tablet, liquid etc.) is available but the salt form of API in dosage form is different from the available monograph, (e.g. diclofenac sodium to diclofenac potassium, ferrous fumarate to ferrous ascorbate etc.) analytical method should be based on the salt form available in the pharmacopoeial monograph and analytical method validation is not required.

Category 4: If the monograph of the single molecule dosage (e.g. Telmisartan tablet, Amlodipine tablet) is available but the monograph of combination dosage form (e.g. Telmisartan and Amlodipine tablet) is not available.

Category 5: External preparations (Cream, Gel, Ointment, Liquid except eye/ear drop)

Category 6: Multivitamins, Enzymes, Mineral containing multi ingredient products.

Category 7: Biological, biosimiliar products (Vaccines, Monoclonal antibodies, Polyclonal antibodies, rDNA product and biosimiliar products), Cytotoxic drugs and transdermal patches.

4.1 <u>Evaluation of the document for non pharmacopoeial product</u>

Analytical method recommendations based on the category of the non pharmacopoeial product

Category 1:

The reference of the test method should be taken from the reliable journal or innovator/comparator where ever possible. Complete analytical method validation should be performed as per recognized pharmacopoeias and guidelines.

Category 2:

The analytical method of the dosage form should be stability indicating (HPLC preferred). If the assay of the raw material in the pharmacopoeial monograph is based on High performance liquid chromatography (HPLC), the analytical method of the dosage form should be based on the raw material. The analytical method can be changed from the pharmacopoeial monograph with suitable justification if necessary. In this category of product a **c**omplete analytical method validation should be performed by the industry.

Category 3:

This category product is subcategorized as mentioned in Table no.1. The analytical method should be followed as per the similar monograph of the dosage form available in pharmacopoeia e.g. plain tablet to chewable, mouth dissolving, dispersible tablets etc. Similarly For e.g. if the monograph of the tablet dosage form is available, the analytical method and acceptance criteria of test parameter of tablet dosage can be applied to capsule dosage form i.e. solid dosage form to solid dosage form wherever possible. Similarly the analytical method and acceptance criteria of test parameter of liquid dosage form (e.g. oral solution) to liquid dosage form (suspension). Analytical method can be changed from the available monograph with suitable justification if necessary. Validation of the analytical method is required for this category product. The document should be evaluated from the committee. Marketing authorization will be given after the approval of the document from the committee.

Category 4:

For this category of product, the assay method can be developed by the pharmaceutical company based on individual monograph of the single molecule of pharmacopoeia. However, the dissolution test parameter in case of tablet/capsule dosage form should be as mentioned in the individual monograph (should be narrowed but not wider e.g. if dissolution time is 45 minutes, it can be varied to 30 minutes with justifications same is the case for RPM). Estimation of the release of drug in case of dissolution can be done by suitable method (e.g. In the pharmacopoeial monograph for single dose, if UV method is mentioned, it can be changed to HPLC method but HPLC method cannot be changed to UV method) with justification unless otherwise available in recognised guidelines (WHO, ICH, FDA and the pharmacopoeias mentioned in drug standard regulation, 2043). Quality control specification should cover the tolerance limit of individual monograph. Assay method and dissolution method should be validated.

Category 5:

Analysis of this category of product will be done as per the analytical method submitted by the pharmaceutical company due to wide variation in the composition of active ingredients and their quantity in the product. Analytical method validation should be performed and the documents

should be submitted to committee. The pharmaceutical company can get market authorization from DDA after the submission of document to the committee.

Category 6:

For this product, Quality control specification should cover the tolerance limit of individual monograph of the pharmacopoeia. The analysis of such products will be done as per the analytical method submitted by the company. The subcategory of this category product is mentioned in Table no.1. Analytical method validation of subcategory 6b (fat soluble vitamins) should be submitted to the committee. Due to wide range of tolerance limit in assay and as mentioned in Indian Pharmacopoeia, the content uniformity of such products are not required, analytical method validation document of Category 6a and 6c should not be submitted to the committee.

Category 7: Documents of this category product should be made available to committee during registration. The pharmaceutical company can get market authorization from DDA after the submission of document to the committee.

