Republic Of Tunisia

MINISTRY OF HEALTH

PHARMACY AND DRUG DIRECTORATE

MEDICINAL PRODUCTS REGISTRATION GUIDE IN TUNISIA

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Foreword

The first edition of "Medicinal products registration guide for human use" published in 2004 has been reviewed to meet the evolution of this activity at the national and international level.

The second edition describes on first part the registration procedure of the drugs for human use as well as the composition of the Marketing Authorization Application files (MAA) and the post-marketing period applications (renewals,transfer...).

The file includes all the modules to be submitted related to the application in compliance to the CTD requirements (Common Technical Document).The references to the different guidelines are mentioned in this document in order to help the applicant to provide the different parts of his file.

The second part will deal with the requirements for medicinal products for veterinary use.

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The present document will become applicable on 1st May 2016.

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GLOSSARY:

PHARMACEUTICAL ESTABLISHEMENTS: Manufacturers of medicinal products are considered as pharmaceutical establishements, which are approved and controlled by a competent authority. They carry on their activity in accordance with the provisions of the decree 90-1400 on Good Manufacturing Practices.

The manufacturing sites of medicinal products work under conditions providing safeguards for all the public health.The Good Manufacturing Practices requirements of medicinal products, their quality control, their packaging, their labeling, their trade names, as well as their advertising are regulated by a decree law (Reference Act n° 85-91 of 22nd November 1985).

EXPORTING COUNTRY: The exporting country is the country from which the finished product is exported to Tunisia (Reference circular N° 80 on the origin of medicinal products).

COUNTRY OF ORIGIN: *The country of origin of the medicinal product is the country where the manufacturing site is located and where one of the following pharmaceutical steps is carried out: The manufacturing, the packaging and the control of the finished product (Reference circular N°80 on the origin of medicinal products).*

THE REFERENCE PRODUCT: Any pharmaceutical product which obtained the marketing authorization with a file including all the necessary and sufficient data required for its assessment. (*Reference Act N°2008-32 of 13rd May 2008 amending and supplementing the law N°73-55 of 03/08/1973*).

THE GENERIC PRODUCT: Any pharmaceutical product having the same pharmaceutical form and the same qualitative and quantative composition in active ingredients as well as the reference product, and for which bioequivalence with the reference medicinal product, has been demonstrated by appropriate bioequivalence studies.The scientific criteria defining the exemption of bioequivalence studies are set by the decree law of the Ministry of Health.

(*Reference Act N°2008-32 of 13 May 2008 amending and supplementing the law N°73-55 of 03/08/1973*).

The different oral pharmaceutical forms with immediate release are considered as the same pharmaceutical form. Similarly, any salts, esters, ethers, isomers, mix of isomers, complexes or derivatives of the active ingredients are considered as having the same composition in active ingredient, except if they show significantly different properties regarding the safety or the efficacy. In such case, additional information providing proof of safety and efficacy of the different salts, esters or derivatives of the authorized active ingredient must be provided by the applicant for the marketing authorization (Reference Frensh Public Health Code).

1. APPLICATION FIELD:

This document applies to all medicinal products intended for human and veterinary use.The provisions related to the registration of specific medicinal products such as biosimilars, homeopathic medicinal products, radiopharmaceuticals and herbal medicinal products are provided in specific documents.

2. REGISTRATION OF MEDICINAL PRODUCTS FOR HUMAN USE:

No medicinal product can be provided for free or against payment without receiving a Marketing Authorization from the Ministry of Health after the committee consultation.This Marketing Authorization is issued for a 5 years period and renewable for a 5 years period.This requirement results from the act n°85-91 of 22nd November 1985, regulating the manufacture and the registration of medicinal products intended for human use in Tunisia.

The different persons involved in the registration procedure

1. Pharmacy and Drug Directorate (DPM) in charge of evaluating the compliance of the dossier with the current regulations in terms of drug registration for human use,of the management and the follow-up of the dossier throughout the registration procedure and the organization of the specialized commitees and the technical commitee of medicinal products.
2. The specialized committees are made of experts appointed by the Ministry Of Health, which assess the pre-clinical and clinical data of the dossier. (Efficacy and safety of the medicinal products).
3. The National Laboratory of Medicinal products Control (LNCM) in charge of the chemical and pharmaceutical assessment of the dossier (Quality) and the control of Medicinal products.
4. The Technical Committee of Pharmaceutical Specialities (CTSP), the members of the CTSP are appointed under a ministerial decision, provides the final opinion regarding the Marketing Authorization Application to the Minister Of Health.
5. The Minister of Health decides whether or not to grant the Marketing Authorization.

The different steps of the registration procedure of the medicinal products intended for human use can be summarized in the figure below:

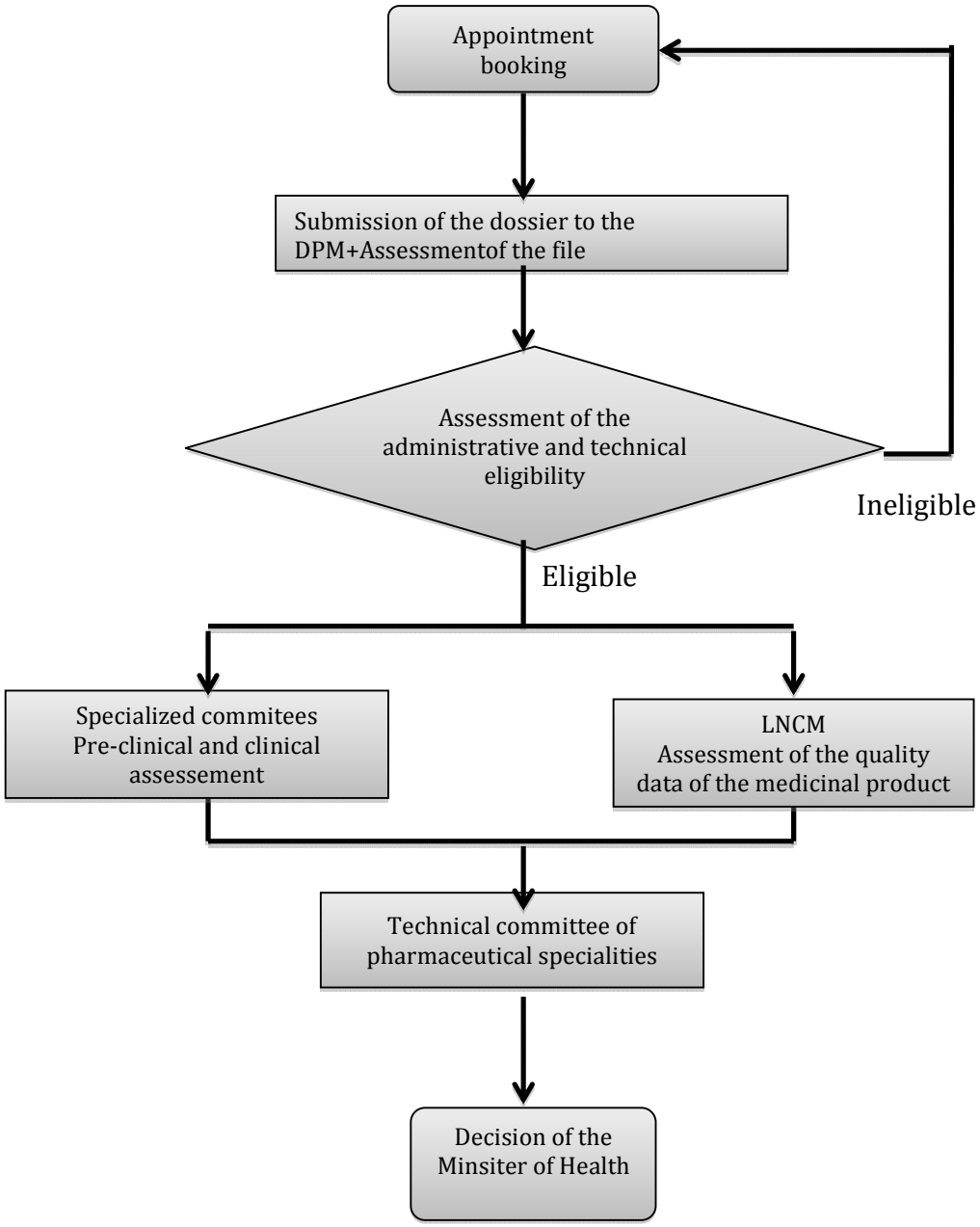

Figure 1: Medicinal product for human use Registration Procedure

2.1. REGISTRATION PROCEDURE:

2.1.1. Appointment booking:

For any application for registration (new application, renewal, variation, transfer..),the applicant has to book an appointment at the DPM via the website.

An appointment requires:

- A prior registration at the list of the pharmaceutical establishements undertaking an activity in Tunisia.
- Sending to the following address: courriel.dpm@rns.tn, a duly filled registration form, available for download on the DPM website (www.dpm.tn)

Once registered, a password will be communicated via email enabling the access to the 'e-booking' portal.

Remark: In case of appointment delay, missing documents or unfilled forms, scheduling another appointment will be mandatory.

Further details on the terms and the submission timelines are available on the portal.

2.1.2. Submission files:

The application dossier has to be submitted to the DPM - Ministry of Health.

The assessment of the technical and administrative eligibility of the file will be carried out at the DPM at the time of the submission. A discharge will be provided to the applicant, only for eligible files, in order to allow the offical registration of the application at the Central registry of the Ministry of Health.

For the non eligible files, a list of the documents to complete will be provided to the applicant at the end of the assessment session, and will be sent by regular mail to the applicant of the Marketing Authorization holder.

2.1.3. Clinical and preclinical data assessment:

The application files for registration have to be submitted at latest three months before the meeting date of the concerned specialized committee.

A calendar with planned meetings of the specialized commitees is published on the DPM website every year, in order to enable the applicant laboratories to submit their files within the applicable time frames.

The dossier is sent for study to one or several expert members of the concerned Specialized Committee which will be in charge to send a report to the DPM by regular mail.

In accordance with article 4 of the decree of the Minister of Health of 15th October 2002, the Specialized Commitees are made for all different therapeutic areas.The members of these Specialized Commitees are appointed by the Minister of Health among the specialists of the health disciplines.The Specialized Commitees assess the files taking into account the therapeutic benefit and the undesirable effects observed as well as the cost-effectiveness.

The president, the rapporteur or a member of the specialized committee, may be invited to present to the Technical Committee of Pharmaceutical Specialities the conclusions of his Specialized Committee.

* List ofcommittees:

COMMITTEES	Number of meetings/year
1- Specialized Committee of the regulators of the cardio-vascular and kidney disorders.	2
2-Specialized Committee of anesthesia, intensive care and nutrition	1
3-Specialized Committee of antibiotics , antifungals and anti-parasitic drugs	1
4- Specialized Committee of phytotherapy and alternative therapeutic techniques	1
5- Specialized Committee of gastro-enterology	1
6- Specialized Committee of ENT and stomatology	1
7- Specialized Committee of carcinology	2
8- Specialized Committee of hematology	2
9- Specialized Committee in rhumatology and antalgics	1
10- Specilaized Committee of dermatology	1
11- Specilaized Committee of pneumology and immuno-allergology	1
12- Specialized Committee of ophtalmology	1
13- Specialized Committee of endocrinology and metabolism	1
14- Specialized Committee of neurology and psychiatry	1
15- Specialized Committeeof radiology	1
16- Specialized Committee of vaccines, serumsand immunoglobulin	1
17- Specialized Committee of gynecology	1

The files of the generics are exempted from this step except for the case where the reference product is not registred in Tunisia.

2.1.4. Data quality assessement of medicinal products

The assessment of the pharmaceutical and chemical dossiers, as well as the analytical and microbial control are carried by the LNCM. The decision of the LNCM is sent to the DPM who sends it to the Marketing Authorization applicant.

2.1.5. Assessement of the Marketing Authorization application by the CTSP:

The Technical committee for Pharmaceutical Specialities (CTSP) study the conclusions reached by the specialized committee, and the LNCM as well as the suggested price of the specialities applying for a new marketing authorization and will propose to the Minister of Health, according to the case, to approve the registration of a medicinal product, toreject it or to ask for further scientific or medical assessement.The rejection must be justified.

The composition and the functioning of the Technical Committee are defined by the provisions of the decree of the Minsiter of Health of 7th March 2005 amending the act of 15thoctorber 2002.

The Technical Committee is made of 21 members who are nominally appointed by a decision of the Minsiter of Health.The Minister, may also appeal to an expert person in the field of the medicinal product in order to participate, in an advisory capacity, in the committee work.

The internal guidelines of the Technical Committee are available on the website of the DPM. (www.dpm.tn).

2.1.6. Marketing Authorization Grant:

The marketing Authorization is issued by the CTSP for a period of 5 years.

The Marketing Authorization applicant has to inform the Minstry of Health of the effective date of the marketing (date of first customer delivery) of the medicinal product by sending a notification letter to the DPM and by providing a mock-up.

