"Regulatory Requirements and Current Challenges related to Labeling and Packaging for Medicinal Products in Europe Region"

A Thesis Submitted to

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in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICAL REGULATORY AFFAIRS

BY

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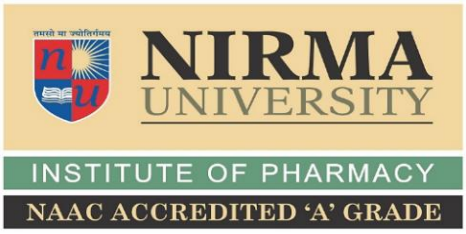

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CERTIFICATE

This is to certify that the dissertation work entitled "Regulatory Requirement and current Challenges related to Packaging and labeling in Europe Region No. (17MPH805) in partial fulfillment for the award of Master of Pharmacy in "Regulatory Affairs" is a bonafide research work carried out by the candidate at the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University under my/our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Place: AHMEDABAD

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Throughout her training she has shown her full devotion in handling assignments entrusted upon her.

During her tenure with us, she was found to be sincere and focused.

We wish her all the best for her career.

For, Intas Pharmaceuticals Ltd.,

Shobhit Dwivedi
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CERTIFICATE OF ORIGINALITY OF WORK

*This is to undertake that the dissertation work entitled "**Regulatory Requirements and Current Challenges related to Labeling and Packaging for medicinal Products in Europe Region**" Submitted by Labdhi Doshi (17mph805) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Regulatory Affairs" is a bonafide research work carried out by me at the "Pharmaceutical Analysis ", Institute of Pharmacy, Nirma University . I am aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, this work is original and not reported anywhere as per best of my Knowledge.*

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DECLARATION

I hereby declare that the dissertation entitled "Regulatory Requirements and Current Challenges related to Labeling and Packaging for medicinal Products in Europe Region" is based on the original work carried out by me under the guidance of Dr. Charmy Kothari, Associate Professor Department of Pharmaceutical Analysis Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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LABDHI DOSHI

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LIST OF ABBREVIATIONS

Short Name	Abbreviation
EC	European Council
EMA	European Medicine Agency
EU	European Council
MHRA	The Medicine and Healthcare products regulatory authority
CTD	Common Technical Document
SmPC	Summary of Product Characteristics
PIL	Patient Information Leaflet
OTC	Over the counter
SOP	Standard Operating Procedure
CEP	Certificate of suitability
MA	Marketing Authorization
MAH	Marketing Authorization Holder
QRD	Quality review by documents
EAN	European article Number
VNR	Nordic Article Number
CmDh	Co-ordination group for mutual recognition and decentralized procedure -human
UI	Unique Identifier
PMR	Patient Medication Record
EUFMD	European union falsified medicine directive
EMVO	European Medicine Verification Organization
EMVS	European Medicine Verification Systems
NMVS	National Medicine Verification Systems
UKMVO	UK Medicine Verification Organization
CEN	The European Committee for Standardization
GTIN	Global Trade Item Number
NTIN	National Trade Item Number
PPN	Pharmacy Product Number
NHRN	National Healthcare Reimbursement Number

ATD	Anti-tempering device
POM	Prescription only medicine
PC	Product Code
SN	Serialization Number
RSI	Request for supplementary information
PVSR	Preliminary Variation Assessment Report
FVAR	Final Variation Assessment Report

