MINISTRY OF PUBLIC HEALTH

GENERAL SECRETARIAT

MADAGASCAR DRUG'S AGENCY

MEDICINE'S REGISTRATION PROCEDURE

IN MADAGASCAR

AGENCE DU MEDICAMENT
DE MADAGASCAR

2016 VERSION

INTRODUCTION

Medical and technical evaluation of registration dossiers for medicines is an essential step in ensuring the quality of products placed on the market. Thus, this volume has been established in order to update the elements required for each type of record and made available for the pharmaceutical sector operators in a common registration process.

The update remains in line with current regulations and is valid for a period of three years. All pharmaceutical sector operators are required to comply with, so in practice, the drugs available to the population meet the required quality standards.

LIST OF FILES TO BE PROVIDED
FOR THE REGISTRATION OF DRUGS

Only words in bold indicate the update provided in the registration procedures.
It is desirable that the application for registration dossiers are submitted in a workbook.

I- NEW APPLICATION FOR MARKETING AUTHORIZATION (MA) :

- Application letter for MA to the Director of Madagascar Drug's Agency
- Summary of Product Characteristics (SPC)
- Leaflet
- Administrative files
- Pharmaceutical, analytical and biological files
- **Clinical, pharmacological and toxicological files (For new active ingredients and new combinations of active ingredients ...)**
- Pharmacovigilance files
- Appointment letter of the official representative in Madagascar with its coordinates
- Samples

Nota Bene :

- **Applications for registration dossiers must be written in French or English.**
- **The chronology of the items of the dossier must follow the order presented in this manual registration procedures.**
- For products for which the molecule is still protected by a patent, the applicant must submit an application to OMAPI (Malagasy Office of Industrial Property) and provide the deposit receipt to Madagascar Drug's Agency.
- The trade name, shape, colour and presentation of the article should not interfere with the existing references.
- **Incomplete MA applications are inadmissible.**
- **The MA applications must relate to products already registered in other countries.**
- **Shipment and clearance of documents for registration are the responsibility of the laboratories. Parcels must be reached in the premises of Madagascar Drug's Agency.**

I-1 MA application letter :

The MA application letter is to be addressed to the Director of Madagascar Drug's Agency and shall mention the following items:

- The name and the address of the MA holder and the manufacturer(s)
- The brand name, the International Non-Proprietary Name, the dosage form, the dosage, the mode and route of administration, the presentation of models for sale (packaging)
- The therapeutic class
- For generics and branded generics, mention the name and pharmaceutical form of reference medicinal product **(attach a copy of the Summary of Product Characteristics of the reference product in the registration dossier)**
- The Proposal of Wholesale Price Excluding Tax (PgUp)
- The circuit of distribution and supply of the drug recommended by the mother laboratory
- The proposed method of distribution (pharmacy, hospital ...)

I-2 Summary of Product Characteristics (SPC) :

The SPC must show all the sections listed below:

- The brand name
- The International Non-Proprietary Names (INNs)
- The pharmaceutical form, dosage and the route of administration
- The qualitative and quantitative composition of active ingredients and excipients: highlight the presence of excipients with known effects
- The therapeutic indications
- The dosage and method of administration
- The contra -indications
- The precautions and warnings
- The drug interactions
- The use during pregnancy and lactation
- The side effects
- The overdosage
- The pharmacodynamic data
- The pharmacokinetic data
- Incompatibilities (for solid solutes and solutions for parenteral use)
- The storage conditions (the mention "Keep out of the reach of children" is desirable)
- The instructions for use / handling (if needed)
- Effect on ability to drive and use machines
- The shelf life
- Inscription in a list of poisonous substances if applicable
- Packaging
- The name and address of manufacturer(s)
- The name and address of the MA holder

I-3 The leaflet :

The leaflet must be legible for easy reading and published in printed version. It must contain the information listed below and be written in French:

- The brand name
- The International Non-Proprietary Names (INNs)
- The pharmaceutical form, dosage and the route of administration
- The qualitative and quantitative composition of active ingredients and excipients: highlight the presence of excipients with known effects
- The therapeutic indications
- The dosage and method of administration
- The contra -indications
- The precautions and warnings
- The drug interactions
- The use during pregnancy and lactation
- The side effects
- The overdosage
- The pharmacodynamic data (desirable)
- The pharmacokinetic data (desirable)
- Incompatibilities (for solid solutes and solutions for parenteral use)
- The storage conditions (the mention "Keep out of the reach of children" is desirable)
- The instructions for use / handling (if needed)
- Effect on ability to drive and use machines
- Inscription in a list of poisonous substances if applicable
- The complete address of the MA holder and the manufacturer(s)
- Packaging (desirable)
- The date of latest update of leaflet (desirable)
- Mention "If in doubt do not hesitate to seek advice from your doctor or pharmacist" (desirable).

Nota Bene :

- Information both in the SPC and the leaflet should be coherent.
- Massive solutes and antiseptics used in hospitals, as a cream, ointment 250g to 500g and solutions 250ml to 500ml do not require a leaflet provided that all the information required in the leaflet by this manual of registration procedures would be indicated on the label and / or the primary packaging.

I-4 The composition of the administrative files:

- **Certified copy of the original certificate of Good Manufacturing Practice (GMP) manufacturer laboratory established by the competent health authority of the country of origin. GMP certificate must be valid at least six (06) months and must include the header of the regulatory authority of the country of origin. If manufacturing is done in several liberators sites provide certified copies of GMP certificates for each site.**
- Valid certified copy of the original of the drug's marketing authorization issued by the competent health authorities of the country of origin.
- Valid certified copy of the original free sale certificate
- Certified copy of the original certificate of pharmaceutical product, WHO model **(see model in Annex 1)**
- **With date and signed (handwritten signature) Commitment of the pharmacist in charge (see model in Annex 3)**
- For medicinal products manufactured in Madagascar, only the certificate (s) of batch analysis **(see model in annex 4)** and the commitment of the pharmacist in charge **(see model in annex 2)** have to be provided
- List of countries where the drug is approved and marketed; enclose copies of the licence of marketing
- Draft label and distinct packaging for each product
- **Certification of pre-qualification granted by the WHO (Optional).**

Nota Bene :

- **Possession of a WHO prequalification ensures product manufacturing quality.**
- **The free sale certificate cannot in any way substitute the market Authorization (MA) issued by the country of origin.**

I-5 The composition of the pharmaceutical, analytical and biological files :

I-5-1 Pharmaceutical File :

- Origin of raw materials: **Information on Manufacturer (s)**
- Raw materials, **intermediates** and finished product Specifications
- **Formula and manufacturing processes**
- **Controls during manufacturing of the product at various stages of mass production (to clarify the role of excipients).**

I-5-2 The analytical file :

- Certificates of analysis of raw materials **(active and inactive materials)**
- **Certificate of analysis of** finished product **corresponding to the batch of the provided samples**
- **Method of analysis** and Validation of control methods in the case of methods **not available in a pharmacopoeia *(In-House methods).***

The analytical protocols shall be sufficiently detailed to enable complete reproduction : all protocols should be validated.