Table no.1: Category and sub category of non pharmacopoeial product

Category of Drug	Sub category	Characteristics	Requirements	Validation
Category 1	N/A	The monograph of API and dosage form not available in any pharmacopoeia	The reference of the test method should be from the reliable journal or innovator/comparator where ever possible.	Complete analytical method validation should be performed.
Category 2.	N/A	The monograph of the API is available but any dosage form is not available in pharmacopoeia.	The analytical method of the dosage form should be stability indicating (HPLC Preferred) based on the API. the method can be changed from the monograph of API with justification	Complete analytical method validation should be performed.
Category 3.	Category 3.a. Tablet to Tablet 3 a.i. chewable, dispersible, mouth dissolving tablet 3 a.ii. Insert tablet (as per type of route of administration)	The monograph of the raw material and dosage form (e.g. tablet) is available but the dosage form submitted is not available in pharmacopoeia.	1. The analytical method should be followed as per the available monograph of dosage form. 2. The acceptance criteria of test parameter should be as per the available monograph.	Complete analytical method validation should be performed.
	Category 3.b: Tablet to capsule/vice versa			
	Category 3.c: liquid to liquid/suspension/powder for oral suspension			
	Category 3.d: Tablet/capsule to powder e.g. vitamin D3 powder			

Table no.1: Category and sub categryof non pharmacopoeial product contd.....

Category of Drug	Sub category	Characteristics	Requirements	Validation
Category 4 (Fixed Dose Combination)	N/A	The monograph of single dosage form is available but the monograph of combination dosage form is not available.	1. Analytical method of assay should be based on individual monograph of the single molecule. 2. The dissolution test parameter should be as per the individual monograph.	1. Analytical method validation should be performed for assay and dissolution. 2. Quality control specification should cover the tolerance limit of individual monograph.
Category 5	N/A	External preparations (Cream, Gel, Ointment, Liquid except eye/ear drop)	Quality control specification should cover the tolerance limit of individual monograph of the pharmacopoeia.	Analytical method validation should be performed. However, the pharmaceutical company can take market authorization from DDA without the approval of the document from the committee.
Category 6	Category 6a. water soluble vitamins and minerals		Quality control specification should cover the tolerance limit of individual monograph of the pharmacopoeia.	1. Analytical method validation document of Category 6 b product should be submitted to committee. 2. Analytical method validation document of Category 6a and 6c should not be submitted to the committee due to wide range of tolerance limit in assay and content uniformity not required in this sub category product.
	Category 6b. fat soluble vitamins			
	Category 6c.Enzymes			

Table no.1: Category and sub category of non pharmacopoeial product contd.....

Category of Drug	Sub category	Characteristics	Requirements	Validation
	Category 7a. Biological, biosimiliar products (Vaccines,	not available in in pharmacopoeia	Document Evaluation	The pharmaceutical company can get market authorization from DDA after the submission of document to the committee.
	Category 7b. Monoclonal antibodies, Polyclonal antibodies, rDNA product and biosimiliar products) .	not available in in pharmacopoeia		
	Category 7c Cytotoxic drugs and transdermal patches	not available in in pharmacopoeia		

5.0 Procedure for the evaluation of document

Standard operating procedure for the evaluation of document of non pharmacopoeial product **(ANNEX-6)** & Analytical method validation Guidelines **(ANNEX-7)** have been developed by the committee. Based upon the SOP no. **NPV/073/SOP-01** & Guideline no **AMVP/073/01,** the evaluation of the documents of the non pharmacopoeial products submitted by the pharmaceutical industry will be done.

All the quality control specification and analytical profile will be valid unless otherwise specified in the individual monograph of the pharmacopoeia.