2.1.7. Prioritization requests:

A prioritization for the treatemnt of the Marketing Authroizationfiles by the LNCM might be granted in the cases below:

- Products requiring call for tender
- New product of major public health benefit / orphan medicinal product
- First generic of a reference product
- Transfer to local manufacturing
- Launching of a new local manufacturer (during its first year)
- Justified major variations (Send the application directly to theLNCM)

The number of the prioritized files cannot exceed 4 molecules (4 INNs) per company and per year. It is applicable for any object of prioritization except for the launch of a new local manufacturer or the extension of a new unit of a manufacturer already in place where the request of prioritization may concern maximum 8 molecules.These 8 molecules must be submitted whithin the first year from the date of the submission of the first marketing authorization application.

The written requests of prioritization for the Marketing Authorization file shall be submitted to the DPM.They will be assessed jointly with the LNCM and with the Central Pharmacy of Tunsia, if required.

An answer is sent to the applicant.

The requests of prioritization are applicable only for the eligible dossiers.

Any regulatory or legal question is sent to the following address: courriel.dpm@rns.tn

If you have any legal or regulatory question regarding the registration of the medicinal product for human use, please send your question to: enregistrement.humain.dpm@rns.tn

2.2. COMPOSITION OF THE REGISTRATION DOSSIER:

2.2.1. New application request for marketing authorization:

For any new application request for Marketing Authorization,a complete file must be submitted in accordance with the CTD format (Common Technical Document) as described in the ICH M4 guideline entitled' Organisation Of The Common Technical Document For The Registration Of Pharmaceuticals For Human Use'.

The modules described in the table below must be submitted to the DPM:

Table1: Composition of a Marketing Authorization dossier application

Module	Reference Medicine	Generic	Assessed by
M1	Administrative data	Administrative data	DPM
M2	Summary of the file (M3, M4, M5)	Summary of the file (M3, M5)	DPM LNCM Experts
M3	Pharmaceutical and chemical data(Quality)	Pharmaceutical and chemical data (Quality)	LNCM
M4	Preclinical data	Exemption	Experts
M5	Complete clinical data	Bioequivalence study/ Exemption*(Biowaiver)* +A bibliographical study is required in the absence of a reference product marketed in Tunisia	Experts LNCM

For the new marketing authorization applications regarding the line extension (new pharmaceutical form, strength, or content of container), the modules to be submitted are listed in table 2.

A request for priorization to be submitted to the DPM is possible for these applications.

When it is planned to stop the sale of the first container content, the change of the container content is considered as a variation to the terms of the Marketing Authroization (see appendice X,B.II.e.5.).

Table2: Modules to be submitted in case of line extension

		Module to be submitted
New pharmaceutical form		M1 - M2 - M3 - M5
New strength		M1 - M2 - M3 - M5
New container content (Newvolume, new number of units)	**With a change in the primary packaging (Type/ Material/ Supplier)**	M1 - M2 - M3
	Whithout achange inprimary packaging (Type/ Material/ Supplier)	M1

The table 3 explains the number of copies and the media type required for each module.

Table3: Number of copies and media type required for each part

Number of copy		Paper	CD-ROM (PDF)
M1		2	-
M2*	Quality (QOS)		2 CD seperately
	Non clinical		3 CD seperately
	Clinical		3 CD seperately
M3		1	2 CD seperately
M4		-	2 CD seperately
M5		-	3 CD seperately
SmPC Tunisia / label and Patient Information Leaflet (PIL) mock-up		Included in M1	1 CD seperately
Information on the pharmacovigilance		Separated from M1	-

The submitted files shall be separated by modules.The different parts of module 2 shall be separated as indicated in table 3.

The applicant must be able to provide additional copies on request. All files need to be submitted together and simultaneously.

2.2.1.1. MODULE 1:

Module 1 concerns administartive information and those related to the prescription. In this part of the file, we will find the following sections:

1.0. APPLICATION LETTER

1.1. TABLE OF CONTENT

1.2. APPLICATION FORM

1.3. INFORMATION ON THE MANUFACTURE

1.3.1. Establishement licence

1.3.2. Certificateof Good Manufacturing Practices

1.3.3. Case of subcontrating

1.4. INFORMATION ON THE PRODUCT

1.4.1. SmPC, Labelling, Patient Information Leaflet (PIL)

1.4.2. Mock-up : PIL and labelling

1.4.3. Samples

1.4.4. Imported medicinal product

1.4.4.1. Marketing authorization inthe exporting country

1.4.4.2. Certificate of a Pharmaceutical Product

1.4.4.3. Status of the Marketing Authroization applications submitted worldwide

1.4.5. Under licence medecinal product

1.4.5.1. *Under licence manufacturing agreement*

1.4.5.2. *Marketing Authorization of the licensor*

1.4.5.3. *Certificate of a Pharmaceutical Product*

1.4.5.4. *Status of the authroization applications submitted worldwide*

1.5. INFORMATION ON THE PRICE

1.5.1. Price proposal

1.5.2. Daily cost treatment and/or cost per cure

1.5.3. Price certification

1.5.4. Price list in the other countries

1.5.5. Refund status and corresponding rate

1.6. INFORMATION ON PHARMACOVIGILANCE

1.7. REGISTRATION PAYMENT RECEIPT

1.0. APPLICATION LETTER:

The applicant company has to submit a written application request in triplicate (see annex) in the name of the Minister of Health, signed and dated by:
-The head pharmacist or where required after his prior approval, by the regulatory affairs pharmacist for the medicines locally manufactured,
- The regulatory affairs pharmacist in the native country or where required, after his prior approval by the local representative (having a scope statement signed by the Minstry of Health) for the imported products.

1.1. TABLE OF CONTENT:

A detailed table of content shallbe provided for each type of request, including all the modules sections in the frame of the concerned request.Each module has to be provided with its own table of content.The table of content shall be detailed in «*Granularity Document*» (Annex of the document of ICH« *Organisation of The Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 »*).
For Module 1:cf paragraph a)Module1.

N.B:If no information is available or necessary under a specific heading “No object” or “Not applicable” by keeping the title of the section and thenumbering.If necessary, a justification of the absence of a study must appear in the Quality Overall Summary (QOS),No clinical overview,and the clinical overview.

1.2. APPLICATION FORM:

The request application form (see annexII) shall be duly filled, signed and dated by the same persons who sign the application letter.

1.3. INFORMATION ON THE MANUFACTURING:

1.3.1. Establishment licence (Holder and manufacturers):

The application file shall be accompanied by copies of the establishment licence for:

- The company holder of the Marketing Authorization

- The site(s) involved in the manufacture of the finished product
- The site(s) involved in the primary and secondary packaging,
- The site(s) involved in the control
- The site(s) involved in the batch release of the product

The establishment licences shall be delivered by local competent authorities.

Note: For the imported medicinal products, if the marketing authorization holder is not a site manufacturing drugs, the following documents shall be provided:

- Extract from the commercial register of this company or the authorization to open it

- Solidarity commitement between the marketing authorization holder and the manufacturer(s) defining the different pahrmaceutical liabilities for each site (production, primary packaging, secondary packaging, control, batch release).

N.B: The establishment licence must be valid.

1.3.2. Certificate of Good Manufacturing Practices:

The application file shall be provided with copies of the Certificate of compliance to current Good Manufacturing Practices (cGMP) of:

- The marketing authorization holder
- Site(s) ensuring the last step of the manufacturing of the active ingredient (AI)
- Establishment(s) involvedin the manufacture of the finished product
- Establishment(s) involved in the primary and secondary packaging
- Establishement(s) involved in the control
- Establishment(s) involved in the batch release of the medicinal product

These certificates of compliance shall be delivered by the local competent authorities.
N.B: the validity of the GMP certificate is 3 years from the last date of the inspection of the site, unless other specification.

1.3.3. Case of subcontracting of one or several manufcaturing steps:

For the products manufactuerd in Tunsia, the subcontracted operations shall be authorized by the competent services of the Ministry of Health, beforehand.

In such case, each part (the holder of the MA and the sub-contractor) shall be a holder of establishment manufacturer's authorisation of pharmaceutical products in Tunsia.

The applicant shall provide a copy of the subcontracting authorization.

Reference: Circular N 15/99 and the decision of DPM N01/2003 and its amending.

1.4. INFORMATION ON THE PRODUCT

1.4.1. SmPC, Labelling, and Patient Information Leaflet (PIL):

For any new application, a Summary of Product Charcateristics (SPC), and a labelling shall be provided.
Annexes III, IV, V and VI may be used as a model in the elaboration of the SmPC and the labelling (the recommendations to be followed for these models are available on annex VII).
A word and a PDF versions of the SmPC as proposed for Tunsia shall be provided separately on a CD in order to be uploaded on the web site of the DPM.
The files shall be provided in Arab and/or French version.
The excipients known to have a recognised action or effect shall be mentioned as indicated in the annex 'List of excipients known to have a recognised action or effect, update of the List and the labels as per the Euroepan Guideline'.

N.B.: For the imported products, it is required to enclose the SmPC of the exporting country.

1.4.2. Mock up:

The applicant has to provide a copy in Arab and/or French of:

- PIL project for Tunisia
- A colored version of the primary packaging labelling project
- A colored version of the secondary packaging project

A PDF version of the PIL and labelling project shall be provided on a separate CD.

1.4.3. Samples:

A detailed list of the submitted samples shall be enclosed.

The samples of the starting material (Active Ingredient(s) and, if needed (antimicrobial preservatives and anti-oxidants) and the sale model samples of the finished products (primary packaging, secondary packaging and PIL) provided with their certificates of analysis (CoAs), shall be provided as described in table 4, unless an exemption is granted by the DPM. For the imported medicinal products, the model marketed in the exporting country is required.

Table4 : Minimal quantity of sample to be submitted

Pharmaceutical form	Quantity of samples required for the **analytical control**(unit) The quantities need to be provided in sufficientquantity in whole packs	Number of sample for **administrative assessement/archiving**
Tablets	210 tablets	3 boxes
Capsules	150 capsules	3 boxes
Sachets	150 Sachets	3boxes
Suppositories/Pessaries	150 Suppositories/Pessaries	3 boxes
Semi-solid dosage formsfor skin application (skin oitment,creamand gels)	20 tubes	3boxes
Eye oitment	50 tubes	3 boxes
Syrups ororal suspensions	20 bottles	3 boxes
Solutions for injection	50 bottles, phials or bags	3 boxes
Powder for injection	50 bottles	3 boxes
Collyres	50bottles	3 boxes
Phials	100 phials	3boxes
Preparation for inhalation	60 units	3 boxes
Other forms	20 units	3boxes
Caseof line extension, : new presentation (same strength and same dosage form)without change inprimary packaging(Type/ Material/ Supplier)	-	3boxes
Reference substance (if required)	Reference substance(s)of the Avtive Ingredient(s) and the impurities specified on the control monograph of the finished product (sufficient quantity for complete analysis)	

The shelf-life date of the samples shall be over 1 year from the date of submission of the file.

The applicant company has to be able to provide additional samples if needed, and all the reagents and the required analytical control tools of the medicinal product (reference substances of the AI and those of the impurities of the finished product specified in the monography)

The chromatography columns necessary for the control of the finished product may be also required.They will be returned to the applicant company once the analysis is completed.

1.4.4. Imported medicinal product:

For the imported medicinal products, the applicant company has to provide the following documents:

1.4.4.1. Marketing Authorization in the exporting country:

The applicant has to provide a valid copy of the Marketing Authorization of the product, delivered by the competent authorities in the exporting country along with the variation notifications.

The marketing authorization shall be provided in the mother tongue language with Arabic, French or the English translations carried by a certified translator.

1.4.4.2. Certificate of the Medicinal Products (CMP):

The applicant has to submit the current Certificate of the Medicinal Products following the recommended model by the WHO delivered by the competent authorities in the exporting country.

N.B: The CMPs cannot be older than one year from the issue date (unless other specification in the CMP)

1.4.4.3. Status of the Marketing Authorization applications submitted worldwide:

The applicant has to submit the list of all the countries where the product is submitted, registered and marketed.

1.4.5. Medicinal product manufactured under licence:

For the reference drugs or generics manufactured under licence, the following documents shall be provided:

1.4.5.*1. Licence agreement:*

The applicant has to provide the licence agreement between the licensor and the manufacturer, or, the certification of the licensor authorizing the company to manufacture.

1.4.5.*2. Marketing Authorization of the licensor:*

It is mandatory to provide a copy of the initial Marketing Authorization.

1.4.5.3. Certificate of the Medicinal Products:

The applicant has to submit the current CMP if applicable, according to the model recommended by the World Health Organization (WHO) delivered by the competent authorities in the exporting country.

N.B: the CMPs cannot be older than a year from the issue date (unless other specification in the CMPs).

1. 5. INFORMATION ON THE PRICE:

1. 5. 1. Price proposal:

For products manufactured locally, the applicant has to provide a price proposal including all taxes.

Forthe imported products, a cost and freight price proposal (CIF) shall be submitted.

The modes of fixing prices are described in the internal regulation of the Technical Committee of the Medicinal Products (CTSP) published on the website of the DPM (www.dpm.tn).

1. 5. 2. Daily tretament cost and per cure:

The applicant has to provide in a table form the daily cost and/or per cure for each required indication.

1.5. 3. Price certification (Imported medicinal products):

The applicant has to submit:

- A certification of the wholesaler pre-tax price and a public price certification endorsed by the competent authority of the exporting country.