I-5-3 Stability studies of finished product :

- Protocol for the stability study indicating the conditions and analyzes
- Real-time and accelerated study results on three (03) different batches, **signed and submitted by the manufacturer (see ICH model in Annex 5).**

Nota Bene : The accelerated study results just serve to demonstrate the relevance of the protocol, only the real-time results will be taken into account.

I-5-4 Biological File: Bacteriological study :

- Microbial Limits
- Sterility
- Endotoxin

Nota Bene :
The methods should be validated, as other analytical methods, if they are not part of the reference methods.

I-6 The composition of the clinical, toxicological and pharmacological file :

For new active ingredients and new combinations of active ingredients, provide toxicological, pharmacological and clinical files to justify the safety, stability and efficiency of the drug **according to the standards published by the competent authorities of highly regulated countries (ICH: Europe – Japan – Canada and USA)** or WHO Type updated certificate.

I-7 Pharmacovigilance file :

- Risk Management Plan for new active ingredients or new combinations of active ingredients
- **Data on post -marketing Medicated Adverse Reactions of product to register, observed in other countries for generic drugs (Desirable)**
- Contact details (name, e-mail, phone number, mail address) of the Pharmacovigilance Country Lead of the concerned laboratory.

I-8 Samples :

- **Samples of sale models with :**

100 units	tablet and capsule
50 vials	solution and powder for injection
50 tubes	Ointment and cream (mass < 5g)
20 tubes	Ointment and cream (5 g ≤ mass ≤ 15g)
10 tubes	Ointment and cream (mass > 15g)
100 vials	solution or suspension liquid (< 5ml)
50 vials	solution or suspension liquid (5ml ≤ solution < 50ml)
20 vials	solution or suspension liquid (50ml ≤ solution < 100ml)
10 vials	solution or suspension liquid (100ml ≤ solution < 500ml)
5 vials	solution or suspension liquid (≥ 500ml)
100 units	suppository
100 units	powder in sachet (mass ≤ 2g)
50 units	powder in sachet (mass < 5g)
20 units	powder in sachet (5 g ≤ mass ≤ 15g)
10 units	powder in sachet (mass > 15g)
20 units	IUD
100 units	condoms
20 units	implant
20 units	patch
2 boxes	**vaccine and anti-cancer products regardless of pharmaceutical form and presentation**

The quantities requested are needed to perform all analyses required by the monograph of the pharmacopoeia of the corresponding product reference and leave a reserve sample. They may vary depending on the method of analysis of the product.

In addition to the number of units requested in the table above, a full presentation of the model is required for each sales presentation for the samples library.

NOTES :

- Samples should be accompanied by the certificate of analysis of the corresponding batch and five grams (**5g**) of active raw materials should be accompanied by their certificates of analysis of corresponding batches
- Samples should be kept in their original packaging and must come from the same batch.

Nota Bene :

The remaining shelf life of the samples must be at least **1 year upon filing of the application.**
On the primary and secondary packaging should be mentioned : the brand name, the International Non proprietary Name (INN), dosage, dosage form, batch number, manufacturing and expiry dates, name and address of the manufacturer (City name/Country), name of the MA holder.
On the secondary packaging should be mentioned precautions (Example: Keep out of reach of children, Keep away from light) and special storage conditions.
Packaging with advertising matter is not allowed. **(Mention or pictures tending to self-medication or overuse).**

Packaging differs according to the list (advisable):

- o List I: the box has a white label with a broad red band
- o List II: the box has a white label with a broad green band

Inscriptions namely batch number; manufacturing and expiry dates must be indelibly printed or printed on non-detachable affixed labels.

II- APPLICATION FOR MARKETING AUTHORIZATION (MA) RENEWAL :

The files for renewal of marketing authorization must include :

- An application letter for renewal of MA addressed to the Director of Madagascar Drug's Agency (see I-1) stating that no changes have been made in the component submitted when granting MA.
- Certified true copy of the certificate of Good Manufacturing Practices (GMP) currently valid
- Summary of Product Characteristics (SPC)
- The circuit of distribution and supply of the drug recommended by the laboratory

- For specialties and brand generic existing in the VIDAL and Dorosz of the current year and / or manufactured by ICH countries : 3 samples from the same batch with their certificate of analysis

- For generic drugs, Method of analysis and Validation of control methods in the case of In-House methods and samples from the same batch with their certificate of analysis (quantities needed to perform all analyses required by the monograph of the pharmacopoeia of the corresponding product reference).

50 units	tablet and capsule
25 vials	solution and powder for injection
25 tubes	Ointment and cream (mass < 5g)
10 tubes	Ointment and cream (5 g ≤ mass ≤ 15g)
5 tubes	Ointment and cream (mass > 15g)
50 vials	solution or suspension liquid (< 5ml)
25 vials	solution or suspension liquid (5ml ≤ solution < 50ml)
10 vials	solution or suspension liquid (50ml ≤ solution < 100ml)
5 vials	solution or suspension liquid (100ml ≤ solution < 500ml)
3 vials	solution or suspension liquid (≥ 500ml)
50 units	suppository
50 units	powder in sachet (mass ≤ 2g)
25 units	powder in sachet (mass < 5g)
10 units	powder in sachet (5 g ≤ mass ≤ 15g)
5 units	powder in sachet (mass > 15g)
10 units	IUD
50 units	condoms
10 units	implant
10 units	patch
2 boxes	**vaccine and anti-cancer products regardless of pharmaceutical form and presentation**

In addition to the number of units requested in the table above, a full presentation of the model is required for each sales presentation for the samples library.

Samples should be kept in their original packaging and must come from the same batch.