6.0 Acceptance criteria for different charecteristics of analytical method validation.

S.No.	**Parameters**	Requirement
a.	**Specificity**	
1	Blank values: Diluents	Resolution: NLT 1.5
2	Sample solution without active	Resolution: NLT 1.5
b.	**Linearity & Range**	r2 $\geq$ 0.98
c	**Repeatability**	RSD $\leq$ 2.0 %
d.	**Intermediate Precision**	RSD $\leq$ 3.0 % **For dissolution** The difference in the mean value for dissolution results between any two conditions using the same strength should not exceed an absolute 10 % at time points with < 85 % dissolved nor exceed 5 % for time points > 85 %.
e	**Accuracy**	98.0 % to 102 %
f	**Solution Stability**	97.5 % to 102.5 % in comparison to the freshly prepared solutions
g	**Robustness (Optional)**	
h	**System Suitability test**	
1	Theoretical plates	NLT 2000
2	Tailing factor	NMT 2.0
3	RSD of five/six replicate injections	NMT 2.0
4	Resolution between two peaks	NLT 2.0

7.0. EVALUATION OF DOCUMENTS

1. All the completed documents from the domestic and foreign pharmaceutical industry will be compiled and stored by the Analytical Method Validation Committee.
2. Committee member check the product application document and check lists for documents required during the submission of non pharmacopoeial product (ANNEX 1-4) using internal checklist (ANNEX 5).
3. Evaluation of the chromatogram, spectrum & calculation.
4. Compare to the acceptance criteria.
5. Prepare product specification and analytical profile of the non pharmacopoeial product.
6. Prepare deviation report if required including justification for the deviation and possible remedies.

8.0. PRELIMINARY REQUIREMENTS

1. Analytical method reference (IP/BP/USP/JP/Any other literature)
2. Calibration of the equipments utilized in the study.
3. Grade of reagents used
4. Reference standard traceability
5. Relevant SOPs
6. Chromatogram, Spectrum & Calculation with formula should be submitted where needed.

(Annex 1): Parameters to be checked for the dosage form for the non pharmacopoeial products.

Product Specification

S.No.	**Parameters to be checked**	Dosage form
1.	Description, Identification, Uniformity of weight, Disintegration test, Friability, Dissolution, Uniformity of content (if required), Assay, Water content (if required), Related substances (if required), Leak test, Any other additional tests if required, storage condition, pack size.	Tablet
2.	Description, Identification, Uniformity of weight, Disintegration test, Dissolution, Uniformity of content (if required), Assay, Water content (if required), Related substances (if required), Leak test, Any other additional tests if required, storage condition, pack size.	Capsule
3.	Description, Identification, Uniformity of volume, Uniformity of weight, Assay, Water content (if required), pH, Related substances (if required), Leak test, Any other additional tests if required, storage condition, pack size.	Liquid, Powder for oral suspension
4.	Description, Identification, Filled weight variation, Assay, pH, Related substances (if required), Leak test, Any other additional tests if required, storage condition, pack size.	Cream, Gel & Ointment
5.	Description, Identification, Uniformity of weight, Assay, Water content (if required), pH, Related substances (if required), Any other additional tests if required, Seal test (only for sachets), storage condition, pack size.	Oral Powder
6.	Description, Identification, Uniformity of weight, Water content (if required), pH, related substances (if required), Any other additional tests if required, leak test, storage condition, pack size.	Suppository
7.	Description, Identification, Uniformity of volume, Assay, Uniformity of content (if required), pH, related substances (if required), Bacterial endotoxin, sterility test, particulate matter, Any other additional tests if required, leak test, storage condition, pack size.	Sterile preparation
8.	Description, Identification, Uniformity of volume, Assay, Uniformity of content (if required), pH, related substances (if required), particulate matter, Any other additional tests if required, leak test, storage condition, pack size.	Non-sterile preparation
9.	Description, Identification, Filled weight variation, Assay, pH, sterility test, isotonicity test, Related substances (if required), Leak test, Any other additional tests if required, storage condition, pack size.	Sterile eye ointment

(Annex 2): Checklist of Product Specification if similar molecule is available in Pharmacopoeia.

S.No.	Parameters	**Monograph available in pharmacopoeia**		**Tolerance Limit**	
		Yes (If Yes, Name of product and Name of Pharmacopoeia)	No	Pharmacopoeial product	Non pharmacopoeial product
1.	API standard				
2.	Description				
3.	Average weight				
4.	Uniformity of weight				
5.	Disintegration test				
6.	Limit of water content if necessary				
7.	Limit of Assay				
8.	Method of analysis of Dissolution if necessary				
9.	Limit of Dissolution if necessary				
10.	Method of analysis of Content Uniformity if necessary				
11.	Limit of Content Uniformity if necessary				
12.	Limit of Related Substance if necessary				
13.	Method of analysis of Related Substance if necessary				
14.	Any other tests if required				

(Annex 3): Analytical Method checklist.