1.5.4. List of the price in the other countries where the product is marketed (imported medicinal products):

The applicant has to submit the price, when it is marketed in the following countries: France, Germany, Spain, Italy, Morocco and Algeria.

1.5.5. Refund status and corresponding rate (Imported medicinal products):

The refund status and the corresponding rate in the exporting country need to be specified at the time of the submission.

1.6. INFORMATION ON PHARMACOVIGILANCE:

The Marketing Authorization applicant has to provide a detailed description (or a summary) of the pharmacovigilance procedure which will be implemented, and if possible, a risk management plan.

1.6.1. Pharmaovigilance procedure:

A descriptive summary of the permenant file of the pharmacovigilance procedure or PSMF (*Pharmacovigilance System Master File*) shall be be provided. If the file has been previously provided, only an update of the PSMF (inclusing the modifications of the last version) is needed. For further details, refer to Module II of « *Guidelines on good pharmacovigilance practices (GVP) For Arab Countries* » and their summaries in french and english versions, available on the website of the National Center Of Pharmacovigilance(CNPV) (www.pharmacovigilance.rns.tn).

1.6.2. Risk Management Plan:

A Risk Management Plan(RMP), in accordance with the format described in « *GVP For Arab Countries* », describing the risk management procedure which will be implemented for the concerned medicinal product, shall be submitted for all the marketing authorization applications regarding the medecinal products with a Risk Management Plan (RMP) in progress in their countries or following a request from the authorities. For further details, refer to Module V of « *GVP For Arab Countries* » and their summaries in English and French versions, available on the website of the National Centre for Pharmacovigilance(NCPV) CNPV (www.pharmacovigilance.rns.tn).

1.7. REGISTRATION PAYMENT RECEIPT:

Any marketing authorization application shall be provided with a proof of a payment of a fixed fee for which the rates and the refund methods are set by joint order issued by the Ministries of Finance and Health, in accordance with the current regulations. (see annex of the act 8th of September 2011).

The payment is done to the accounting agent of the National Laboratory Of the Control Of Medicament.

2.2.1.2. Module 2:

The module 2 shall be presented in compliance with the ICH M4 Guideline entitled '*OrganisationOf The Common Technical Document For The Registration Of Pharmaceuticals For Human Use*'.

2.2.1.3. Module 3:

In the Module 3, we find the following sections:

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3.2.S.1.3.	General properties
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3.2.S.2.3.	Control of materials
3.2.S.2.4.	Controls of critical steps and intermediates
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3.2.S.4.5. Justification of specification

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3.2.S.7. Stability

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3.2.P.3.	**Manufacture**
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3.2.P.3.2.	Batch formula
3.2.P.3.3.	Description of manufacturing process and process controls
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3.2.P.4.	**Control of excipients**
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3.2.P.5.	**Control of drug product**
3.2.P.5.1.	Specification(s)

3.2.P.5.2.	Analytical procedures
3.2.P.5.3.	Validation of analytical procedures
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3.2.P.5.5.	Characterisation of impurities
3.2.P.5.6.	Justification of pecifications
3.2.P.6.	**Materials or reference standards**
3.2.P.7.	**Container closure system**
3.2.P.8.	**Stability**
3.2.P.8.1.	Stability summary and conclusions
3.2.P.8.2.	Post-approvalstability protocol and commitement
3.2.P.8.3.	Stability data

3.1. Table of content of module 3:

The applicant has to join the table of content to the module 3 by considering the annex of the ICH M4 guideline with the mention of the adopted numbered pagination.

3.2. Body of data:

3.2.S. DRUGSUBSTANCE:

The documents to be provided depend on whether the active ingredient is subject of a CEP or a DMF,

- AI subject of a CEP:

The Marketing authorization applicant has to provide:

- A valid copy of the CEP with all annexes in which the declaration of access needs to be duly filled and the retest date clearly mentioned, otherwise a complete stability study needs to be provided.

- A certificate of analysis of the manufacturer of the active ingredient

- A certificate of analysis of the manufacturer of the active ingredient of the speciality

The competent authority can request any additional information necessary for the assessement of the AI quality,

- AI subject of a DMF :

A declaration of access shall be provided (to be sent in the name of the LNCM).

The composition of a DMF is the following:

The guidelines CPMP "Drug substance Master File procedure"

3.2.S.1. General information

3.2.S.1.1. Nomenclature

In this chapter, the followings shall be detailed:

- International nonproprietary name (INN)
- Chemical name
- Laboratory code
- Other namesor codes
- *Chemical Abstracts Service* (CAS) : regitration number

Theguidelines CPMP: Chemistry of New Active Substance" et "Chemistry of the Active Substance"

3.2. S.1.2. Structure

The structural formula including the relative and absolute stereochemistry, the molecular formula and the molecular mass shall be provided.

The guidelines CPMP: Chemistry of the New Active Substance" et "Chemistry of the Active Substance"

3.2.S.1.3. General properties

The main physico-chemical characteristics and other relevant properties shall be provided. In particular, a physical descripition of the active ingredient such as the appearance, the color and the physical state, solubility, hygroscopy, crystalline form, pH/pKa, the chirality or any other relevant property.

Theguidelines CPMP: Chemistry of the New Active Substance" and"Chemistry of the Active Substance".

The Guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria forNew Drug Substances and New Drug Products – Chemical Substances"

3.2.S.2. Manufacture

3.2.S.2.1. Manufacturer(s)

The name and the address of the manufacturer(s) shall be stated by specifying the responsibilities of each site (site involved in the production and/or the control of the drug substance or the alternative sites, including the subcontracting)

The Guidelines CPMP: Chemistry of the New Active Substance" and "Chemistry of the Active Substance";

3.2.S.2.2. Description of manufacturing process and process controls:

A flowchart of the synthesis process shall be provided with the molecular formula, the molecular weights, yield ranges, chemical structures of starting materials and intermediates, as well as the stereochemistry. The operating conditions, reagents and solvents shall be specified.

A narrative description of the manufacturing process shall be provided including the quantities of raw materials, solvents, catalysits and reagents required for batch scale for commercial manufacture.

It is important to identify the critical steps of the process and the process control, it is also required, whenever appropriate, to mention the non isolated intermediates.

The applicant has to identify and justify the choice of the active ingredient which is considered as a starting material, the name and the manufacturer address of the starting material(s) shall be provided, the synthesis data in the form of figures may be useful for the assessement of the relevance of the control specifications.

It is necessary to discuss the stereochemistry of the starting materials, if the chiral compounds are involved.

The alternative process shall be justified and described using the same details as the principal process.

The guidelines CPMP: Chemistry of the New Active Substance" and "Chemistry of the Active Substance"

3.2.S.2.3. Control of raw materials

It is required to enumerate all the raw materials required for the manufacturing of the drug substance and/where they are involved in the manufacturing process.

Information on the quality and the control of materials are to be provided:

The guidelines CPMP: "Chemistry of the New Active Substance" and "Chemistry of the Active Substance"

The guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances",

3.2.S.2.3 is a closed part which is not required but it might be requested by the laboratory of control.

3.2.S.2.4 Control of critical steps and intermediates

For the critical steps: It is required to provide the control tests (along with justifications and experimental data carried out during the critical steps of the process which have been identified in 3.2.S.2.2 by specifying the acceptation criteria.

For the intermediates, it is required to provide information regarding the quality control of the isolated intermediate products during the process.

The guidelines CPMP-ICH: Chemistry of the New Active Substance" et "Chemistry of the Active Substance".

The guidelines Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances"

3.2.S.2.4. is a closed part which is not required but it might be requested by the laboratory of control.

3.2.S.2.5. Process validation and/or evaluation

The validation and/or the evaluation studies for aseptic process and sterilization shall be provided.

3.2.S.2.5.is a closed part which is not required but it might be requested by the laboratory of control.

3.2.S.2.6. Manufacturing process development

It is required to describe and justify the significant change made to the manufacturing process of the drug substance in case of scaling-up product batches.

3.2.S.2.6. is a closed part which is not required but it might be requested by the laboratory of control.

3.2.S.3. Caracterisation

3.2. S.3.1. Elucidation of structure and other characteristics

The structure of the molecule of the drug substance shallbe confirmed on the basis of the route of synthesis and the spectral studies (NMR, IR, mass spectrometry, UV spectrum…).

Information related to potential isomerism and polymorphism shall be also provided, in the case of the existence of several polymorphic forms, the manufacturer has to proove that the synthesis flowchart provides the same form of polymorph on 3 industrial batches.

The guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances

the guidelines CPMP: "Chemistry of the New Active Substance" and "Chemistry of the Active Substance"

3.2.S.3.2. Impurities

All data related to impurities shall be provided. These impurities can be related to the substance (raw materials, intermediates ,chiral impurities, degradation products, organic or non-organic) or related to the process –(residual solvents, catalysts or reagents). The choice of impurities to be included in the control of drug substance monography and the acceptance crieteria shall be justified.

It should be noted that the monographs of phamacopeia have been developed to control the specific impurities with considered synthesis routes during the elaboration of the monograph, and the specific impurities with other synthesis routes are not necessarily controlled.

The manufacturer has to demonstrate that the monography enables the control of the impurities which are related to the used synthesis route.

The guidelines CPMP-ICH: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents, "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products –Chemical Substances",

Theguidelines CPMP: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4. Control of drug substance

3.2.S.4.1. Specifications

The guidelines of the drug substance shall be indicated, specifying the used tests and their acceptance criteria.

The guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances",

The guidelines CPMP: "Chemistry of the New Active Substance", "Chemistry of the Active Substance" and "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4.2. Analytical procedures

All the analytical procedures used for the control of the drug substance shall be described in details. Indicate the references to the pharmacopeia (European, member state, USA, international or Japan), provide a detailed description for undescribed methods of the above mentioned pharmacopeia, whenever appropriate.

The procedures of analyses adopted by the manufacturer of the medicinal product shall be described.

If the drug substance is tested according to the monography of a pharmacopeia, a copy of this pharmacopeia needs to be provided.

The guidelines CPMP-ICH: "Validation of analytical methods: test and methodology",

The guidelines CPMP: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.4.3. Validation of the analytical procedures:

The reports of the validation of the analytical procedures used for the control of the drug substance needs to be provided.

The analytical procedures not refered to a monography shall be validated.

When analytical procedures applied by the manufacturer of the medicinal product are different from those used by the manufacturer of the active ingredient, a validation shall be provided.*

The guidelines PA/PH/OMCL (05) 47 DEF –OMCL Guideline on validation of Analytical Procedures

3.2. S.4.4. Batch analyses

Batches description (n°, size, date and place of manufacture) and the results of analyses carried out on 3 consecutive industrial batches shall be provided.

The guidelines CPMP-ICH: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New drug substances and New Drug Products – Chemical Substances",

3.2.S.4.5. Justification of specifications

The choice of specifications must be justified:

The guidelines CPMP-ICH: "Impurities testing guideline: impurities in new drug substances", "Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances",

The guidelines CPMP: "Control of Impurities of Pharmacopoeial Substances"

3.2.S.5. Materials or reference standards

The used substances or reference materials shall be provided if needed.

The certificate of analysis of the reference substances used for the control of the drug substanceshall be provided.

The guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances"

3.2. S.6. Container closure system

The applicant has to describe the primary packaging of the drug substance specifying the nature and the specifications of each component.The specifications shall include an identification test.The choice of the material shall be justified for its intended use (protection from humidity, light, in case of need compatibility with the active ingredient…).

It is also required to specify the dimensions of the packaging and to provide a technical description sheet. The secondary packaging shall be briefly described.

3.2. S.7. Stability

3.2.S.7.1. Stability summary and conclusions

A summary table of the conducted stability studies, of the protocol and of the specifications adopted as well as the obtained results, shall be provided.

The numbers and the size of the tested batches, their respective manufacture date, and the primary packaging used in the stability studies, need to be specified.

All the analytical methods applied during the stability study (e.gforced degradation studies, accelerated conditions, intermediateand long-term conditions) shall be described.

The conclusion shall be presented by specifying the re-test date.

The guidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", ", "Evaluation of stability data", "On stability testing for a type II variation to a marketing authorisation",

The guidelines CPMP: "Chemistry of the New Active Substance" "Chemistry of the Active Substance", "On the declaration of storage conditions for medicinalproducts in the products particulars and for active substances", "on stability testing of existing active substances and related finished products"

3.2. S.7.2. Post-approval stability protocol and commitment

The stability protocol to be followed after the Marketing Authorization grant shall be provided. A commitment to provide the stability study results as they become available, shall be submitted.

Theguidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products", "On stability testing for a type II variation to a marketing authorisation",

*The guideline CPMP: "on stability testing of existing active substances and related finished products"***.**

3.2. S.7.3. Stability data

The results of the stability studies on, at least, 3 industrial batches shall be presented in a table.

The guidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "On stability testing for a type II variation to a marketing authorisation", "Evaluation of stability data",

The guideline CPMP: "on stability testing of existing active substances and related finished products"

3.2.P. Drug product

3.2. P.1. Description and composition

The applicant has to describe and present the finished product and the following data:

- The dosage form
- Composition: the list of all the components and their respective quantities (indicate an overage), the function of each component and the reference of their standard quality (pharmacopeia or inhouse monography).
- A description of the reconstitution solvents
- The type of the primary packaging for the finished product and the solvent (if applicable).