Filing of the application for marketing authorization renewal must be made three (3) months before its validity date expiry and not later than six (6) months after expiration. After this period, any application must comply with the new registration procedure for marketing authorization.

III- APPLICATION FOR MARKETING AUTHORIZATION MODIFICATION :

Any modification of one or more elements of the MA dossier of the drug must be subjected to assessment by Madagascar Drug's Agency.

The Marketing Authorization modification may cover the following :

- **excipients composition**
- **manufacturing process**
- **primary packaging nature**
- **brand name**
- **Summary of Product Characteristics and leaflet**
- **packaging design**
- **manufacturing site**
- **manufacturer's name**
- **MAH**
- **content**
- **duration and / or storage conditions**
- **raw materials specifications**
- **analytical methods**

Nota Bene :
Changing related to the active ingredient composition, dosage form, route of administration, dosage, therapeutic indications must comply with new marketing authorization application.
All modification files are subject to notification, no approval is tacit.
Updating is applicable to marketing authorization currently valid.
Approvals must include the header of the competent health authority.

- **For any other modifications, please check with the Registration Service.**

The files for marketing authorization modification must include :

III-1 : Modification of : excipients composition, primary packaging nature, brand name and Summary of Product Characteristics updating :

- An application letter for MA updating addressed to the Director of Madagascar Drug's Agency stating the reason of the change (see I-1)

- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**

- Summary of Product Characteristics (SPC) **updated**

- Approval of the change by the regulatory authority of the country of origin

- **03 updated samples** from the same batch with corresponding certificate of analysis

III-2 Modification of the manufacturing process :

The modification of the manufacturing process means that operations are changed, or when the in-process control is changed.

- An application letter for MA updating addressed to the Director of Madagascar Drug's Agency stating the reason of the change (see I-1)
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- **text of the new process or new control protocol (with validation in case of need) compared with the old one**
- Approval of the change and the GMP currently valid from the regulatory authority of the country of origin
- **3 updated samples** from the same batch with corresponding certificate of analysis.

III-3 Modification of packaging design :

- An application letter for MA updating addressed to the Director of Madagascar Drug's Agency stating the reason of the change (see I-1)
- A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported
- 3 updated samples from the same batch with corresponding certificate of analysis or packaging mock up with the commitment from the responsible pharmacist to provide the samples

III-4 Changing or addition of alternative site manufacturing, modification of manufacturer's name :

- An application letter for MA updating addressed to the Director of Madagascar Drug's Agency stating that no changes have been made in the manufacturing process (see I-1)
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- **Certified true copy of the certificate of Good Manufacturing Practices (GMP) currently valid of the new site or the new name of the manufacturing site**
- **Approval of the change from the regulatory authority of the country of origin**
- **certificate of analysis and samples (see II) or for modification of manufacturer's name : 3 updated samples from the same batch with corresponding certificate of analysis or packaging mock up with the commitment from the responsible pharmacist to provide the samples.**

III-5 Marketing Authorization holder transfer or modification of MAH's name :

- An application letter for license holder transfer by the former license holder or modification of the MAH's name to the Director of Madagascar Drug's Agency stating the reason of the change (see I-1)
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- Letter from the new Marketing Authorization holder or the binding agreement (in case of MAH transfer)
- **3 updated samples** from the same batch with corresponding certificate of analysis or packaging mock up with the commitment from the responsible pharmacist to provide the samples.

III-6 Content modification or extending :

- An application letter for **content modification** or extending addressed to the Director of Madagascar Drug's Agency stating scientific reason for the change (except for hospital packs) (see I-1)
- **3 updated samples** from the same batch with corresponding certificate of analysis.

III-7 Modification of the duration and / or storage conditions :

- An application letter for MA modification addressed to the Director of Madagascar Drug's Agency stating the reason of the changing (see I-1)
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- Approval of the change by the regulatory authority of the country of origin
- **Stability studies (see annex V)**
- **Summary of Product Characteristics (SPC) and the updated leaflet**
- **certificate of analysis and samples (see II).**

III-8 Analytical methods modification :

- An application letter for MA modification addressed to the Director of Madagascar Drug's Agency stating the reason of the changing (see I-1)
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- The old and new method
- New method validation (if in-house)
- **certificate of analysis with samples (see II)**

III-9 Changing in raw materials specifications :

- An application letter for MA modification addressed to the Director of Madagascar Drug's Agency stating the reason of the changing
- **A certificate from the responsible pharmacist stating that no changes have been made in addition to that reported**
- Approval of the change by the regulatory authority of the country of origin
- **Raw materials (1g) with certificate of analysis**

IV- Interruption or cancellation of marketing authorization :

- **marketing authorization interruption :** a letter of application for marketing authorization interruption addressed to the Director of Madagascar Drug's Agency
- **recovery of marketing is permitted in case of marketing authorization valid and / or the competent authority notify the resumption of marketing following the revaluation benefit / risk of the product which is subjected to batch recall**
- Cancellation of AMM following the manufacturer's request

V- Pharmaceutical products import :

Preferably, the first imported products batch must match the batch of marketing authorization application samples.

To guarantee the quality and ensure the traceability of pharmaceutical products distributed in Madagascar, each laboratory must notify to Madagascar Drug's Agency, the distribution networks and supply of its products. Therefore, any product imported, not respecting the circuits required by the laboratory concerned, will be banned from sale.

SPECIAL DISPOSITIONS :

- The application for marketing authorization for a medicinal product manufactured under license must have a certificate from the laboratory owner of the patent. This certificate describes the control procedure that is or will be applied to the specialty whose marketing is required. This certificate is mandatory for processing.

- Drugs manufactured under license in Madagascar are discharged of, unless otherwise specified by the Madagascar Drug's Agency, files relating to pharmaco-toxicological and clinical trials, provided that the corresponding products of the country of origin have already gotten the MA in the Republic of Madagascar.