S.No.	Parameters	Yes	No	Remarks
1.	Analytical Method Reference (IP/BP/USP/JP/Any other literature)			
2.	Reagents used and Grade			
3.	Reference standard traceability			
4.	Analytical Method ✓ Reagent Preparation ✓ Diluents ✓ Mobile phase preparation ✓ Standard preparation ✓ Sample preparation			
5.	Chromatogram, Spectrum & Calculation with formula should be submitted where needed.			
6.	Analytical method validation			

(Annex 4): Analytical Method Validation checklist. (To be filled by authorized person of industry)

S.No	Parameters	Limit	Requirements	YES	NO	REMARKS
1.	**Specificity**	Resolution: NLT 1.5	Should be investigated by injecting the blank (solvent)/ placebo (matrix solution), standard solution, sample solution to demonstrate the absence of interference with the elution of analytes.			
2.	**Linearity**	$r^2 \geq 0.98$	Standard solutions should be prepared at minimum of 5/6 concentrations within the range of typically 80% to 120 %, of target concentration.			
3.	**Range**		Assay of drug substances (80 % to 120 % of the test concentration) Content Uniformity (minimum 70% to 130 % of the test concentration) Dissolution testing (+/-20 % over the specified range)			
4.	**Repeatability**	RSD $\leq$ 2.0 %	For instrument precision determinations of five replicate of reference standard should be made. For the method at least nine determinations covering specified range of 3 concentration and 3 replicates should be made.			
5.	**Intermediate Precision** **Assay** **For dissolution**	RSD $\leq$ 3.0 % The difference in the mean value for dissolution results between any two conditions using the same strength should not exceed an absolute 10 % at time points with < 85 % dissolved nor exceed 5 % for time points > 85 %.	Test procedure Intermediate precision (within-laboratory variation) should be demonstrated by at least two analysts, using at least two HPLC/UV-vis spectrophotometer on different days and evaluating the relative percent purity data across the two systems of triplicate sample of one concentration.			
6.	**Accuracy**	98.0 % to 102 %	Spiked samples should be prepared at three concentrations over the range of 80 %, 100 % and 120 % of the target concentration. Three individually prepared triplicates at each concentration will be analyzed.			

(Annex 4): ANALYTICAL METHOD VALIDATION CHECKLIST (To be filled by authorized person of industry) **contd…..**

S.No.	Parameters	Limit	Requirements	YES	NO	REMARKS
7.	**Solution Stability**	97.5 % to 102.5 % in comparison to the freshly prepared solutions	Solutions of drug product should be analysed in comparison to the fresh prepared solutions stored at room temperature in auto sampler and stored at 2 - 8 °C, in refrigerator at least 24 hours.			
8.	**Robustness**		The investigation of robustness can be done by change of flow rate of the mobile phase, change of temperature of column, change of composition of the mobile phase, change in the pH of the mobile phase and use of different column.			
9.	**System Suitability test**	Theoretical plates (NLT 2000) Tailing factor (NMT 2.0) RSD (NMT 2.0 %)	System suitability tests should be performed on HPLC systems to determine the accuracy and precision of the system by injecting five/ six injections of a solution containing analyte (standard solution) at 100% of test concentration. Determine relative standard deviation (rsd) of the replicate injections, theoretical plate and tailing factor.			

Note: Every page should be signed with date by the authorized person with company stamp.