The guidelines CPMP-ICH: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products –Chemical Substances",

3.2. P.2.Pharmaceutical development

The applicant has to to provide the development studies carried out, justify the choice of the galenic form, of the formulation, of the manufacturing process,of the container closure system,and identify the critical parameters which may affect the quality ,the reproductibility of the batches of the finished product.

The data or results from specific studies or published in the literature can be presented in support of the galenic development.

In the case of sterile products, the adopted strategy to guarantee the sterility of the products shall be justified.

For dry forms of the generics, an in vitro comparative dissolution study with the reference product according to annex 1 of the guideline *CPMP/ EWP/QWP/1401/98 Rev1 Corr** is required.

The guidelines CPMP-ICH: "On development pharmaceutics", "Annex to Development Pharmaceutics – Decision Trees for Selection of Sterilisation methods"

The Guidelines CPMP: "on investigation of bioavailability and bioequivalence"

3.2. P.2.1. Components of the drug product

3.2. P.2.1.1.Drug substance

The applicant has to discuss the compatibility of the active ingredient with the excipients, as well as their physicochemical characteristics, (hygroscopy, particle size, solubility, water content, polymorphism), which may affect the process quality of the finished product.

In the case of the combination of two or several active ingredients, it is required to discuss and provide the compatibility studies with each other.

3.2.P.2.1.2. Excipients

The applicant has to justify the choice of the excipients, their concentrations, their characteristics and their functions.

The guidelines CPMP: "Excipients in the Dossier for application for marketing authorisation of a medicinal product".

3.2.P.2.2. Drug product

3.2. P.2.2.1.Formulation development

The applicant has to provide a description of the product development taking into account the proposed route of administration and usage.

The choice of the definitive formulation and the difference with the formulations used for the clinical tests, must be justified.

3.2. P.2.2.2. Overages

Any overage in the formulation must be justified.

3.2.P.2.2.3. Physicochemical and biological properties

It is mandatory to define all parameters related to the performance of the pharmaceutical product namely the pH, ionic state, dissolution, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity.

3.2. P.2.3. Manufacturing process Development

The choice and the optimization of the manufacturing process (described in 3.2.P.3.3.) must be justified, especially the critical parameters. If applicable, the sterilization method shall be explained and justified.

If other manufacturing process have been used for example for the clinical tests, the differences with the adopted process shall be addressed and explained.

3.2.P.2.4. Container closure system

The applicant has to justify the choice of the container closure system (refer to 3.2.P.7), used for the storage and the transportation of the finished product.The justification shall take into account the nature of the materials, of the protection from humidity and light, the safety of the materials and their performances.

Guideline on Plastic Immediate Pakaging Materials. Note for guidance on development pharmaceutics. CommitteFor Medicinal Product For Human Use"EMEA, London 2005.

3.2. P.2.5.Microbiological properties

The applicant has to justify, in appropriate cases, the absence of microbiological tests for non mandatory sterile pharmaceutical dosage forms.

The efficacy of the antimicrobial protection shall be established, as per European pharmacopeia, for the products containing one or several antimicrobial preservatives « *challenge test* ».

For the sterile products, the efficacy of the packaging to prevent the microbial contamination shall be demonstrated.

The Guidelines CPMP: "Guideline on the use of antioxidants and preservatives in medicinal products"

3.2. P.2.6. Compatibility

In the case of a reconstitued product, the applicant has to provide the interaction of the finished product with the solvent of reconstitution and/or the medical device used for the administration (the product solubility, absorption, stability of the reconstituted solution).The recommendations arising from this study must be indicated on the labelling.

3.2. P.3. Manufacturing

3.2.P.3.1. Manufacturer(s)

The applicant has to mention the name and the address of all the manufacturing sites participating in the production of the finished product including the subcontractors and any other alternative site involved in the production and/or the control of the finished product.

The applicant has also to mention the operations carried out in each site (manufacturing, packaging, labeling, control, release, etc.) and the sites involved in specific steps (Manufacturing of an intermediate product).

The Guidelines CPMP: "On Manufacture of the finished dosage form"

3.2.P.3.2. Manufacturing formula of the batch

The applicant has to provide a definitive fomulation selected for an industrial manufacturing batch, for a pilot batch and for a unique dose. He has to indicate the function of each component, their respective quantities and the refrence of their standard quality.

The size of the pilot batch needs to be at least equal to 1/10 of the industrial batch.This size shall correspond at least to the minimal capacity of the equipment used for the manufacturing.

In such case, the type of equipment, the minimum and maximum capacity must be mentioned.

In case of use of equipments for manufacturing of mini batches different from those used on industry, a scale-up transposition protocol shall be provided.

The guidelines CPMP: "On Manufacture of the finished dosage form"

3.2.P.3.3. Description of the manufacturing process and process control

The applicant has to provide a flowchart including the different steps of the manufacturing process, showing when the raw materials are added. The intermediate tests carried out during the process must be identified.

It is also required to describe in details all steps of the manufacturing process including the packaging, stating the production scale.

Any new technology or packaging operation which may affect the product quality must be described.

The applicant has also to provide a list of the equipments and identify the type and the capacity of each device, when relevant.

It is also required to identify the parameters to control during the process (time, temperature, pH). The numeric values or norms related to tests will be provided.

In some cases, the humidity ratio may be relevant and must be specified (sensitive principle ingredient, effervescent tablet…).

The guidelines CPMP: "On Manufacture of the finished dosage form"

3.2. P.3.4.Control of critical steps and intermediates

Critical steps: it is required to provide the control tests (with justifications and experimental data) carried out during the critical steps of the process, which have been identified in 3.2.P.3.3 by specifying the acceptation criteria.

When semi-finished product (microgranules, granules…) is manufactured in a site different from the one of the finished product, it is required to provide information regarding the

composition, the manufacturing, the quality control and the stability of the semi-finished product.

The guidelines CPMP-ICH: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products -Chemical Substances",

The guidelines CPMP: «On Manufacture of the finished dosage form"

3.2.P.3.5. Process validation and/or evaluation

The applicant has to provide a protocol on 3 industrial batches describing the critical steps, the equipment and the process parameters which may affect the product quality.The applicant has also to define the parameters to be monitored, the sampling plans, the analytical procedures and the acceptation criteria.

For sterile products, it is required to provide the sterilization process or aseptic filling.

For the local manufacture, in case if no manufacturing validation process is performed, the applicant has to present, a commitment from the head pharmacist to provide the results and a detailed process validation report of 3 industrial batches.

The guidelines CPMP: «On Manufacture of the finished dosage form", "Process Validation", "Parametric Release"

3.2.P.4. Control of excipients

3.2. P.4.1. Specifications

The applicant has to define the specifications for each excipient, to indicate the reference to pharmacopeia (European, of a member state, of USA or international or Japan) and to attach the certificate of analysis of the manufacturer of the finished product.

For excipients not decribed in the above stated pharmacopeia, it is required to indicate their specifications and to attach the certificates of analysis of the supplier of the excipient.

The guidelines CPMP: "Excipients in the Dossier for application for marketing authorisation of a medicinal product", "Guideline on the use of antioxidants and preservatives in medicinal products"

Reference CPMP-ICH Guidelines: "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances",

3.2. P.4.2. Analytical procedures

The applicant has to provide the analytical procedures used for the control of excipients.

The guidelines CPMP-ICH: "Validation of analytical methods: definitions and terminology",

3.2. P.4.3. Validation of analytical procedures

The applicant has to provide, if applicable, the analytical validations (along with the data and the experimental results) of the procedures of control of excipients.

The guidelines CPMP-ICH: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology",

3.2.P.4.4. Justification of specifications

Justifications shall be provided for the specifications proposed for the control of excipients.

The guidelines CPMP-ICH: "Impurities: residual solvents",

3.2.P.4.5. Excipients from human or animal origin

The applicant has to demonstrate that the product is manufactured in compliance with the guideline on the risk of transmission of bovine spongiform encephalopathy.

For the excipients from animal or human origin, the manufacturer has to provide data relative to adventitious agents (source, specifications, description of carried tests, viral safety data).

The guidelines CPMP-ICH: "Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin", "Derivation and Caracterisation of Cell Substrates Used For Production of Biotechnological/Biological Products", "Specifications-Test Procedures and Acceptance Criteria for Biotechnological, Biological Products."

The guidelines CPMP-ICH: "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products."

3.2.P.4.6. Novel excipients

For the excipients used for the first time in the manufacturing of the finished product or for a new administration route, it is required to provide details related to the production, caracterisation and the control with references related to safety data (clinical or nonclinical).

The guidelines CPMP: "On developmentpharmaceutics"

3.2.P.5. Control of drug product

3.2.P.5.1. Specifications

The applicant has to provide the specifications of the finished product: a list of analyses, the references to analytical methods and acceptation criteria to judge the results.

The average dosage specifications limits fall within 95-105%, unless justified.

The guidelines CPMP-ICH: "Impurities in new drug products", "Specifications –Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products– Chemical Substances",

3.2. P.5.2.Analytical procedures

It is required to provide references to pharmacopeia or describe the analytical procedures used for the control of the finished product.

The guidelines CPMP-ICH: "Validation of analytical methods: definitions and terminology",

3.2.P.5.3. Validation of the analytical procedures

The applicant has to provide the validation of the analytical procedures of control of the finished product with results. These reports shall include a detailed description of the used validation protocol, and the analytical procedures for each of the validation parameters and a discussion of results.

The guidelines CPMP-ICH: "Validation of analytical methods: definitions and terminology", "Validation of analytical procedures: methodology",

PA/PH/OMCL (05) 47 DEF –OMCL Guideline on validation of Analytical Procedures (current version)

3.2.P.5.4. Batch analyses

The applicant has to provide a description of the provided sample batch (number, size, date and place of manufacture) and the results of the carried analyses.

The guidelines CPMP-ICH: "Impurities in new drug products", » Impurities: residual solvents", "Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products".

3.2.P.5.5. Characterisation of impurities

The information related to impurities must be documented if not described in section 3.2.S.3.2 Impurities or if the data are required for the assessement of product security.

"Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products – Chemical Substances".

The degradation products shall be characterized from an analytical perspective (chromatography profiles resulting from for example a forced degradation products study).

The guidelines CPMP-ICH: "Impurities in new drug products",

3.2. P.5.6. Justification of specifications

The applicant has to justify specifications proposed for the control of the finished product.

Reference CPMP-ICH Guidelines: "Impurities in new drug products",

3.2.P.6. Reference standards or materials

The applicant has to indicate the reference standards or materials (active ingredients and impurities) used for the control of the finished product, and to provide the corresponding certificate of analysis in the case where the standard is subject to an inhouse monograph.

3.2. P.7. Container closure system

The applicant has to describe the primary packaging, and to desmonstrate that the used packaging is suitable for the storage, the transportation and the use.

The applicant has to provide a description and present the specifications for all or a part of the container/closure system in direct contact with the product.

It is required to identify the nature, the origin and the specifications of each component.The specifications shall include an identification test. The absence of interaction container/content will be demonstrated, if required.

It is required to indicate the dimensions of the packaging and to attach a safety data sheet. The methods of control not listed in a pharmacopeia shall be described.

It is mandatory to describe and provide the specifications of each medical device associated to the packaging and used for the administration of the finished product and attach a diagram.

It is required to provide the food certificates, the supplier certificates of analysis of the packaging and the certificates of analysis of the packaging of the manufacturer of the finished product.

It is also required to describe and address specifications of the reconstitution solvent of the finished product. If the secondary packaging is uneffective and doesn't bring additional protection to the product, then a short description will be enough.

Reference the guidelines CPMP: "Plastic Primary Packaging Materials".

3.2.P.8. Stability

3.2.P.8.1. Stability summary and conclusions

The applicant has to provide a summary in a table, with stability studies conducted, protocol studies, the adopted specifications and the obtained results

The applicant has to mention the numbers and the tested batches size, their date of manufacture, their stability testing and their primary packaging used in the stability studies.

It is mandatory to describe the general methods of the used tests (e.g: forced degradation studies, accelerated conditions, intermediate and long-term conditions).

This summary shall include the conclusions related to the storage conditions and the required shelf-life period. If applicable, the storage conditions during the product use will be specified.

The guidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Impurities in new drug products",

"Specifications – Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products -Chemical Substances".

The guidelines CPMP: "on stability testing of existing active substances and related finished products ", "On maximum shelf-life for sterile products for human use after first opening or following reconstitution", "On the declaration of storage conditions for medicinal products in the products particular and for active substances", "In-Use stability testing of human medicinal products".

3.2.P.8.2. Post-approval and stability commitments

The applicant has to provide the stability protocol to be followed after the marketing authorization grant.

For the locally manufactured products, it is required to present the commitments to provide the stability results when they become available. If the batches under stability conditions are pilot batches, then the applicant has to present a commitment to provide the stability results of the 3 first industrial batches.

The guidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products",

The guideliensCPMP: «on stability testing of existing active substances and related finished products»

3.2.P.8.3. Stability data

The applicant has to provide the results of the stability studies presenting them in tables and to complete them with text and graphics.

The stability study of the finished product shall be performed on at least 3 industrial batches for the whole claimed preservation period under real time and 6 months under accelerated conditions.

For the locally manufactured product, a study on at least 2 pilot batches for a minimum period of 6 months under real conditions and 6 months under accelerated conditions is required, at the time of the submission.

NB: At the time of submission, a minimum period of 3 months under real conditions and 3 months under accelerated conditions might be accepted, however the marketing authorization won't be granted before submitting the stability testing results over 6 months minimum period. The used analytical procedures along with their validations shall be included.

The applicant has to provide a description of batches (number, size, date and place of manufacture) and to indicate the climatic conditions (temperature, relative humidity) adopted according to the above mentioned references.

The guidelines CPMP-ICH: "Stability testing guidelines: stability testing of new drug substances and products", "Stability testing: photostability testing of new drug substances and products", "Validation of analytical methods: definitions and terminology","Validation of analytical procedures: methodology", "on stability testing of existing active substances and related finished products ", "In-Use stability testing of human medicinal products".

2.2.1.4. Module 4:

The Module 4 shall be provided in accordance with the ICH M4 guideline entitled *'Organisation Of The Common Technical Document For The Registration Of Pharmaceuticals For Human Use'* (M4S).

2.2.1.5. Module 5:

The Module 5 shall be presented according to the ICH M4 guideline called '*OrganisationOf The Common Technical Document For The Registration Of Pharmaceuticals For Human Use' (M4E).*

For the locally manufactured medicinal products, the bioequivalence studies are required for:

- The extended release dosage forms (ER): when the manufacturing process of a locally manufactured ER is limited to capsule filling or a compression in bulk which shows ER properties, the bioequivalence study of another product manufactured from the same bulk, might be accepted.
- Narrow Therapeutic Range drugs(NTR)
- Immunosuppressive medicinal products
- The products corresponding to a first generic (A biowaiver justifying the exemption of bioequivalence study can be provided).

The Technical Commitee for Medicinal Products (CTSP) remains sovereign to require bioequivalence studies when they deem it necessary.

It is noteworthy that, following the amendment to act n° 90—1401 of 3rd September 1990, laying down the modalities of medical or scientific experimentation of medicines intended for human use, a procedure specifying the date from which the bioequivalence studies will be required for the locally manufactured generics and the eligibility criteria for the biowaiver,are under preparation.

Where required, the bioequivalence study shall be evaluated in compliance with Reference CPMP Guidelines: '*Guideline on the Investigation of Bioequivalence'.*

2.2.2. VARIATION OF MARKETING AUTHORISATION:

Variation applications are subject to a notification or to an approval according whether the variation is considered as minor or major.

- Minor variation: a variation is minor when the impact on the quality, safety or efficacy of the concerned product is minimal or non-existant.

Such variations do not require a prior authorization. It only needs to be notified at the DPM by the holder before their implementation in Tunisia.

- Major variation: a variation is major when it has a significant impact on the quality, safety and efficacy of the concerned product.

Such variations need to be approved by the DPM before their implementation in Tunisia.

N.B: An application for major variation can be submitted for a marketing authorization dossier under registration.

For each variation, the classification is minor or major, the necessity to submit the samples, the payment entitlement, and the structure or the committee concerned by the assessment of the variation, are specified in the table '*Requirements for the different categories of modification of a marketing authorization for medicines for human use(see appendice X)'.*

N.B: the dossiers of variations application are assessed in accordance with the Communication of the EC— *Guidelines regarding the characteristics of the different categories of the variations to the terms of a marketing aurhorization for medicinal products for human use and veterinary medicinal products.*

- Treatment of groups of variations:

It is possible to provide in a single application several changes regarding one or several marketing authorization when it concerns:

1. Quality variations affecting the drug substance and entering into the composition of one or several products independently from the form. A single right to payment is applicable.

2. Changes of indications of a product for the same pharmaceutical dosage form and the same strength for several presentations. A single right to payment is applicable.
3. Validation of an update or change of a CEP for one or several products.The validation of such an application concerns all the products containing the raw material subject to this CEP. A single right to payment is applicable.
4. Validation of a new supplier of primary packaging materials with the same specifications, concerning several products. A single right to payment is applicable.
5. Change of the shelf life period for the same pharmaceutical dosage form and the same strength for several presentations. A single right to payment is applicable.

- Required documents:

For the dossiers of variations applications, the sections of the module concerned by the changes shall be submitted, by respecting the table of content of the CTD format.

1. Module 1

1.0. **APPLICATION LETTER**

1.1. **TABLE OF CONTENT**

1.2. **APPLICATION FORM**

1.3. **INFORMATION ON MANUFACTURE**

1.3.1. Establishement licences (*if concerned by the change)*

1.3.2. Certificates of Good Manufacturing Practices (*if concerned by the change)*

1.3.3. Case of sub-contracting *(If concerned by the change)*

1.4. **INFORMATION ON THE PRODUCT**

1.4.1. SmPC, Labelling, Leaflet *(If concerned by the change)*

1.4.2. Mock-up : Leaflet and labeling *(If concerned by the change)*

1.4.3. Samples *(if required)*

1.4. 4. Imported medicinal products *(if applicable, MA and CPP)*

1.4. 5. Medicinal products manufactured under licence *(if applicable, MA and CPP)*

1.6. **INFORMATION ON THE PRICE** *(if concerned by the change)*

1.7. **INFORMATION CONCERNING PHARMACOVIGILANCE** (*if concerned by the change)*

1.8. **REGISTRATION PAYMENT RECEIPT** (where required)

2. Module 2

3. Module 3 *(sections concerned by the change)*

4. Module 4 *(sections concerned by the change)*

5. Module 5 *(sections concerned by the change)*

A variation application file shall include:

Imported and locally manufactured medicinal products	**Imported medicinal products**
- Application letter - Table of content - Application form (including the comparative table and the document history of variations submitted in Tunisia) - Sections of the CTD file concerned by the changes - Samples (see annex X and table 4 P24) - receipt (see annex X)	- Copy of the MA variation of holder / "Approval" or "application form" related to the exporting country for minor variations. - valid CPP

2.2.3. TRANSFER OF A MARKETING AUTHORIZATION:

A transfer of the marketing authorization is defined as a transfer of a Marketing Authorization from one given Pharmaceutical company to another Pharmaceutical company; the two entities still exist after transfer.

The application file of transfer shall be submitted to the DPM by the pharmaceutical establishment the future holder of the marketing authorization, or if applicable, by the local representative (having a scope statement signed by the Minister of Health).

Following to the transfer application,a new marketing authorization repealing the first granted one, will be edited.

The situation resulting from the merger of the activities with or the removalof the activities from a company to another is not considered as a transfer of a marketing authorization. In this case, only the legal elements regarding the new pharmaceutical entity shall be provided such as the modification of the establishement licence of the pharmaceutical company and the changes of the marketing authorization. In such case, a notification shall be submitted to the DPM indicating the list of the concerned products accompanied by a decision of a merger/removal.

For any application for the transfer of a marketing authorization, the required documents shall include:

1. Application letter

   Application letter addressed by the future marketing authorization holder or if applicable, the local representative (having a scope statement signed by the Ministry of Health), describing the current and the new proposed situation specifying the sites of manufacture, of control, of packaging, of batch release and the time necessary to dispose of the stock of the current holder.

2. Application form (including the comparative table)

3. Approval of the Marketing Authorization transfer issued by a competent authority of the exporting country, *for the imported products.*

   *When it comes to under licence products locally manufactured, the approval of the licensor in the country of origin, is required for any transfer application.

4. Copy of the tunisian marketing authorization of the current holder
5. Copy of the establishement licences
6. Copy of the certificates of Good Manufacturing Practices (GMP)
7. SmPC, labelling, Leaflet (new version)
8. Mock-up : Leaflet and labelling (new version)
9. 2 sale model samples *accompanied by the corresponding CoA

   **for the imported products:* 2 sale model samples in the exporting country along with the corresponding certificates.
10. Attestation from the applicant on the change or not of the summary of the pharmacovigilance system.
11. A commitment from the applicant to comply with the terms under which the marketing authorization was granted, and, in particular, to meet the methods of manufacture and control.
12. Attestation signed by the head pharmacist certifying that no change affecting the materials suppliers, the primary packaging, the composition, the shelf-life period, the indications or the sites of manufacture (except the batch release site), has occured.
13. Receipt payment of the registration fee
14. *CPP, exporting country , *for the imported products*
15. *SmPC, exporting country, *for the imported products*
16. *Price certificate from the exporting country, *for the imported products*

In the case where the transfer application is accompanied by one or several changes, refer to paragraph 2.2.2 variation of MA, for the documents necessary to complete and for the required samples. The new MA will be edited only after the validation of the variations submitted for approval.

NB: the application for a transfer of a marketing authorization is considered as a new application.The renewal of the marketing authorization is not necessary in this case.

2.2.4 RENEWAL OF A MARKETING AUTHORIZATION:

The marketing authorization is delivered for 5 years period; it is renewed for a 5 years period. An application for a renewal shall be submitted at the earliest 6 months before the expiration date of the marketing authorization.The applications for renewal are treated at the DPM.

For any application for renewal, the following documents need to be submitted:

1. Application letter
2. Application form
3. Attestation notifying that no change has occured in elements provided at initial submission, apart the changes submitted in Tunisia. (see annex IX)
4. GMP certificates of the manufacturing sites of the finished product
5. Updated SmPC as approved in Tunisia (Word and PDF versions /CD)
6. 2 sale model samples* accompanied by their corresponding CoAs

   *For the imported products : 2 sale model samples in the exporting country and 2 sale model samples in Tunisia

   A derogation can be granted by the DPM for the products of calls for tender. In such case, a mock-up shall be provided and 2 samples shall be submitted in case the product is retained.
7. Registration payment receipt
8. * Last renewal of the marketing authrorization if applicable or a proof of the validity of the marketing authorization in the exporting country, for the imported products.
9. * CPP, *for the imported products*
10. * SmPC, exporting country, *for the imported products*
11. * Pre-tax wholesale price certificate from the exporting country endorsed by the competent authority *for the imported products.*

2.3. TIMELINES FOR ANSWERING:

The time limit to send a reply to the applicant by the DPM is set according to the nature of the application as follows:

Nature of the application	Reply time limit (from the date of the submission of the dossier)
New marketing authorization application	1 year for the first reply after the assessment of the quality file 2 months for the treatment of replies to reservations made by the LNCM
Line extension, new presentation without change in primary packaging (Type/ Material/ Supplier)	2 months
Marketing authorization renewal	15 days

2.4. REQUEST FOR APPEAL:

In case of refusal to grant the marketing authorization, the applicant can submit an appeal application to the DPM.

The application shall be accompanied by detailed arguments related to the reason of refusal, and the price receipt. Besides, the marketing authorization applicant has to provide the updated dossier if applicable, or the head pharmacist commitment that no change has occurred compared with the initial dossier submitted.

2.5. MARKETING AUTHORIZATION WITHDRAWAL:

The withdrawal of the marketing authorization of a medicinal product is decided by the Minster of Health after consultation with the technical committees laid down in article 5 of the n°85-91 of 22nd November 1985, regulating the manufacture and the registration of medicinal products intended for human use, when it is established, in particular that:

a) The medicinal product has not anymore the qualitative or quantitative declared composition witthout prejudice to the application of the penal provisions provided by the legislation on fraud prevention;

b) The intended therapeutic effect is not reached;

c) The controls on materials, products on the process of manufacturing or finished product are not normally performed,

d) The marketing authorization holder has not proceeded to the commercialization of the medicinal product within one year from the date of obtention of this authorization.

In case where the medicinal product proves to be dangeroeus to the health, the Minister of Health, may decide urgently to withdraw it from the market and to destroy it.

The withdrawal and the destruction of the medicinal product does not give a rise to compensation of any nature.The decision to withdraw may be subject to all advertising measures deemed necessary by the Minister of Health.

The marketing authorization may be also revoked upon the request of the manufacturer.

In such case the applicant may adress a request letter to the central registry of the Minstry of Health explaining the reasons of withdrawal.

2.6 GENERAL RECOMMENDATIONS:

2.5.1. Language:

Documents which are not drafted in Arabic or if applicable in French or English, shall be accompanied by a translation in one of the above mentioned languages carried out by a sworn translator.
The word and PDF version of the SmPC, PIL, labeling shall be drafted in Arabic and/or French.

2.5.2. Organization:

The submitted documents shall be seperated by module.The different parts of module 2 shall be seperated as specified in table 3(cf paragraph B.1).

All the documents belonging to the same module should be related, whetherthermosealed or by “spiral binding”of good quality with possibility to separate them into volumes.

The chapter order shall befully respected.

2.5.3. Original document:

The following original documents shall be provided:

- A valid Certificate of the Pharmaceutical Product (CPP).
- Price certificate endorsed by the competent authority of the exporting country
- Covering letters, application forms and any type of document requiring the signature of the Head Pharmacist

2.5.4. Font:

Times New Roman, size 12 is recommended for the text and Times New Roman, from 9 to 10 for the text content of tables.