- **All drugs used by national programs (NP Tuberculosis, NP STI/AIDS, NP Malaria ...) must be registered with Madagascar Drug's Agency before their dispensation in public health facilities. National programs must provide the following documents:**

  - **Application files slip established by submitting national programs**
  - **Summary of Product Characteristics (SmPC)**
  - **Certified true copy of the certificate of Good Manufacturing Practice (GMP) currently valid**
  - **WHO pre-qualification Product Certification (optional)**
  - **3 updated samples from the same batch with corresponding certificate of analysis.**

Nota Bene :

- **The registration of medicinal products used by national programs is exempt from registration fee.**
- **Before the submission of dossiers, the national programs are required to contact the registration service for more details.**
- **Preferably, the supply of these products must pass through the Essentials Drugs and Medical Equipment Purchasing Central (SALAMA).**

- Bulk presentations for hospital packs are not allowed in order to prevent microbial contamination during handling and dispensing when repackaging.

- **Registration of drugs with the same INN, dosage, dosage form, manufactured by the same laboratory manufacturer for different operators, is allowed provided that the operator submit a copy of the operating license in the application files. Furthermore, the name and address of the manufacturer with mentions "manufactured by ..... for ..... " is mandatory on the box (secondary packaging).**

- For specialties and brand generic existing in the VIDAL and Dorosz of the current year **and / or manufactured by ICH countries**, files required for market Authorization application are :

  - An application letter addressed to the Director of Madagascar Drug's Agency (cf. I-1)
  - Summary of Product Characteristics (SmPC)
  - Certified true copy of the certificate of Good Manufacturing Practices (GMP) currently valid
  - Copy of MA from country of origin
  - 3 updated samples from the same batch with corresponding certificate of analysis
  - The circuit of distribution and supply of the drug recommended by the laboratory

- **Files to provide for the registration of condoms and Intra-Uterine devices (IUD):**

  - An application letter addressed to the Director of Madagascar Drug's Agency (cf. I-1)
  - Name and address of the manufacturer
  - Samples (See I-5)
  - Inscriptions given on primary and secondary packaging are required to be written in French
  - Summary of the technical descriptions, Indications, Contra - indications, Action and instructions, Tips, Advantages, Disadvantages
  - Effectiveness and instructions for using these products. (This information must be given in French).
  - **For males condoms (see circular No. 169/MSANP/SG/AGMED/Enr of April 14, 2015) : referring to ISO 4074, WHO specifications and UNFPA, the following documents are required with application files :**
    - **materials related tests :**
      - **Toxicity test**
      - **Awareness Test and irritation**
      - **Water-soluble protein levels**
      - **Microbial Limits**
      - **Limiting the formation of nitrosamines**
      - **Dusting**
    - **Data stability studies over a period of 3 to 5 years**
    - **Performance data: Volume burst and pressure, no perforation and visible defects and package integrity**
    - **Data related to the design: form and texture, bead, smell, size, thickness, quantity of lubricant and powder coating as well as the nature and labeling of individual packages. Note that the individual package should include: the manufacturer's name, batch number and expiration date (month / year).**

VI- NOTES :

- All registration file whose application has been refused may be reassessed provided to resubmit modified file. **The re-application of refused file is subject to payment of registration fees.**

- **The validity of pending file needing additional information is three (03) months from the claiming letter date. In case of overtaking limit-time or after three (03) claims, Madagascar Drug's Agency puts forward an unfavourable opinion and will no longer consider the case already filed.**

- **Cause of refusal are maintained for non-modified re-application file.**

- **Assessed file are the property of Madagascar Drug's Agency and cannot be restituted to applicants.**

- **Application is no longer acceptable after two unfavorable decisions.**

- **The first deadline for supplement information may be extended following the request of the applicant. The maximum time of extension is 12 months from the date of issuance of the first claiming. Second and third claiming deadline cannot be extended.**

VII- VALIDITY OF REGISTRATION FILE

- New MA : four (04) months **from the receipt date of the bank credit payment notice.**
- Renewal of MA : two (02) months **from the receipt date of the bank credit payment notice.**
- Variation of MA : two (02) months from the submission date of applications.

VIII- TYPES OF REGISTRATION FEE

- Registration Fee for new product
- Annual Fee for all products having an valid MA
- Renewal Fee.

Any final invoice will be improbable to change.

IX- TERMS AND CONDITIONS OF PAYMENT:

• Payment of fees must be made strictly within the period mentioned in the invoice "three (03) months".

• No payment should be made before the file submission and issuance of the final invoice.

• No full or partial refund of the fee paid is provided even if the request is denied because these rights do not match the cost of the application, but at the cost of investigating the file.

• All bank charges for transfers are the responsibility of the laboratory.

• Any payment made directly to the bank accounts of the Medicines Agency in Madagascar must be notified promptly to the accounting department of Madagascar Drug's Agency (Enclosure : Original of credit slip or the copy of Swift Transfer of with Reference of paid fees).

X- CATEGORIZATION OF DRUGS FOR REGISTRATION :

- **Category 1** : comfort specialty, vitamins, phyto-medicines and dietary
- **Category 2** : innovative product (under license)
- **Category 3** : branded generics specialty and essential public health specialty
- **Category 4** : generic and drugs manufactured locally

XI- LABORATORY VISIT :

As part of the verification of the implementation of GMP, pharmaceutical industries are requested to support access to their manufacturing factories to representatives of Madagascar Drug's Agency.

ANNEX

ANNEX 1

MEDICINAL PRODUCT CERTIFICATE

This certificate complies with the format recommended by the World Health Organisation

(See general instructions and explanatory notes attached)

Exporting country (certifying):.....Certificate number .....

Importing country (applicant): MADAGASCAR

1. Name and pharmaceutical form of the medicinal product:

.....

1.1 Active ingredient(s) and amount(s) per unit dose or unit volume

The full composition of the medicinal product including excipients is as follow: .....

.....

1.2 Is this medicinal product the subject of a marketing authorisation in the exporting country?

a) Yes / No

b) Application pending: Yes / No (circle the appropriate response and complete it, if applicable)

1.3 Is this medicinal product marketed in the exporting country?

Yes / No (circle the appropriate response)

If the response to 1.2 a) is YES, fill in section 2A.

Fill in section 2B in all other cases.

2A Medicinal product with marketing authorisation in the certifying country: .....

2A.1 Marketing authorisation number and date of issue: .....

2A.2 Marketing authorisation holder (name and address):.....

2A.3 Status of the marketing authorisation holder: a / b / c (circle the appropriate response(s))

a) is the manufacturer or the importer (delete whichever is not applicable) responsible for batch release;

b) is involved in one of the steps of the finished product manufacturing without being the manufacturer or the importer (delete whichever is not applicable) responsible for batch release;

c) is involved in none of the operations mentioned in a) and b).