Authorized Person:
Signature:
Name:
Designation:
Stamp:
Date:

ANNEX (5): Internal checklist for the study of document of analytical method validation

Checklist for document study of analytical method validation

Page 1 of 1

Brand name: Registration number:

Composition: Registration date: Date:

Manufactured by: Submitted by:

Method validation of :

Assay Dissolution Related substances Any other impurities

Checklist

S.N	Documents	Yes	No	Remarks
a.	Summary Validation Report/Protocol no.			
b.	Analytical Method Reference (IP/BP/USP/JP Any other			
c.	Instruments used and calibration date			
d.	Reagents used and Grades			
e.	Reference standard (Traceability)			
	Primary			
	Secondary			
f.	Resolution standard (Traceability)			
g.	Internal standard			
h.	Analytical Method			
1	Reagent preparation			
2	Diluent			
3	Mobile Phase preparation			
4	standard preparation			
5	sample preparation			

Analytical Method validation parameters

S.No	Parameters	Requirements	Documents		
			Raw data		
			Chromatogram with detail chromatographic condition	Calculation with formula	Remarks
a.	**Specificity**				
1	Blank values: Diluents	Resolution: NLT 1.5			
2	Sample solution without active	Resolution: NLT 1.5			
b.	**Linearity & Range**	r2 ≥ 0.98			
c	**Repeatability**	RSD ≤ 2.0 %			
d	**Intermediate Precision**	RSD ≤ 3.0 %			
e	**Accuracy**	98.0 % to 102 %			
f	**Solution Stability**	97.5 % to 102.5 % in comparison to the freshly prepared solutions			
g	**Robustness (Optional)**				
h	**System Suitability test**				
1	Theoretical plates	NLT 2000			
2	Tailing factor	NMT 2.0			
3	RSD of five/six replicate injections	NMT 2.0			
4	Resolution between two peaks	NLT 2.0			

Recommendation:

Product Specification: ▫ Yes ▫ No

ANNEX (6): SOP FOR STUDY OF DOCUMENTS OF NON PHARMACOPOEIAL PRODUCTS FOR REGULATORY APPROVAL

DEPARTMENT OF DRUG ADMINISTRATION	**SOP FOR STUDY OF DOCUMENTS ON NON PHARMACOPOEIAL PRODUCTS FOR REGULATORY APPROVAL**	SOP No.: NPV/073/SOP-01
	Analytical method Validation Committee for Non Pharmacopoeial product	Page no.: 1 of 5
Effective Date:	Review Date:	Supersedes: None

Purpose:

1. To provide the documented evidence that whether the analytical method submitted by the pharmaceutical industry is suitable for the analytical operation.

Objective:

To evaluate the available validated analytical method and give recommendation to DDA for the approval of the Product (Quality Control) specification and standard analytical method of non pharmacopoeial product.

Scope:

This will provide procedure for the study of documents related to analytical method validation of non pharmacopoeial product as mentioned in the "Protocol for the Guidance and Recommendation of documents for non pharmacopoeial product for National Regulatory Approval."

Responsibility:

1. The entire committee member will be responsible for the guidance and recommendation regarding the parameters for the product specification and analytical profile of the non pharmacopoeial product.
2. Final approval of the document will be given by the Department of Drug Administration.

Prepared by:	**Checked by:**	**Approved by:**
……..	……..	…….

<table>
<tr><td rowspan="2">DEPARTMENT OF DRUG ADMINISTRATION</td><td>SOP FOR STUDY OF DOCUMENTS ON NON PHARMACOPOEIAL PRODUCTS FOR REGULATORY APPROVAL</td><td>SOP No.: NPV/073/SOP-01</td></tr>
<tr><td>Analytical method Validation Committee for Non Pharmacopoeial product</td><td>Page no.: 2 of 5</td></tr>
<tr><td>Effective Date:</td><td>Review Date:</td><td>Supersedes: None</td></tr>
<tr><td colspan="3">Procedure:

Procedure for the incoming of documents in the committee :

1. First the pharmaceutical company registers the document of non pharmacopoeial product along with the analytical method validation test report to Department of Drug Administration. Domestic pharmaceutical company registers the document to Industry section and foreign pharmaceutical company registers the document to import section through importers.
2. The authorized person from Industrial section and Import section will check the completeness of the document as mentioned in check list (ANNEX 1-4) prepared by the committee.
3. From Industrial section and Import section, the authorized person prepares note & Instruction (Tippani & Aadesh in Nepali) and submits the document file to Director General, DDA.
4. After that the document will be send to Analytical method validation committee for non pharmacopoeial product in order to check the document for the approval.</td></tr>
<tr><td>Prepared by:

……..</td><td>Checked by:

……..</td><td>Approved by:

…….</td></tr>
</table>

5. The document of the non pharmacopoeial product will be kept by committee.
6. The document will be registered in **Entry Register Book** which contains all the information regarding the entry date and remarks of the documents. **The format of the document entry book will be as follows:**

S.No.	Date	Product Name	API Name	Category of product	Company Name	Document Submitted by	Checked By	Date	Remarks

Procedure for the checking of the documents

1. The received product application along with analytical method validation will be distributed to all the member of the committee.
2. The committee member will check all the parameters of the documents and checklist filled by the company using the **internal check list (Annex 5)**.
3. All the documents required and acceptance criteria are available in the internal check list.
4. **If there is some deficiency and mistakes in the documents, the committee will decide about the deficiencies and errors of the document.** The committee will correspondence the manufacturers/importers about their deficiencies.
5. The committee will recommend for the analysis of sample after obtaining the complete documents from the manufacturers/importers.

Procedure for the analysis of the finished product and approval of the report

4.2 After the completion of the document required for the AMV, the domestic pharmaceutical company/importers will be informed to deposit the required amount of payment for the analysis as per the NML payment rate.

4.3 The committee will request National Medicine Laboratory (NML) for analysis of the sample.

4.4 NML will give identification number to the product for the testing purpose after the payment.

4.5 The product will be analyzed in NML using the recommended method from the committee and report of analysis will be prepared.

4.6 AMV committee will make the discussion about the result and report of analysis of the product.

4.7 The committee will prepare Product (Quality Control) Specification and Analytical profile.

4.8 Committee will send letter to DDA along with Product (Quality Control) Specification and Analytical profile for the final approval.

4.9 The analytical method will be approved by the Department of Drug Administration/Drug Advisory Committee for the official use.

4.10 Analytical report will be prepared and verification will be done by the section in charge.

4.11 Final approval of the report of analysis will be done by NML, Director.

Prepared by:	**Checked by:**	**Approved by:**
……..	……..	…….

Procedure for the numbering of the document

4.12 The name of the approved method from the DDA will be given as **NML/AMV protocol.**

4.13 Numbering of the product specification prepared by the committee will be done as **Product Name/Year/Number.** For e.g. Numbering of Product specification of Amlodipine & Telmisartan Tablet will be as Amlo-Telmi/073/074/001.

4.14 Similiarly, Numbering of analytical profile will be done as **Product Name/Year/AP Number.** For e.g. Numbering of Analytical Profile of Amlodipine & Telmisartan Tablet will be as Amlo-Telmi/073/074/AP001.

4.15 Numbering of the protocol of the committee will be as **AMVP/Year/Number.** For e.g. AMVP/073/01

4.16 Numbering of SOP will be as **NPV/Year/SOP-Number.** For e.g. NPV/073/SOP-01.

ANNEX (7): ANALYTICAL METHOD VALIDATION GUIDELINE FOR NON PHARMACOPOEIAL PRODUCT

GUIDELINE NO.: AMVP/073/01

1. Requirements of Analytical method validation documents:

Identification of method type and validation approach, test method applications and validation protocol, the intended use of each test method application, and the analytical performance characteristics for each test method application.

Resources: This section identifies the following:

- Laboratory where the method validation is performed;
- Equipments and its calibration status used in the method validation;
- Materials: References, special instructions on handling, stability, and storage for each material.
- Appendices: This section should contains references, a review worksheet of all personnel, listings of all equipment, materials, test procedure(s) necessary to perform method validation,
- Chromatogram, Spectrum & Calculation with formula should be submitted where needed.

2. **Analytical Performance Characteristics**

Procedure: Before undertaking the task of methods validation, it is necessary that the analytical system itself should be adequately designed, maintained, calibrated, and validated. All personnel who will perform the validation testing must be properly trained. For each of the validation characteristics in this document should defines the test procedure, documentation, and acceptance criteria. Specific values are taken from the ICH, U.S. FDA, USP and pertinent literature as references.

2.1. Specificity

2.1.1. Test procedure:

The specificity of the assay method should be investigated by injecting the blank (solvent)/ placebo (matrix solution), standard solution, sample solution to demonstrate the absence of interference with the elution of analytes.