2.5.5. Trade name:

The trade name may be whether an invented name or an INN accompanied by the name of the manufacturer, the applicant for the authorization.

For the imported products, the name of the product shall be the same as the one of the exporting country.

N.B: the invented name must be different from the name of an already approved medicinal product (marketed or not) by,at least 3 letters

The trade name of the medicinal product should not:

1. Misleading about the therapeutic or pharmaceutical characteristics
2. Misleading about the product composition
3. Create confusion with other existing medicinal products.
4. Be derived from an INN or contain an INN key segment.

3. REGISTRATION OF MEDICINAL PRODUCTS FOR VETERINARY USE:

This part is under preparation.

Annexes

ANNEXI : APPLICATION LETTER

<Applicant>
<Adress>
<ZIP code><Town>
<Country>

Pharmacy and Drug Directorate
31, Rue de Khartoum
Belvédère-1002 Tunis
Tunisie
<Place and date>

To the attention of the Minister of Health,

Subject: Application for a Marketing Authorization for the <trade name, INN, pharmaceutical form, strength, presentation>

Dear Sir,
We have the honour to seek « *New application / Variation/ Renewal, …*», with the characteristics stated as follows :
Trade name:

Pharmaceutical form and strength:

Pack size:

Date of first submission: (if application for appeal)

The dossier shall include the following volumes and copies:

	Number of volume	Number of paper copies	Number of electronic copies (CD)
Module 1			
Module 2			
Module 3			
Module 4			
Module 5			
SmPC/ Mock-upLeafletand labelling			

Please find enclosed:

- 2 copies of the application letter
- 2 copies of the application form
- Receipt of payment
- X samples ...

Yours Faithfully

<Name><Title>
<Phone n°>
<Email >

ANNEXII: APPLICATION FORM

<table>
<tr><td colspan="3">1. Name and address of the applicant</td></tr>
<tr><td colspan="3">2. Name and address of the representative in Tunisia</td></tr>
<tr><td colspan="3">3. responsible for regulatory affairs in Tunisia</td></tr>
<tr><td colspan="3">4. Advertising agency
NO/ YES Responsible for samples</td></tr>
<tr><td colspan="3">5. Nature of application</td></tr>
<tr><td colspan="2">□ Application for a MA (Marketing Authorisation) of a reference drug product
□ Application for a MA of a generic
□ Application for a MA of biosimilar
□ Renewal of a MA
□ Minor variation
□ Major variation</td><td>□ Re-introduction
□ Appeal
□ MA transfer
□ Line extension
□of presentation
□of strength
□ of pharmaceutical form</td></tr>
<tr><td colspan="3">6. Type of variation</td></tr>
<tr><td>Administrative variation
□Corporate name
□INN
□Other: ……</td><td>Quality variations:
□ Drug substance
□ Finsihed product
□ CEP/Monographs
□ Changes specific to vaccines and blood derivatives
□ Others: ….</td><td>Variations related to safety, efficacy and pharmacovigilance
□ Indications
□ Contra-Indications
□ Special Warnings and precautions for use
□ Interaction with other medicinal products and other forms of interaction
□ Pregnancy and lactation
□ Effects on ability to drive and use machines
□ Undesirable effects
□ Conditions of prescription
□Table of poinsonous substances
□ Posology and method of administration
□Other: ……</td></tr>
</table>

7. INFORMATION ON THE PRODUCT

<table>
<tr><td colspan="2">Trade name :</td><td colspan="2">Name of the reference product :(if applicable)</td></tr>
<tr><td>INN :</td><td colspan="2">Strength:</td><td>Contents of container:
(number of dosage units, of blisters.)</td></tr>
<tr><td colspan="2">Pharmaceutical form :</td><td colspan="2">Administration Route: (IM /IV / Oral)</td></tr>
<tr><td colspan="2">Nature of the primary packaging:</td><td colspan="2">Required storage period:</td></tr>
<tr><td colspan="2">Pharmaco-therapeutic class:</td><td colspan="2">Table of poisonsous substances:</td></tr>
<tr><td colspan="2">ATC code:</td><td colspan="2">BCS class:</td></tr>
<tr><td colspan="4">Qualitative and quantitative composition of active ingredient and excipients:</td></tr>
<tr><td colspan="4">Therapeutic indications:</td></tr>
</table>

8. INFORMATION ON THE MANUFACTURING:

	Name / Corporate name	Address
1- Marketing authorization holder in the exporting country		
2- Owner (if applicable)		
3- Licensor (for under licence production)		
4- Manufacturing site(s) of the active ingredient		
5- Manufacturing site(s) of the finished product (Specify the operations for each site)		
6- Primary packaging site(s)		
7- Secondary packaging site(s)		
8-Control Site(s)		
9-Batches release site(s)		
10- Storage site of the finished product		
11- Site of the provenance of the finished product		
12- Site/Person in charge of pharmacovigilance		
13- Site responsible for batch recall		
14- Site responsible for advertising		

<Date>
<Signature>
<Name>
<Title>

9. CHANGES DESCRIPTION:

(For any variation/ MA transfer, the applicant should fill the tables below):

Existing heading(s)	Proposed heading(s)

10. COMPLETE HISTORY OF CHANGES SUBMITTED IN TUNISIA

Submission date	Application type	Decision of the competent authority	Decision date

<Date>
<Signature>
<Name>
<Title>

ANNEX III :
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) NAME of product Strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Excipients known to have a recognised action or effect :>

<For full list of excipients, see section 6.1.>

3. PHARMACEUTICAL FORM

<The score line is only to facilitate the tablet intake, not to divide into equal doses.>

<The scoreline is not intended to break the tablet.>

<The tablet can be divided into equal doses.>

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<This medicinal product is intended for diagnostic use only.>

<{X} is indicated in< adults><new-born><infants><children><adolescents><aged {x to y}><years><months>.>

4.2. Posology and method of administration

Posology

Pediatric population

<<the safety><and><the efficacy>of {X} in child aged {x to y} <month><years> {or any other relevant subsets of the population,forexample,according to the weight, pubertal age, gender} <has ><have> not <yet>been <established>.>

<No data is available.>

<Currently available data are described in section <4.8><5.1><5.2> but no recommendation on posology can be made.>

< {X} should not be used in children aged{x to y} <years><month> [or any other relevant subset, for example, according to the weight, pubertal age, gender] because of< efficacy>< safety> concern(s).>

<There is no relevant use of {X} <in pediatric population><in children aged {x to y} <months><years> {or any other relevant subset, for example, according to the weight, pubertal age, gender} <in the indication …>.>

< {X} is contraindicated in children aged {x to y} <years><months>[or any other relevant subset, for example, according to the weight, pubertal age, gender] <in the indication …>] (see section 4.3).>

Method of administration

<Precautions to be taken prior to the manipulation or administration of the medicinal product>

<For instructions regarding<reconstitution><dilution>of the medicinal product prior to administration, see section <6.6><and><section 12>.>

4.3. Contraindications

<Hypersensitivity to the active ingredient(s) or to any excipient mentioned on section 6.1 <or {name(s) of residue(s)}>.>

4.4. Special warnings and precautions for use

<Pediatric population>

4.5. Interaction with other medicinal products and other forms of interaction

<No interaction study has been performed.>

<Pediatric population>

<Interaction studies have been performed only in adults.>

<Contraindicated combinations>

<Unrecommended combinations>

<Combinations subject to precautions for use>

<Combinations to be taken into account >

4.6. Pregnancy and lactation

<Pregnancy>

<Lactation>

<Fertility>

4.7. Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence><minor influence> <moderate influence><major influence> on the ability to drive and use machines.>

<Not applicable>

4.8. Undesirable effects

<pediatric population>

Notification of suspected side effects

The notification of the suspected undesirable effects after the marketing authorization grant is important. It allows a continuous monitoring of the benefit/risk ratio. Health professionals notify any suspected undesirable effects via a National Reporting System:

4.9. Overdose

<Pediatric population>

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic class: {class}, ATC code: {code}<not yet allocated>.

< {Invented NAME} is a biosimilar medicinal product. Detailed information are available on the website: {name of the member state/Agency}>

<Mechanism of action>

<Pharmacodynamic effects>

<Efficacy and clinical safety>

<Pediatric population>

5.2. Phramacokinetic properties

<Absorption>

<Distribution>

<Biotransformation>

<Elimination>

<Linearity/non-linearity>

<Pharmacokinetic/pharmacodynamic relationships>

5.3. Pre-clinical safety data

<Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, functions of reproduction and development.>

< Effects were observed in animal only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

<Environmental risk assessement>

6. PHARMACEUTICAL DATA

6.1. List of excipients

<none>

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.>

<This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6><and in section><12>.>

6.3. Shelf-life

<…><6 months><...><1 year><18 months><2 year><30 months><3 years><…>

6.4. Special precautions for storage

<For the medicinal products storage conditions after <reconstitution><dilution><first opening>, see section 6.3.>

6.5. Nature and contents of container:

<No all pack sizes may be marketed.>

6.6. Special precautions for disposal and handling

<Use in pediatric population >

<No special requirements <for disposal>.>

<Any unused product or waste material should be disposed of in accordance with the existing regulation.>

7. MARKETING AUTHORIZATION HOLDER

NAME
ADDRESS
ZIPCODEHOLDERTOWN<HOLDERCOUNTRY>
<TEL>
<FAX>
<E-MAIL >
[Tel, fax, e-Mail: to fill later by the applicant]

8. MARKETING AUTHORIZATION NUMBER(S)

[to complete later by the applicant]

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORISATION

[To complete later by the applicant]

10. DATE OF REVISION OF THE TEXT

[to complete later by the applicant]

11. DOSIMETRY

<Not relevant.>

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

<Not relevant.>

13. CONDITIONS OF PRESCRIPTION AND DISPENSING

<Table of poisonous substances >

<Tab A>, <Tab B>,<Tab C>

ANNEX IV :
PARTICULARS TO APPEAR ON THE OUTER PACK AND ON THE IMMEDIATE PACKAGING

NATURE/TYPE of the outer pack or immediate packaging

< {Outer pack}><and><{Immediate packaging (s)}>

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

{Active ingredient(s)}

2. COMPOSITION ON ACTIVE INGREDIENTS

{ }

Amount of each active ingredient

3. LIST OF EXCIPIENTS

<Not relevant.>

<Excipient(s) known to have a recognised action or effect:

See the Patient Information Leaflet for further information.>

4. PHARMACEUTICAL FORM AND CONTENTS

{ }

5. MODE AND ROUTE(S) OF ADMINISTRATION

Read the patient information leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STOTRED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

<Not relevant.>

8. EXPIRY DATE

EXP {MM/YYYY}

[Shelf life of medicinal product<reconstituted><dilued>:]

9. SPECIAL PRECAUTION FOR STORAGE

<Not relevant.>

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS IF THEY EXIST

<Not relevant.>

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Holder

NAME
ADDRESS 1
ADDRESS 2
ZIP CODE – HOLDERTOWN<HOLDER COUNTRY>
<TEL.>
<FAX >
<E-MAIL>

Owner

NAME
ADDRESS 1
ADDRESS 2
ZIP CODE – TOWN – <COUNTRY>
<TEL.>
<FAX>
<E-MAIL>
[Or<not notified /to notify later>]

Manufacturer

<Not relevant.>

12. NUMBER(S) OF THE MARKETING AUTHORIZATION

Licence N°:

13. BATCH NUMBER AND MANUFACTURE DATE

Batch {number} {manufacture date}

14. CONDITIONS OF PRESCRIPTION AND DISPENSING

[Copy/paste the wordings available on the section « conditions of prescription and dispensing » of SmPC]

15. INDICATIONS FOR USE

<Not relevant.>

16. PICTOGRAM TO APPEAR ON THE OUTER PACK OR, WHERE THERE IS NO OUTER PACK, ON THE PRIMARY PACKAGING

<Not relevant.>

17. RETAIL PRICE:

<Not relevant.>

ANNEX V:
MINIMUM PARTICULARS TO FIGURE ON BLISTERS OR STRIPS

NATURE/TYPE OF BLISTER / FILMS

< {Blister}>< {strips}>

<Not relevant.>

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name, strength, pharmaceutical form}

{Active ingredient(s)}

<Not relevant.>

2. NAME OF THE MARKETING AUTHORIZATION HOLDER

Holder

NAME OF THE HOLDER

<Not relevant.>

Owner

<Not relevant.>

3. EXPIRY DATE

EXP {MM/YYYY}

<Not relevant.>

4. BATCH NUMBER

Batch {number}

<Not relevant.>

5. OTHERS

<Not relevant.>

ANNEX VI:
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGINGS

NATURE/TYPE SMALL IMMEDIATE PACKAGING

< {Small immediate packaging}>

<Not relevant.>

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

{(Invented) NAME, strength, pharmaceutical form}

{Active ingredient(s)}

{Route of administration}

<Not relevant.>

2. ROUTE FO ADMINISTRATION

<Not relevant.>

3. EXPIRY DATE

EXP {MM/YYYY}

<Not relevant.>

4. BATCH NUMBER

Batch {number}

<Not relevant.>

5. CONTENT by WEIGHT, VOLUME OR UNIT

<Not relevant.>

6. OTHERS

<Not relevant.>

ANNEX VII:
RECOMMANDATIONS ON DRAFTING
ANNEXES III, IV, V, ET VI

	Not to modify the wording of TITLES AND SUBTITLES IN BLUE COLOR
<> (Brackets)	Optional sentence which can not be modified, if it is used.
[ ] (square brackets)	Draft recommendation. These sentences shall not be kept in the body of the text.
{ } (braces)	The content should be replaced by what it refers to.
TITLES AND NUMBERING	Conventionally, the titles constituting the structure of the document shall be written in blue.This enables to identify them more easily and to preserve their integrity: they shall not in any case be modified, or deleted. Do not modify the wording of the titles of the sections highlighted in blue. Do not delete the titles or sections. Nonetheless, when the section is not notified, it should be systematically completed by the mention “Not relevant”. Do not create titles or sub-titles. The numbering and the classification of the sections proposed in the sample must be abiden by.
REFRENCING	In case of referencing or cross referencing in the SmPC, it is recommeded to only report the number of the section and not the totality of its title.
DENOMINATION	The long medicinal product name « XXX »: (Invented) NAME strengh, pharmaceutical form: is applied to all sections 1. MEDICINAL PRODUCT NAME (SmPC / Leaflet / Labelling), as well as to the titles and the subtitles of the PIL. The short name « X »: (Invented) NAME: is applied only to the body of the text.