2A.3.1 For categories b and c, name and address of the manufacturer or the importer (delete whichever is not applicable) responsible for batch release: .....

2A.4 Is a public assessment report appended?

Yes / No (circle the appropriate response)

2A.5 Is the information of the medicinal product (officially approved and included in the marketing authorisation) appended to the present certificate?

Yes / No (circle the appropriate response)

2A.6 Applicant for the certificate if the latter is not the holder of the marketing authorisation (name and address): .....

2B Medicinal product with no marketing authorisation in the certifying country:

2B.1 Applicant for the certificate (name and address): .....

2B.2 Status of the applicant: a/ b/ c (circle the appropriate response)

a) is the manufacturer or the importer (delete whichever is not applicable) responsible for batch release;

b) is involved in one of the steps of the finished product manufacturing without being the manufacturer or the importer (delete whichever is not applicable) in charge of the batch release;

c) is involved in none of the operations mentioned in a) and b).

2B.2.1 For categories b and c, name and address of the manufacturer or the importer (delete whichever is not applicable) responsible for batch release;

2B.3 Reason why the marketing authorisation is lacking:

not required (in that case, fill in 2B.4) / under consideration / refused (circle the appropriate response)

2B.4 Reasons why the marketing authorisation has not been required:

a) the medicinal product has been exclusively developed for the treatment of diseases – especially for tropical diseases – which are not endemic in the exporting country;

b) the medicinal product has been reformulated in order to improve its stability under tropical conditions;

c) the medicinal product has been reformulated to exclude excipients which are not approved in the importing country;

d) the medicinal product has been reformulated to comply with a requirement regarding the dosage of an active ingredient;

e) the medicinal product has a marketing authorisation for another dose, another pharmaceutical form or a different formulation;

f) other reason (specify).

2B.5 The Export Statement which has been sent to the certifying authority in accordance with the regulations relating to the export of medicinal products without marketing authorisation in the certifying country is appended to the present certificate.

3. Does the certifying authority arrange for periodic inspections of the manufacturing plant in which the dosage form is produced?

Yes / No / not applicable (circle the appropriate response)

Alternative site(s) (fill if relevant): .....

Name and address of the manufacturer or the importer (delete whichever is not applicable) responsible for batch release : .....

Yes / No / not applicable (circle the appropriate response)

3.1 Periodicity of routine inspections (years)

At least once every two years

3.2 Has the manufacture of this type of dosage form been inspected?

Yes / No (circle the appropriate response)

3.3 The pharmaceutical site is subject to the European Union rules for GMP recognized in perfect agreement with GMP recommended by the WHO.

Yes / No / not applicable (circle the appropriate response)

Commitment of the responsible pharmacist (see appended annex)

(Section 4 filled in by the certifying authority)

4. Does the information submitted by the applicant satisfy the certifying authority on parts 1 and 2 as well as on part 3 as all the aspects of the medicinal product manufacturing are concerned?

Yes / No (circle the appropriate response). If the response is no, explain why:

Address of the certifying authority:

.....

Phone number:.....

Fax number:.....

Signature of the Director General of the Indian Health Products Safety Agency:

Stamp and date:

General instructions

1. Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the scheme.
2. These forms may be produced by computer. They must always be submitted in typeface.
3. Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1. In accordance with the format recommended by the WHO, this certificate indicates the status of the medicinal product and of the applicant for the certificate in the exporting country. Each certificate applies to a single medicinal product only, as the manufacturing process and the approved information for different pharmaceutical forms and different concentrations may vary.
2. Use, whenever possible, the international non-proprietary name (INN) or the national non-proprietary name.
3. The formulation (full composition) of the pharmaceutical form should be specified on the certificate or appended.
4. The quantitative composition of excipients should be indicated subject to the agreement of the marketing authorisation holder.
5. As section 2A concerns medicinal products with a marketing authorisation and section B concerns medicinal products without a marketing authorisation, section 2A and 2B are mutually exclusive.
6. Specify wherever the marketing authorisation holder or, for medicinal products without a marketing authorisation, the applicant for the certificate:
    a) is the manufacturer or the importer responsible for batch release;
    b) is involved in one of the steps of the finished product manufacturing without being the manufacturer or the importer responsible for the batch release;
    c) is involved in none o the operations mentioned in a) and b).
7. This information can only be provided with the consent of the marketing authorisation holder. If no response is given in this section (2A.3.1), this will indicate that the concerned party has refused the inclusion of this information. Please note that the information relating to the manufacturer or the importer responsible for the batch release is provided in the marketing authorisation.
8. This refers to the document prepared by some national regulatory authorities which summarizes the technical data leading to the marketing authorisation issue.
9. This refers to the information on the medicinal product approved by the competent national authority such as the Summary of Product Characteristics (SPC), the patient information leaflet and the labelling. The SPC specifies the conditions for delivery and use of the medicinal product in particular (special precautions for storage and use, contra-indications).
10. Only if the applicant is not the marketing authorisation holder. The conditions of delivery and use of the medicinal product (special precautions for storage and use, contra-indications) should be specified. In all other cases, the copy of the marketing authorisation must be provided.

11. In this case, the consent of the marketing authorisation holder is required for the certificate to be issued. This consent must be communicated to the authority by the applicant.

12. Please indicate the reason(s) why the applicant has not submitted an application for marketing authorisation:

    a) the medicinal product has been exclusively developed for the treatment of diseases – especially for tropical diseases – which are not endemic in the exporting country;

    b) the medicinal product has been reformulated in order to improve its stability under tropical conditions;

    c) the medicinal product has been reformulated to exclude excipients which are not approved in the importing country;

    d) the medicinal product has been reformulated to comply with a requirement regarding the dosage of an active ingredient;

    e) the medicinal product has a marketing authorisation of another dose, another pharmaceutical form or a different formulation;

    f) other reason (specify).

13. "Not applicable" indicates that the medicinal product is manufactured in a country other than the one which issues the certificate ant that the inspection is carried out on the responsibility of the competent authority in the country where the medicinal product is manufactured.

14. The rules of Good Practices applicable to the manufacture of medicinal products and to their quality control mentioned in the certificate are those which are provided in the thirty-second report of the WHO Experts Committee on specifications relating to pharmaceutical preparations (WHO, Technical Reports Series, n°823, 1992). Recommendations specifically applicable to biological products have been formulated by the WHO Experts Committee on biological standardization and are published in the WHO Technical Report Series.