2.1.2. Documentation:
Print chromatograms.
2.1.3. Acceptance criteria:
The excipient compounds must not interfere with the analysis of the targeted analyte.

2.2. Linearity

2.2.1. Test procedure:

Linearity will be determined by preparing samples of at least five different concentrations within the range of 80 % to 120 % of the target concentration. The method of standard preparation and the number of injections should be same as used in the final procedure. Linearity curve will be plotted for peak area response or absorbance against concentration. The linear relationship will be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. Range is an expression of the lowest and highest level of analyte that have been demonstrable to be determinable with acceptable precision, accuracy and linearity.

2.2.2. Documentation:

Record the results on a datasheet. Calculate the mean, standard deviation, and Relative Standard Deviation (RSD) for each concentration. Plot concentration (x-axis) versus mean response (y-axis) for each concentration. Calculate the regression equation and coefficient of determination (r2). Record these calculations on the datasheet.

2.2.3. Acceptance criteria:

The correlation coefficient for minimum of five/six concentration levels should be $\geq$ 0.999 for the range of 80 to 120% of the target concentration. The y-intercept must $\leq$ 2 % of the target concentration response. A plot of response factor versus concentration must show all values within 2.5% of the target level response factor, for concentrations between 80 and 120% of the target concentration.

2.3. Range

For the assay of a drug substance or a finished product: normally from 80 to 120 percent of the test concentration; for content uniformity, 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 form (e.g., metered dose inhalers), is justified; and for dissolution testing: +/-20 % over the specified range.

2.3.1. Test procedure:

The data obtained during the linearity and accuracy studies will be used to assess the range of the method.

The precision data used for this assessment is the precision of the three replicate samples analyzed at each level in the accuracy studies.

2.3.2. Documentation: Record the range on the datasheet.

2.3.3. Acceptance criteria:

The acceptable range will be defined as the concentration interval over which linearity and accuracy are obtained per the above criteria, and in addition, that yields a precision of ≤ 3% RSD.

2.4. Accuracy

2.4.1. Test procedure:

Spiked samples will be prepared at three concentrations over the range of 80 %, 100 % and 120 % of the target concentration. Three individually prepared replicates at each concentration will be analyzed. When it is (Spiked samples) difficult to prepare use a low concentration of a known standard.

2.4.2. Documentation:

For each sample, report the theoretical value, assay value, and percent recovery. Calculate the mean, standard deviation, RSD, and percent recovery for all samples. Record results on the datasheet.

2.4.3. Acceptance criteria: 100 ± 2% is typical for an assay of an active ingredient in a drug product over the range of 80 to 120% of the target concentration. The measured recovery in case of dissolution is typically 95 % to 105 % in case of dissolution.

2.5. Precision

2.5.1 Repeatability

2.5.1.1 Test procedure:

Repeatability of system and method should be performed. For instrument precision determinations of five replicate of reference standard should be made. For the method nine determinations covering specified range of 3 concentration and 3 replicates should be made or six determinations at 100 % of the test concentration. For dissolution purpose, nine determinations covering specified range of 3 concentration and 3 replicates should be made or six determinations at 100 % of the test concentration or 2 or 3 determinations on each of 3 days should be performed.

2.5.1.2 Documentation

Record the retention time, peak area on the datasheet. Calculate the mean, standard deviation, and RSD.

2.5.1.3 Acceptance criteria:

RSD should be 1% for drug substances and drug products, less than 2% for the assay and dissolution of bulk drugs and finished products.

2.5. 2 Intermediate Precision

2.5.2.1 Test procedure

Intermediate precision (within-laboratory variation) will be demonstrated by two analysts, using two HPLC systems on different days and evaluating the relative percent purity data across the two HPLC systems.

For dissolution testing purpose, if possible intermediate precision can be evaluated using a well characterised lot of drug product with tight content uniformity. If this type of lot is not available, premeasured placebo and active ingredients may be used to identify intermediate precision. The dissolution procedure on the same sample may be run by at least two different analysts from the same laboratory, with each analyst preparing the standard solutions and the medium and following the defined quantification procedure.