Annex IX : Statement for non-variation

<Applicant>
<Address>
<Zip code><Town>
<Country>

Pharmacy and Drug Directorate
31, Rue de Khartoum
Belvédère-1002 Tunis
Tunisie
<Place and date>

To the attention of the Minister of Health,

Subject: Statement of no modification related to the medicinal product <name of the medicinal product, INN, pharmaceutical form, strength, content of container>

Dear Sir,

I undersign, « *name and title* », that no modification has been occured to the product elements provided in the initial application outside the variations submitted in Tunisia.

Yours Faithfully

<Signature>
<Name>
<Title>
<Phone n°>
<Email >

Annex X : Requirements for the different catogories of variations to the terms of the marketing authorization of medicinal products for human use

A. ADMINISTRATIVE CHANGES

B. QUALITY CHANGES

I. Active ingredients
a) Manufacture
b) Control of active ingredient
c) Container closure system
d) Stability
e) Design space

II. Finished product
a) Description and composition
b) Manufacture
c) Control of excipients
d) Control of finished product
e) Container closure system
f) Stability
g) Design space

III. CEP/TSE/monographs

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

A. ADMINISTRATIVE CHANGES:

	Procedure	Samples	Payment	Decision
A.1. Change in the name and/or address of the marketing authorization holder	Min	1 box	-	DPM
A.2. Change in the (invented) name of the medicinal product	Min	1 box	-	DPM
A.3. Change in the name of the active substance	Min	1 box	-	DPM
A.4. Change in the name and /or the address of a manufacturer (without change in the site) or a supplier of the active substance, starting material, reagent, or an intermediate used in the manufacture of the active susbtance (where specified in the technical dossier).	Min	-	-	DPM
A.5. Change in ATC code	Min	1 box	-	DPM
A.6. Deletion of manufacturing sites (for an active substance, intermediate or finished product), packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of starting materials, reagent or excipient (when mentioned in the dossier).	Min	-	-	DPM
A.7. Change in the exporting country	Min	1 box	-	DPM

Abrev.
Min : Minor changes
DPM: Pharmacy and Drug Directorate

B. QUALITY CHANGES

B.I. ACTIVE SUBSTANCE

B.I.a) Manufacture

	Procedure	Samples	Payment	Decision
B.I.a.1. Change in the manufacturer of a starting material, a reagent or an intermediate product used in the manufacturing process of the active substance or change in the manufacturer of the active substance (including where relevant quality control testing sites), where no Ph.Eur.Certificate of Suitability is part of the approved dossier.				
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	Min	-	HT	LNCM
b) Introduction of a manufacturer of the active substance supported by an ASMF	Maj	Active ingredient+ CoA	HT	LNCM
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability	Maj	-	HT	LNCM
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	Maj	-	HT	LNCM
e)The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product	Maj	-	HT	LNCM
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	Maj	-	HT	LNCM
B.I.a.2. Change in the manufacturing process of the active substance				
a) Minor change in the manufacturing process of the active substance	Maj	-	HT	LNCM
b) Substantial change to the manufacturing process of the active substance which may have asignificant impact on the quality, safety or efficacy of the medicinal product	Maj	-	HT	LNCM
c) The change refers to a biological / immunological substance or the use of a different chemically derived substance in the manufacture of a biological/immunological substance, and is not related to a protocol	Maj	-	HT	LNCM

d) The change relates to a herbal medicinal product and concerns the geographical source, the manufacturing process or the production	Maj	-	HT	LNCM
e) Minor change to the restricted part of an Active substance Master File	Maj	-	HT	LNCM
B.I.a.3. Change in batch size (including batch size ranges) of active substance or intermediate				
a) Up to 10-fold increase compared to the originally approved batch size	Min	-	HT	LNCM
b) Downscaling of the batch size	Min	-	HT	LNCM
c) The change requires assessment of the comparability of a biological/immunological activesubstance	Maj	-	HT	LNCM
d) More than 10-fold increase compared to the originally approved batch size.	Maj	-	HT	LNCM
e) The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line).	Maj	-	HT	LNCM
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance				
a) Tightening of in-process limits	Maj	-	HT	LNCM
b) Addition of new in-process tests and limits	Maj	-	HT	LNCM
c) Deletion of a non-significant in-process test	Maj	-	HT	LNCM
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	Maj	-	HT	LNCM
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	Maj	-	HT	LNCM
f) Addition or deletion of an in-process test as aresult of a safety or quality issue	Maj	-	HT	LNCM
B.I.a.5. Changes to the active substance of a seasonal, prepandemic or pandemic vaccine against human influenza				
a) Replacement of the strain(s) in a seasonal, prepandemic or a pandemic vaccine against human influenza	Maj	-	HT	LNCM

Abrev.
Maj :Major Change
HT :Half Tariff
LNCM : National Laboratory of Medicinal Products Control

B.I.b) Control of active substance

	Procedure	Samples	Payment	Decision
B.I.b.1. Change in the specification parameters and/or limits of an active substance, starting material, intermediate, reagent used in the manufacturing process of the active substance				
a)Tightning of the specification limits	Min	-	HT	LNCM
b)Addition of a new specification parameter with its corresponding test method	Min	-	HT	LNCM
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter).	Maj	-	HT	LNCM
d) Deletion of a specification parameter which may have a significant effect on the overall quality ofthe active substance and/or the finished product	Maj	-	HT	LNCM
e) Change outside the approved specifications limits range for the active substance	Maj	-	HT	LNCM
f) Widening of the approved specifications limits for starting materials and intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	Maj	-	HT	LNCM
g) Addition or replacement (excluding biological or immunological substance) of a specification parameter asa result of a safety or quality issue.	Maj	-	HT	LNCM
B.I.b.2. **Change in test procedure for active substance or starting material, reagent, intermediate used in the manufacturing process of the active substance**				
a) Minor changes to an approved test procedure	Min	-	HT	LNCM
b) Deletion of a test procedure for the active substance or a sstarting material/reagent/ intermediate, if an alternative test procedure is already authorised.	Maj	-	HT	LNCM
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance.	Min	-	HT	LNCM
d) Change (replacement) of abiological, immunological, immunochemical test method or a method using a biological reagent for a biological active substance e.g peptidic or glucidic	Maj	-	HT	LNCM
e) Other changes to a test procedure (including replacement or addition) for the active substance, a starting material or intermediate	Maj	-	HT	LNCM

B.I.c) Container closure system

	Procedure	Sampless	Payment	Decision
B.I.c.1. Change in immediate packaging of the active substance				
a) Qualitative and/or quantitative composition	Maj	-	HT	LNCM
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	Maj	-	HT	LNCM
c) Liquid active substances (non sterile)	Maj	-	HT	LNCM
B.I.c.2. Change in the specification parameters and/or limits of the immediate packaging of the active substance				
a) Tightening of specification limits	Min	-	HT	LNCM
b) Addition of a new specification parameter to the specification with its corresponding test method.	Min	-	HT	LNCM
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Maj	-	HT	LNCM
d) Addition or replacement of a specification parameter as a result of a safety or quality issue	Maj	-	HT	LNCM
B.I.c.3. Change in test procedure for the immediate packaging of the active substance				
a) Minor changes to an approved test procedure	Min	-	HT	LNCM
b) Other changes to a test procedure (including replacement or addition)	Min	-	HT	LNCM
c) Deletion of a test procedure if an alternative test procedure is already authorised	Min	-	HT	LNCM

B.I.d) *Stability*

B.I.d.1. Change in the re-test period/storage period or storage conditions of the active substance				
a) Re-test period/storage period				
1. Reduction	Min	-	HT	LNCM
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH guidelines	Maj	-	HT	LNCM
3. Extension of storage period of a biological/ immunological active substance not in accordance with an approved stability protocol	Maj	-	HT	LNCM
4.Extension or introduction of a re-test period/storage period supported by real time data	Maj	-	HT	LNCM
b) Storage conditions				
1. Change to more restrictive storage conditions of the active substance	Min	-	HT	LNCM
2**.** Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol	Maj	-	HT	LNCM
3. Change in storage conditions of the active substance	Maj	-	HT	LNCM

B.I.e) Design space

B.I.e.1. Introduction of a new design space or extension of an approved design space for the active substance, concerning:				
a) One unit operation in the manufacturing process of the active substance including the resulting inprocess controls and/or test procedures	Maj	-	HT	LNCM
b) Test procedures for starting materials/reagents/ intermediates and/or the active substance	Maj	-	HT	LNCM
B.I.e.2.Introduction of a post approval change management protocol related to the active substance	Maj	-	HT	LNCM
B.I.e.3. Deletion of an approved change management protocol related to the active substance	Maj	-	HT	LNCM

B.II FINISHED PRODUCT

B.II.a) Description and composition

	Procedure	Samples	Payment	Decision
B.II.a.1. Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.				
a) Changes in imprints, bossing or other markings(inks)	Min	-	FT	LNCM
b) Changes in scoring/break lines intended to divide into equal doses	Maj	Cf Tab 4	FT	LNCM
B.II.a.2. Change in the shape or dimensions of the pharmaceutical form				
a) Immediate release tablets, capsules, suppositories and pessaries	Maj	Cf Tab 4	FT	LNCM
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses	Maj	Cf Tab 4	FT	LNCM
B.II.a.3. Changes in the composition (excipients) of the finished product				
a) Changes in components of the flavouring or colouring system				
1. Addition, deletion or replacement	Maj	Cf Tab 4	FT	LNCM
2. Increase or reduction	Maj	Cf Tab 4	FT	LNCM
b) Other excipients				
1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	Maj	Cf Tab 4	FT	LNCM
2. Qualitative or quantitative changes in one or more excipients that may have asignificant impact on the safety, quality or efficacy of the medicinal product	Maj	Cf Tab 4	FT	LNCM
3. Change that relates to a biological/immunological product	Maj	Cf Tab 4	FT	LNCM
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk	Maj	Cf Tab 4	FT	LNCM
5.Change that is supported by a bioequivalence study	Maj	Cf Tab 4	FT	LNCM

	Procedure	Samples	Payment	Decision
6. Replacement of a single excipient with a comparable excipient with the same functional solubility characteristics and at a similar level	Min	Cf Tab 4	FT	LNCM
B.II.a.4. Change in coating weight of oral dosage forms or change in weight of capsule shells				
a) Solid oral pharmaceutical forms	Maj	Cf Tab 4	FT	LNCM
b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism	Maj	Cf Tab 4	FT	LNCM
B.II.a.5. Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	Maj	Cf Tab 4	FT	LNCM
B.II.a.6. Deletion of the solvent / diluent container from the pack	Maj	-	-	TC

Abrev.
FT : Full Tariff
TC : Technical Commitee
Cf.Tab 4: to refer to table 4 P.21 to identify the quantity of samples to be submitted.