15. The data have particular importance when foreign supplies or when several manufacturers are involved in the medicinal product manufacture. In this case, the applicant must provide to the certifying authority information identifying the contractual parties responsible for each step of the manufacture of the finished pharmaceutical form and defining the nature and the extent of all controls applied on each of these parties. All additional information about these manufacture sites, which may be required by the certifying authority, should be provided by the applicant.

ANNEX 2

COMMITMENT OF PHARMACIST IN CHARGEFOR MANUFACTURING IN THE REPUBLIC OF MADAGASCAR

Name of Drug : .....

Active ingredient (s) (INN.): .....

I, undersinged

(First name, NAME)

Pharmacist responsible for:

(Name of applicant company)

- Certify that the information in the batch certificate attached is correct and commit myself to submit a new certificate in case of change of any information contained on the document,

Date

Signature and stamp

ANNEX 3

COMMITMENT OF THE PHARMACIST IN CHARGE OR THE PERSON RESPONSIBLE FOR BATCH RELEASE

Name of the medicinal product: .....

Active ingredient (s) (INN): .....

Intended for: .....

(Applicant country)

I, the undersigned, ...

(Forname, SURNAME)

Responsible pharmacist for the company:

(Name of applicant company)

- certify that the information provided in the attached certificate is accurate and I undertake to apply for a new medicinal product certificate if any of the information which appears on the above-mentionned document is modified,

- certify that the following items are attached to the certificate (*):

1°) copy of the authorization of the exporting pharmaceutical site,

2°) copy of the certificate of Good Manufacturing Practice (GMP) and copy of the authorization of the manufacturer or of the importer responsible for the batch release,

3°)

Medicinal product with a marketing authorization	Medicinal product without a marketing authorization
☐ Copy of the marketing authorization I certify that the copy of the marketing authorization is complete and I undertake to apply for a new medicinal product certificate if a major modification is made to the marketing authorization. **And/or, if the applicant is not the marketing authorization holder:** ☐ Authorization of the marketing authorization holder for issuing the certificate	☐ Copy of the export statement I undertake to apply for a new medicinal product certificate if a modification is made to the export statement.

(*) the appropriate box (es) must be ticked for the third item

- certify that, if necessary, the following item is attached to this commitment:

4°) list of the manufacturers (name, address) and certificates equivalent to the GMP certificate for the corresponding manufacture sites, if more than one manufacturer is involved in the manufacturing of the medicinal product.

Country Date

Signature (+ stamp)

ANNEX 4

BATCH CERTIFICATE OF A PHARMACEUTICAL PRODUCT ESTABLISHED BY THE MANUFACTURER

This certificate (s) is (are) set (s) for (s) Lot (s) from which the samples provided with the file.

This certificate conforms to the format recommended by the World Health Organization

(See general instructions and explanatory notes overleaf)

1. Certificate:N°.....

2. Authority requests: Medical Products Agency of Madagascar.

3.Name of product: .....

3.1 Form Pharmaceutical .....

3.2.Principe (s) active (s) 1 and amount per unit dose:

The Paragraphs 3 and 4 are not applicable to drugs manufactured in Madagascar.

3.2.1 The composition of the product it is identical to the registered product in the exporting country? yes / no / non-registered product manufacturer in the country.

If the answer is no, please attach the quantitative formula (including excipients) of both products.

4. Holder's authorization to market product2 (name and address): .....

.....

4.1 Number of authorization to market product2 :.....

.....

4.2 Date of délivrance2 :.....

4.3 Authorisation for placing on the market issued par2: .....

4.4 Number of certificate of product2, 3: .....

5.1 Number Lot: .....

5.2 Date of Manufacture: .....

5.3 Duration of storage (years): .....

5.4 Content of the container: .....

5.5 Nature of primary packaging: .....

5.6 Nature of secondary container / packaging: .....

5.7 Special storage conditions:.....

5.8 Differences in temperature: .....

6. Observation4: .....

7. Quality Analysis:

7.1 Specifications applicable to this formulation. Indicate the pharmacopoeia in question or join specifications 5.

7.1.1 In the case of a registered product manufacturer in the country, these specifications have been approved by the competent authority? (Yes / no)

7.2 The consignment are there any special conditions to the above specifications?

yes / no *(introduce in your answer)*

7.3 Attach the certificate of analysis.6

This is to certify that the above statements are correct.

Name and address of authorized person: .....

.....

Phone: .....

Fax: .....

Signature of authorized person: .....

Stamp and date:

General Instructions

1. For more complete information on how to complete this form and the application system, please refer to the text of the guidelines.
2. These forms can be produced by computer. They must always be submitted typewritten.
3. Add, if necessary, additional sheets for comments and explanations.

Explanatory notes for the batch certificate

The competent authority of the exporting country shall not be only exceptionally to the certification of individual batches of a pharmaceutical product. Even in this case, certification is rarely applied to other products as vaccines, sera and biologicals. For other products, is the holder of the authorization of placing on the market in the exporting country's responsibility to require the presentation of certificates of lots. It is preferable that the importing agent who is responsible for forwarding the certificates to the competent authority of the importing country.

Any request or complaint regarding a batch certificate should be addressed in all cases, the competent authority of the exporting country. A duplicate will be sent to the holder of the authorization for marketing the product.

1. Use as much as possible, ***International Non-proprietary Names*** (INN)
2. All items in Section 4 refer to the permission marketing of product or the product certificate issued pharmaceutical manufacturer in the country.
3. Concerns certificate of pharmaceutical product recommended by the World Health Organization.
4. Display all recommended precautions for storage for the product as supplied.
5. The specifications are the values of various parameters to be measured and have been accepted for the release of the consignment at the time of product registration.
6. Identify and explain any deviations from the specifications. Certificates of release of a batch may be issued by a government office for some organic products provide additional confirmation that a particular batch has been released but does not necessarily specify what were the results of the tests. These are included in the analysis certificate from the manufacturer.

ANNEX V

STABILITY TESTING FOR DRUG PRODUCTS

1. *General*

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

3. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

4. Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug product is addressed in Q3B.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

5. Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

6. Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product.

The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested.