2.5.2.2 Documentation: Record the relative % purity (% area) of each concentration on the datasheet.

Calculate the mean, standard deviation, and RSD for the operators and instruments.

2.5.2.3 Acceptance criteria:

The assay results obtained by two operators using two instruments on different days should have a statistical RSD $\leq$ 2%.

For dissolution, a typical acceptance criteria is the difference in mean value for dissolution results between any two conditions, using the same strength, does not exceed an absolute 10 % at time points with < 85 % dissolved and does not exceed 5 % for time points > 85 %.

2.6. Limit of Detection: (Not necessary for assay)

2.6.1. Test procedure:

The lowest concentration of the standard solution will be determined by sequentially diluting the sample. Five/Six replicates should be made from this sample solution.

2.6.2. Documentation: Print the chromatogram and record the lowest detectable concentration and RSD on the datasheet.

2.6.3. Acceptance criteria: The ICH references recommend a signal-to-noise ratio of 3:1.

2.7. Limit of Quantitation (it is not necessary for assay)

2.7.1. Test procedure:

Limit of quantitation can be determined based on the standard deviation of the response and the slope with the instrumental response obtained from the linearity. Establish the lowest concentration at which an analyte in the sample matrix can be determined with the accuracy and precision required for the method in question. This value may be the lowest concentration in the standard curve. Make six replicates from this solution.

2.7.2. Documentation:

Print the chromatogram and record the lowest quantified concentration and RSD on the datasheet. Provide data that demonstrates the accuracy and precision required in the acceptance criteria.

2.7.3 Acceptance criteria:

The limit of quantitation for chromatographic methods has been described as the concentration that gives a signal to noise ratio (a peak with height at least ten times as high as the baseline noise level) an RSD of approximately 10% for a minimum of six replicate determinations.

2.8. System Suitability

2.8.1. Test procedure:

System suitability tests should be performed on HPLC systems to determine the accuracy and precision of the system by injecting five/ six injections of a solution containing analyte at 100% of test concentration. The following parameters will be determined:

- Theoretical Plate count
- Tailing factors,
- Resolution if required , and
- Reproducibility (percent RSD of retention time, peak area, and height for six injections).

2.8.2. Documentation:

Print the chromatogram and record the data on the datasheet

2.8.3. Acceptance criteria:

Retention factor (k): the peak of interest should be well resolved from other peaks and the void volume; generally k should be ≥ 2.0.

Resolution (Rs): Rs should be ≥ 2 between the peak of interest and the closest eluted peak, which is potentially interfering (impurity, excipient, and degradation product).

Reproducibility: RSD for peak area, height, and retention time will be 1% for six injections. Tailing factor (T): T should be ≤2.

Theoretical plates (N): ≥2000.

2.9. Robustness:

As defined by the USP, robustness measures the capacity of an analytical method to remain unaffected by small but deliberate variations in method parameters. Robustness provides some indication of the reliability of an analytical method during normal usage. Parameters, which will be investigated, are percent organic content in the mobile phase or gradient ramp, pH of the mobile phase, buffer concentration, temperature, and injection volume. These parameters may be evaluated one factor at a time or simultaneously as part of a factorial experiment.

The effects of the following changes in chromatographic conditions will be determined: methanol content in mobile phase adjusted by ± 2%, mobile phase pH adjusted by ±0.1 pH units, column temperature adjusted by ±6°C. If these changes are within the limits that produce acceptable chromatography, they will be incorporated in the method procedure.

2.9.1. Stability of Standard and sample solutions

2.9.1.1 Test procedure:

Analysing solutions of drug product in comparison to the fresh prepared solutions and original solutions stored at room temperature in auto sampler (at least 24 h) stored at 2 - 8 °C, in refrigerator (at least 48 hour).

The stability of the standard is analyzed over the specified period of time (at least the time of the entire dissolution procedure) using a freshly prepared standard solution at each time interval for comparision.

2.9.1.2. Documentation

Stability should be documented by:

A table with mean values.

2.9.1.3. Acceptance criteria

The mean value of the standard solutions should be between 97.5 % and 102.5 % in comparison to the fresh prepared standard solutions in case of the stability of the standard solution.