B.II.b) *Mmanufacture*

	Procedure	Samples	Payment	Decison
B.II.b.1. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product				
a) Secondary packaging site	Min	-	HT	LNCM
b) Primary packaging site	Maj	Cf Tab 4	HT	LNCM
c) Site where any manufacturing operation(s) takes place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products	Maj	Cf Tab 4	HT	LNCM
d) Site which requires an initial or product specific inspection	Maj	Cf Tab 4	HT	LNCM
e) Site where any manufacturing operation(s) takes place, except batch-	Maj	Cf	HT	LNCM

	Procedure	Samples	Payment	Decison
release, batch control, primary and secondary packaging, for non sterile medicinal products		Tab 4		
f) Site where any manufacturing operation(s) takes place, except batch release, batch control, and secondary packaging, for sterile medicinal products that are aseptically manufactured excluding biological/ immunological medicinal products	Maj	Cf Tab 4	HT	LNCM
B.II.b.2. Change in batch release arrangements and quality control testing of the finished product				
a) Replacement or addition of a site where batch control takes place	Min	-	HT	LNCM
a) **Replacement or addition of a manufacturer responsible for the batch release**				
Not including batch control	Min	-	-	LNCM
Including batch control	Min	-	HT	LNCM
Including batch control for biological/immunological medicinal product and any of the test methods performed at that site is a biological, immunological or immunochemical method	Maj	-	HT	LNCM
B.II.b.3. Change in the manufacturing process of the finished product				
a) Minor change in the manufacturing process of a solid dosage form by oral route or immediate release solution by oral route	Maj	Cf Tab 4	DT	LNCM
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	Maj	Cf Tab 4	HT	LNCM
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability	Maj	Cf Tab 4	HT	LNCM
d) Introduction of a non-standard terminal sterilisation method	Maj	Cf Tab 4	HT	LNCM
e) Introduction or increase in the overage that is used for the active substance	Maj	Cf Tab 4	HT	LNCM
f) Minor change in the manufacturing process of an aqueous oral suspension	Maj	Cf Tab 4	HT	LNCM
B.II.b.4. Change in the batch size (including batch size ranges) of the finished product				
a) Up to 10-fold compared to the originally approved batch size	Min	-	HT	LNCM

	Procedure	Samples	Payment	Decison
b) Downscaling down to 10-fold	Min	-	HT	LNCM
c) The change requires assessment of the comparability of a biological/immunological medicinal product	Maj	-	HT	LNCM
d)The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	Maj	-	HT	LNCM
e) More than 10-fold increase compared to the originally approved batch size for immediate release pharmaceutical forms	Maj	-	HT	LNCM
f)The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line)	Maj	-	HT	LNCM
B.II.b.5. Change to in-process tests or limits applied during the manufacture of the finished product				
a) Tightening of in-process limits	Min	-	HT	LNCM
b) Addition of new test(s) and limits	Min	-	HT	LNCM
c) Deletion of a non-significant in-process test	Maj	-	HT	LNCM
d)Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	Maj	-	HT	LNCM
e)Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	Maj	-	HT	LNCM
f) Addition or replacement of an in-process test as a result of a safety or quality issue	Maj	-	HT	LNCM

B.II.c) Control of excipients

	Procedure	Sampless	Payment	Decision
B.II.c.1. Change in the specification parameters and/or limits of an excipents				
a) Tightening of specification limits	Min	-	HT	LNCM
b) Addition of a new specification parameter to the specification with its corresponding test method	Min	-	HT	LNCM
c) Deletion of a non-significant specification parameter (e.g. deletion of	Maj	-	HT	LNCM

	Procedure	Sampless	Payment	Decision
an obsolete parameter)				
d) Change outside the approved specifications limits range	Maj	-	HT	LNCM
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	Maj	-	HT	LNCM
f) Addition or replacement (excluding biological or immunological product) of a specification parameter, as a result of a safety or quality issue	Maj	-	HT	LNCM
B.II.c.2. Change in test procedure for an excipient				
a)Minor changes to an approved test procedure	Min	-	HT	LNCM
b) Deletion of a test procedure if an alternative test procedure is already authorised	Min	-	HT	LNCM
c) Replacement of abiological/ immunological/ immunochemical test method or a method using a biological reagent	Maj	-	HT	LNCM
d) Other changes to a test procedure (including replacement or addition	Maj	-	HT	LNCM
B.II.c.3. Change in source of an excipient or reagent with TSE risk				
a) From TSE risk material to vegetable or synthetic origin				
1. For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	Maj	-	HT	LNCM
2. For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	Maj	-	HT	LNCM
b) Change or introduction of a TSE risk material or replacement by another TSE risk material l, not covered by a TSE certificate of suitability	Maj	-	HT	LNCM
B.II.c.4. Change in synthesis or recovery of a non pharmacopoeial excipient (when described in the dossier)				
a) Minor change in synthesis or recovery of a non pharmacopoeial excipient	Maj	-	HT	LNCM
b) The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished	Maj	-	HT	LNCM

	Procedure	Sampless	Payment	Decision
product.				
c) The excipient is a biological/immunological substance	Maj	-	HT	LNCM

B.II.d) Control of finished product

	Procedure	Sampless	Payment	Decision
B.II.d.1. Change in the specification parameters and/or limits of the finished product				
a) Tightening of specification limits	Min	-	HT	-
b) Addition of a new specification parameter to the specification with its corresponding test method	Min	-	HT	-
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Maj	-	HT	LNCM
d) Change outside the approved specifications limits range	Maj	-	HT	LNCM
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	Maj	-	HT	LNCM
f) Addition or replacement (excluding biological or immunological product) of a specification as a result of a safety or quality issue	Maj	-	HT	LNCM
B.II.d.2. Change in test procedure for the finished product				
a) Minor changes to an approved test procedure	Maj	-	HT	LNCM
b) Deletion of a test procedure if an alternative method is already authorised	Maj	-	HT	LNCM
c) Replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent	Maj	-	HT	LNCM
d) Other changes to a test procedure (including replacement or addition)	Maj	-	HT	LNCM
B.II.d.3. Changes related to the introduction of real-time release or parametric release in the manufacture of the finished product	Maj	-	HT	LNCM

B.II.e) **Container closure system**

	Procedure	Sampless	Payment	Decision
B.II.e.1. Change in immediate packaging of the finished product				
a) Qualitative and quantitative composition				
Solid pharmaceutical forms	Maj	Cf Tab 4	HT	LNCM
Semi-solid and non-sterile liquid pharmaceutical forms	Maj	Cf Tab 4	HT	LNCM
Sterile medicinal products and biological/immunologicalmedicinal products.	Maj	Cf Tab 4	HT	LNCM
The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life	Maj	Cf Tab 4	HT	LNCM
b) Container type				
1.Solid, semi-solid and non-sterile liquid pharmaceutical forms	Maj	Cf Tab 4	HT	LNCM
2. Sterile medicinal products and biological or immunological medicinal products	Maj	Cf Tab 4	HT	LNCM
B.II.e.2. Change in the specification parameters and/or limits of the immediate packaging of the finished product				
a) Tightening of specification limits	Min	-	HT	LNCM
b) Addition of a new specification parameter to the specification with its corresponding test	Min	-	HT	LNCM
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Maj	-	HT	LNCM
d) Addition or replacement of a specification parameter as a result of a safety or quality issue	Maj	-	HT	LNCM
B.II.e.3. Change in test procedure for the immediate packaging of the finished product				
a) Minor changes to an approved test procedure	Min	-	HT	LNCM
b) Other changes to a test procedure (including replacement or addition)	Maj	-	HT	LNCM
c) Deletion of a test procedure if an alternative test procedure is already authorised	Maj	-	HT	LNCM

	Procedure	Sampless	Payment	Decision
B.II.e.4. Change in shape or dimensions of the container or closure (immediate packaging)				
a) Non-sterile medicinal products	Maj	Cf Tab 4	HT	LNCM
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	Maj	Cf Tab 4	HT	LNCM
c) Sterile medicinal products	Maj	Cf Tab 4	HT	LNCM
B.II.e.5. Change in pack size of the finished product				
a)Change in the number of units (e.g. tablets, ampoules, etc.) in a pack *				
1. Change within the range of the currently approved pack sizes limits (without change in the immediate packaging)	Maj	3boxes	FT	DPM
2.Change outside the range of the currently approved pack sizes limits (with change in the immediate packaging nature (Type/ Material/ Supplier))*	Maj	Cf Tab 4	HT	LNCM
a) Deletion of pack size(s)	Maj	1 box	HT	DPM
b) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products*	Maj	Cf Tab 4	HT	LNCM
c) Change in the fill weight/fill volume of non parenteral multi-dose (or single-dose, partial use) products*	Maj	Cf Tab 4	HT	LNCM
**these changes in pack sizes are considered as varaitions only when the initial pack size ceases to be marketed.Otherwise, a new marketing autorisation needs to be submitted. (Cfline extension).*				
B.II.e.6. Change in any part of the primary packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))				
a) Change that affects the product information	Min	-	-	LNCM
b) Change that does not affect the product information	Min	-	-	LNCM
B.II.e.7. Change in supplier of packaging components or devices (without change in packaging nature)				
a) Deletion of a supplier except for liquid pharmaceutical forms in contact with plastic	Min	-	HT	LNCM
b) Replacement or addition of a supplier	Min	-	HT	LNCM

	Procedure	Sampless	Payment	Decision
c) Any change to suppliers of spacer devices for metered dose inhalers	Maj	-	HT	LNCM
d) Any change to suppliers of liquid forms bags in contact with plastic	Maj	-	HT	LNCM

B.II.f) *Stability*

	Procedure	Sampless	Payment	Decision
B.II.f.1. Change in the shelf-life or storage conditions of the finished product				
a) Reduction of the shelf life of the finished product				
As packaged for sale	Min	-	HT	-
After first opening	Min	-	-	-
After dilution or reconstitution	Min	-	-	-
b) Extension of the shelf life of the finished product				
As packaged for sale (supported by real time data)	Maj	-	HT	LNCM
After first opening (supported by real time data)	Maj	-	HT	LNCM
After dilution or reconstitution (supported by real time data)	Maj	-	HT	LNCM
Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines	Maj	-	HT	LNCM
Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.	Maj	-	HT	LNCM
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	Maj	-	HT	LNCM
d) Change in storage conditions of the finished product or the diluted/reconstituted product	Maj	-	HT	LNCM

B.II.g) *Design space*

	Procedure	Sampless	Payment	Decision
B.II.g.1. Introduction of a new design space or extension of an approved design space for the finished product, excluding biological products concerning:				
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures	Maj	-	HT	LNCM
b) Test procedures for excipients / intermediates and/or the finished product.	Maj	-	HT	LNCM
B.II.g.2. Introduction of a post approval change management protocol related to the finished product	Maj	-	HT	LNCM
B.II.g.3. Deletion of an approved change management protocol related to the finished product	Maj	-	HT	LNCM

B.III. CEP/TSE/MONOGRAPHS

	Procedure	Samples	Payment	Decision
B.III.1. Submission of a new or updated Ph. Eur. Certificate of suitability				
For an active substance **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**				
Certificate of Suitability to the relevant Ph. Eur. Monograph.				
New certificate from an already approved manufacturer	Min	-	HT	LNCM
Updated certificate from an already approved manufacturer	Min	-	HT	LNCM
New certificate from a new manufacturer (replacement or addition)	Maj	-	HT	LNCM
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient				
1. New certificate for an active substance from a new or an already approved manufacturer	Maj	-	HT	LNCM
2.New certificate for a starting material/reagent/ intermediate/or excipient	Maj	-	HT	LNCM

from a new or an already approved manufacturer				
3. Updated certificate from an already approved manufacturer	Min	-	HT	LNCM
B.III.2.Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State				
a) Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member state				
1. Active substance	Min	-	HT	LNCM
2. Excipient/active substance/ starting material	Min	-	HT	LNCM
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	Min	-	HT	LNCM
c) Change in specifications from a national Pharmacopoeia of a Member State to the Ph. Eur.	Min	-	HT	LNCM

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I. HUMAN MEDICINAL PRODUCTS

	Procedure	Sampless	Payment	Decision
C.I.1. Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet	Min	-	-	CNPV
C.I.2. Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product				
a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH	Min	-	-	CNPV
b) Implementation of change(s) which require to befurther substantiated by new additional data to be submitted by the MAH (e.g. comparability)	Min	-	-	CNPV
C.I.3. Variations related to important change(s) in the Summary of Product Characteristics,due to new quality,preclinical and linical or pharmacovigilance data	Min	-	-	CNPV
C.I.4. Change(s) to therapeutic indication(s)				

	Procedure	Sampless	Payment	Decision
a) Addition of a new therapeutic indication or modification of an approved one	Maj	-	HT	CS TC
b) Deletion of a therapeutic indication	Min	-	-	DPM
C.I.5. Deletion of:				
a) a pharmaceutical form	Min	-	-	DPM
b) a strength	Min	-	-	DPM
C.I.6. Introduction of a new pharmacovigilance system	Min	-	-	CNPV
C.I.7. Change(s) to an existing pharmacovigilance system				
a) Change related to the person in charge of pharmacovigilance	Min	-	-	CNPV
b)Change in the contact details of the person in charge of Pharmacovigilance	Min	-	-	CNPV
c) Change in the back-up procedure related to the person in charge of pharmacovigilance	Min	-	-	CNPV
d) Change(s) in the safety database (for example, introduction of a new security database, the collection transfer of security database and/or analysis and the declaration to the new system)	Min	-	-	CNPV
e) Changes in the principal contractual arrangements with other persons or organisations who and/or which play a role in the fullfillement of the obligations with respect to pharmacovigilance and are descriebd in the DDSP,namely in case of subcontracting of the electronic notification of the safety reports ,the principladatabases,detection of the signals or the establishement of periodic safety update report (PSUR)	Min	-	-	CNPV
f) Deletion of themes subject to one or several written procedures, describing pharmacovigilance activities.	Min	-	-	CNPV
g) Change in site undertaking pharmacovigilance activities.	Min	-	-	CNPV

Abrev.
CNPV : National Pharmacovigilance Centre
SC :Specialised Committee