6.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RHor 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form:
4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

6.2. Drug products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

6.3. Drug products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below.

Study	Storage condition	Minimum time period covered by data at submission
Long term*	**25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH**	**12 months**
Intermediate**	**30°C ± 2°C/65% RH ± 5% RH**	**6 months**
Accelerated	**40°C ± 2°C/not more than (NMT) 25% RH**	**6 months**

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

**If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition

Data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

6.4. Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

6.5. Drug products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

6.6. Drug products intended for storage below -20°C

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

7. Data presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included.

REFERENCES

- **Stability testing of new drug substances and products Q1A(R2), ICH Harmonised tripartite guideline, 2003**
- **Evaluation for stability data Q1E, ICH Harmonised tripartite guideline, 2003**
- **ICH Stability zones**

ICH STABILITY ZONE

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IV b	ASEAN testing conditions hot/higher humidity

STUDY	LONG TERM	INTERMEDIATE	ACCELERATED
DURATION	> 12 months	12 months	6 months
TESTING FREQUENCY	Every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.	4 time points: 0, 6, 9 and 12 months	3 time points: 0, 3 and 6 months
Number of batches to be tested	3	3	3
STORAGE CONDITIONS / DRUG PRODUCTS	ZONE IV	ZONE IV	ZONE IV
General case	30°C ± 2°C 65% RH ± 5% RH	30°C ± 2°C 65% RH ± 5% RH	40°C ± 2°C 75% RH ± 5% RH
Drug products packaged in impermeable containers	30°C ± 2°C RH controlled or ambient		40°C ± 2°C RH controlled or ambient
Drug products packaged in semi-permeable containers	30°C ± 2°C 35% RH ± 5% RH	30°C ± 2°C 65% RH ± 5% RH	40°C ± 2°C Not more than 25% RH
Drug products intended for storage in a refrigerator	5°C ± 3°C		25°C ± 2°C 60% RH ± 5% RH
Drug products intended for storage in a freezer	-20°C ± 5°C		5°C ± 3°C
Drug products intended for storage below -20°C	treated on a case-by-case		

MANUFACTURER

STABILITY DATA : LONG TERM STUDY

PRODUCT NAME (INN)		STORAGE CONDITIONS	TEMPERATURE	
BRAND NAME			RELATIVE HUMIDITY	
PHARMACEUTICAL FORM		MANUFACTURING DATE		
COMPOSITION		EXPIRY DATE		
		BATCH NUMBER		
PACKAGING		PROPOSED STORAGE STATEMENT		

PARAMETERS	SPECIFICATIONS	INITIAL	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS	18 MONTHS	24 MONTHS	36 MONTHS
DATE OF ANALYSIS		01/12/15	01/03/16	01/06/16	01/09/16	01/12/16	01/06/17	01/12/17	01/12/18
Physical attributes									
Chemical attributes									
Pharmacotechnical attributes									
Biological attributes									
Microbiological attributes									
Preservative content									
Functionality tests									
Others									

Observations:

Prepared by :	Checked by :	Approved by :
(Function, Name, Signature, Date)	(Function, Name, Signature, Date)	((Function, Name, Signature, Date)

MANUFACTURER

STABILITY DATA: ACCELERATED STUDY

PRODUCT NAME (INN)		STORAGE CONDITIONS	TEMPERATURE	
BRAND NAME			RELATIVE HUMIDITY	
PHARMACEUTICAL FORM		MANUFACTURING DATE		
COMPOSITION		EXPIRY DATE		
		BATCH NUMBER		
PACKAGING		PROPOSED STORAGE STATEMENT		

PARAMETERS	SPECIFICATIONS	INITIAL	3 MONTHS	6 MONTHS
DATE OF ANALYSIS		01/12/15	01/03/16	01/06/16
Physical attributes				
Chemical attributes				
Pharmacotechnical attributes				
Biological attributes				
Microbiological attributes				
Preservative content				
Functionality tests				
Others				

Observations:

Prepared by :	Checked by :	Approved by :
(Function, Name, Signature, Date)	(Function, Name, Signature, Date)	((Function, Name, Signature, Date)

ANNEX VI :

ASSESSMENT CRITERIA

Assessment criteria of registration files are based on the following parameters (not exhaustive list) :

1. Major parameters (cause of refusal) :

- SPC and leaflet : omissions of major medical information
- Inconsistency of the application file
- Inconsistency and incompatibility of data with reference
- Low ratio Profit / Risk Product
- Non-compliance with reference and laboratory specifications (description, identification, assay, dissolution ....)
- Irrational association, unsuitable active ingredient for the target population, non-recommended active ingredient by national programs, non-adapted presentation to clinical practice
- Handling problem
- Lack of references in highly regulated countries (new dosage form, new association)

2. Minor parameters (cause of claiming) :

- Expired administrative file
- SPC and leaflet : omissions of minor medical information
- Quality control notes : erasable legal mention, advertising matter...
- Incomplete quality module
- Unreadable and/or incomplete leaflet

ANNEX VII

REPOBLIKAN'I MADAGASIKARA
Tanindrazana-fahafahana-Fandrosoana

Ministère de la Santé et du Planning Familial

Ministère de l'Economie, des Finances et du Budget

ARRETE INTERMINISTERIEL N° 24364/2004
Modifiant et rectifiant l'arrêté n° 5311/98 du 07 juillet 1998 portant tarification des actes de l'Agence du Médicament

---

Le Ministre de la Santé et du Planning familial,
Le Ministre de l'Economie, des Finances et du Budget :

Vu la Constitution ;
Vu l'ordonnance n° 62-072 du 29 septembre 1962 portant codification des textes législatifs concernant la santé publique ;
Vu le décret n° 62-046 du 24 janvier 1962 relatif à l'organisation de la profession de médecin, de chirurgien dentiste, de sage-femme et de pharmacien exerçant à Madagascar ;
Vu le décret n° 98-086 du 27 janvier 1998 portant création et organisation de l'Agence du Médicament de Madagascar ;
Vu le décret n° 2003-007 du 12 janvier 2003 portant nomination du Premier Ministre, Chef du Gouvernement ;
Vu le décret n° 2003-008 du 16 janvier 2003 portant nomination des Membres du Gouvernement modifié par les décrets n° 2004-001 du 04 janvier 2004 et n° 2004-680 du 05 juillet 2004 portant nomination des membres du Gouvernement ;
Vu le décret n° 2004-989 du 19 octobre 2004 fixant les attributions du Ministre de la Santé et du Planning Familial ainsi que l'organisation générale de son Ministère ;
Vu l'arrêté n° 5311/98 du 07 juillet 1998 portant tarification de l'Agence du Médicament ;

ARRETENT :

Article premier : Certaines dispositions des articles 1, 9, 10, 11, 12 et 13 de l'arrêté n° 5311/98 du 07 juillet 1998 sus-visé sont modifiées comme suit. Les articles 13 bis et 13 ter sont à rajouter.

Article 2 : L'article 1 de l'arrêté n° 5311/98 du 7 juillet 1998 sus visé est libellé comme suit :
« Article 1 » (nouveau) : Les redevances prévues pour l'enregistrement du médicament à usage humain, l'octroi d'Autorisation de Mise sur le Marché et les analyses de contrôle de qualité prévues à l'article 25 du décret n° 98-086 du 27 janvier 1998 portant création et organisation de l'Agence du Médicament de Madagascar, comprennent :

- un droit fixe pour l'obtention de l'Autorisation de Mise sur le Marché.

- un droit fixe pour l'obtention du renouvellement de l'Autorisation de Mise sur le Marché, tous les cinq ans.

- Un droit annuel de débit pour les produits dont la commercialisation est autorisée à Madagascar.

- Un droit fixe pour l'obtention des visas de publicité

- **Un droit d'analyses pour le contrôle de qualité.**

Ces redevances s'acquittent auprès de Monsieur l'Agent comptable de l'Agence du Médicament de Madagascar. **Les montants en euros sont payables en monnaie locale au taux du jour.**

Article 3 : L'article 9 de l'arrêté n° 5311/98 du 07 juillet 1998 sus visé est libellé comme suit :
« *Article 9* » *(nouveau)* : Le montant des droits pour l'obtention de l'Autorisation de Mise sur le Marché est fixé comme suit :

- Médicament d'origine étrangère : **200 euros**
- Médicament fabriqué localement : **164 000 ariary**

Article 4 : L'article 10 de l'arrêté n° 5311/98 du 07 juillet 1998 sus visé est libellé comme suit :
« *Article 10* » *(nouveau)* : Le montant des droits pour l'obtention du renouvellement de l'Autorisation de Mise sur le Marché, fonction d'une catégorie attribuée au médicament par la Commission Nationale d'Enregistrement et qui prend en compte l'importance thérapeutique du médicament définie en termes de bénéfice pour la santé publique, est fixé comme suit :

- Catégorie 1 : **300 euros**
- Catégorie 2 : **240 euros**
- Catégorie 3 : **190 euros**
- Catégorie 4 : **140 euros**

Le droit de renouvellement de visa pour le médicament fabriqué localement, classé automatiquement dans la catégorie 4, est fixé à 160 000 ariary.

Article 5 : L'article 11 de l'arrêté n° 5311/98 du 07 juillet 1998 sus visé est libellé comme suit :
« *Article 11* » *(nouveau)* : Le montant des droits de débit annuels, fonction de la catégorie attribuée au médicament par la Commission Nationale d'Enregistrement et qui prend en compte l'importance thérapeutique du médicament en termes de bénéfice pour la santé publique, est fixée comme suit :

- Catégorie 1 : **61 euros**
- Catégorie 2 : **48 euros**
- Catégorie 3 : **43 euros**
- Catégorie 4 : **38 euros**

Le droit de débit annuel pour le médicament fabriqué localement, classé automatiquement dans la catégorie 4, est fixé à 20 000 ariary.

Article 6 : L'article 12 de l'arrêté n° 5311/98 du 07 juillet 1998 sus visé est libellé comme suit :
« *Article 12* » *(nouveau)* : Le montant des droits pour l'obtention d'un visa de publicité est fixé à **300 000 ariary, le paiement peut être effectué en devise au taux du jour.**

Article 7 : L'article 13 de l'arrêté n° 5311/98 du 07 juillet 1998 sus visé est libellé comme suit :
« *Article 13* » *(nouveau)* : **Les montants des droits pour la réalisation d'analyse dans le laboratoire de contrôle de qualité des médicaments de l'Agence du Médicament de Madagascar sont fixés comme suit pour les formes autres que injectables :**

Désignation des analyses	Etablissement public / à but non lucratif	Etablissement privé
Analyse complète	100 euros	150 euros
Uniformité de masse	17 euros	23 euros
Désagrégation	17 euros	23 euros
Dissolution	34 euros	46 euros
Identification du principe actif	42 euros	53 euros
Dosage du principe actif	50 euros	60 euros
Recherche des substances apparentées	42 euros	53 euros
Autre test pharmacotechnique	17 euros	23 euros
Autre test physico-chimique	42 euros	53 euros

Article 8 : Les articles suivants sont à rajouter :
***« Article 13 bis » (nouveau) :* Les montants des droits pour la réalisation d'analyse dans le laboratoire de contrôle de qualité des médicaments de l'Agence du Médicament de Madagascar sont fixés comme suit pour les formes injectables :**

Désignation des analyses	Etablissement public / à but non lucratif	Etablissement privé
Analyse complète	250 euros	350 euros
Uniformité de masse	17 euros	23 euros
Identification du principe actif	42 euros	53 euros
Dosage du principe actif	50 euros	60 euros
Recherche des substances apparentées	42 euros	53 euros
Autre test pharmacotechnique	17 euros	23 euros
Autre test physico-chimique	42 euros	53 euros
Essai de stérilité	75 euros	97 euros
Test LAL	75 euros	97 euros

Article 9 Les articles 14, 15 demeurent inchangés.

Article 10 Le présent arrêté sera enregistré et publié au Journal Officiel de la République.

Antananarivo, le **17 décembre 2004**

Le Ministre de la Santé
et du Planning Familial

signé : Docteur JEAN LOUIS ROBINSON

Le Ministre de l'Economie,
des Finances et du Budget

signé : RADAVIDSON Andriamparany Benjamin

- POUR AMPLIATION CONFORME TRANSMISE -

AGENCE DU MEDICAMENT
DE MADAGASCAR

N° 001 -Agmed/Enr.

à

Voir Destinataires

DESTINATAIRES :
- Tous laboratoires fabricants de médicaments
- Tous grossistes répartiteurs de médicaments

10 JAN. 2005

Antananarivo, le

Le Directeur,

Docteur Jean René RANDRIASAMIMANANA