ABSTRACT

The Common Technical Document format was developed by the ICH to streamline the inconsistency of submission requirement in the Different Countries. There are guidelines for basic information for labeling and packaging to prepare mock ups. Packaging and labeling serve information directly to the patients and therefore required to be updated in stipulated time, to meet the compliance and to minimize the query and to mitigate risk to the consumer due to substandard medicine. According to the labeling there are three elements of the Medicinal Product label: Summary of product characteristics (SmPC) and Patient Information Leaflet (PIL), Outer/Immediate label. The Summary of product characteristics, Labeling and packaging leaflet are located in Module 1. Labeling is the most crucial factor to determine the safety of the medicine. For the purpose of safety and efficacy of the product, the medicinal product has been evaluated by the respective regulatory authority of the country. Medicinal product may be approved, if application found suitable by the agency. Prior to marketing a medicinal product in the EU, a marketing authorisation (product licence) is must. There are so many updates in labeling rather minor or major, that changes should be updated with in timeline suggested by EU authority and according to guidelines. Thus, the variation filing is must to regulatory authority according to the changes and types of variation. Patient detects the information on label but as additional requirement on label in different countries in Europe region that called Blue box requirement. As mention in article 57 and 62 of directive 2004/83/EC. Blue box requirement contains information like legal status, symbols and pictogram and identification and authenticity on label for medicinal products. Europe faces the current challenges related pack and label that ate to meet the labeling compliance and to minimize the risk of market complaints which affected by the identification, readability and dispensing perspective. Compilation to EUFMD along with the regulatory compliance and confirm with supply chain in a scenario of Brexit. Europe has been concerned about the growing threat of falsified medicine to the purpose of patient health and safety. Falsified medicine directive regulation is passed by European union parliament, with the main concern is to increase the patient safety and to prevent falsified medicine from entering the supply chain. To improve the patient safety and security, there are main three key components are involved in FMD. Manufacturer should comply with EUFMD before February 2019 to export and distribute medicinal product in Europe Region.

Chapter 1
Introduction

European Medicine agency have guidelines for basic information for labeling and packaging to prepare mock ups. The European Medicine Agency is the EU regulatory body responsible for the scientific evaluation and supervision of medicine developed by Pharmaceutical companies for use in the European Union (Human and veterinary). The EMA is the Regulatory body in Europe that ensures that medicines are safe and that they work as expected. The European Regulatory system for medicines is a unique model in the global regulatory environment. The Agency's main responsibility is the protection and promotion of public and animal health, by carrying out scientific evaluations of medicine for human and veterinary use.[1] EMA secures open and creature wellbeing in 27 EU Member States, also as the nations of the European Economic Area, by guaranteeing that all drugs accessible on the EU advertise are protected, viable and of high quality.[2] Regulatory framework for drugs is a one of a kind models in the worldwide administrative condition.[3] Labeling is a crucial part that determines the safety of the medicine. Medication errors can alter the mortality and morbidity rates. Thus, patient safety is the foremost concern for the medicines manufacturers. The importance of the labeling that are to fulfil a legal Requirement, to ensure the appropriate and safe use of the approved product, to provide consumer with information on the product to enable to take the medicinal dose and to distinguish the products from same supplier or different suppliers. Packaging and labeling serve information directly to the patients and therefore required to be updated in stipulated time, to meet the compliance and to minimize the query and to mitigate risk to the consumer due to substandard medicine. Blue box requirement needs to be followed nationally to prepare Cartans and Patient information leaflet. According to the regulatory framework in Europe, there are three important elements of the label which contains detail information that are beneficial for the patient. For the purpose of safety and efficacy of the product, the medicinal product has been evaluated by the respective regulatory authority of the country. Medicinal product may be approved, if application found suitable by the agency. Prior to marketing a medicinal product in the EU, a marketing authorisation (product licence) is essential. For EU region, Identification and authentication of medicine is major, as there are many countries and their local languages. So that submission of SmPC, patient information leaflet (PIL), outer and immediate label is very important part of dossier. As per Directive 2004/83/EC by EMA. Having well established guidelines by EMA still it is big challenge for generic manufacturer to have the all criteria for labeling

followed and also to include additional country specific requirement in mockups during submission of mockups. Language is also the barrier during submission in Europe region as most countries require labeling in their local language. To reduce the occasions on which falsified medicines enter the legitimate supply chain. Thus, European union parliament passes the regulations and adopt the directive that is European Union Falsified medicine directive (EUFMD) which aims to build the security of the assembling and conveyance of drugs crosswise over Europe and shield patients and keep distorted meds from entering the inventory network. In EUFMD main three components that are play a vital role to improve patient security and safety. The final phase of the FMD was February 9,2019. This whole system accomplished by European Medicine Verification Organization (EMVO).

1.1 Module 1 of CTD:

Common Technical Document (CTD) format was developed by the International Conference on Harmonization (ICH) to streamline the inconsistency of submission requirements in the Different countries. CTD Represents quality; safety and efficacy information into a common format which is adopted by the EMA for the submission of Dossier.

The CTD is comprised of 5 modules:

Module 1: Administrative Information

Module 2: CTD Summaries

Module 3: Quality

Module 4: Non-clinical Study Reports

Module 5: Clinical Study Reports

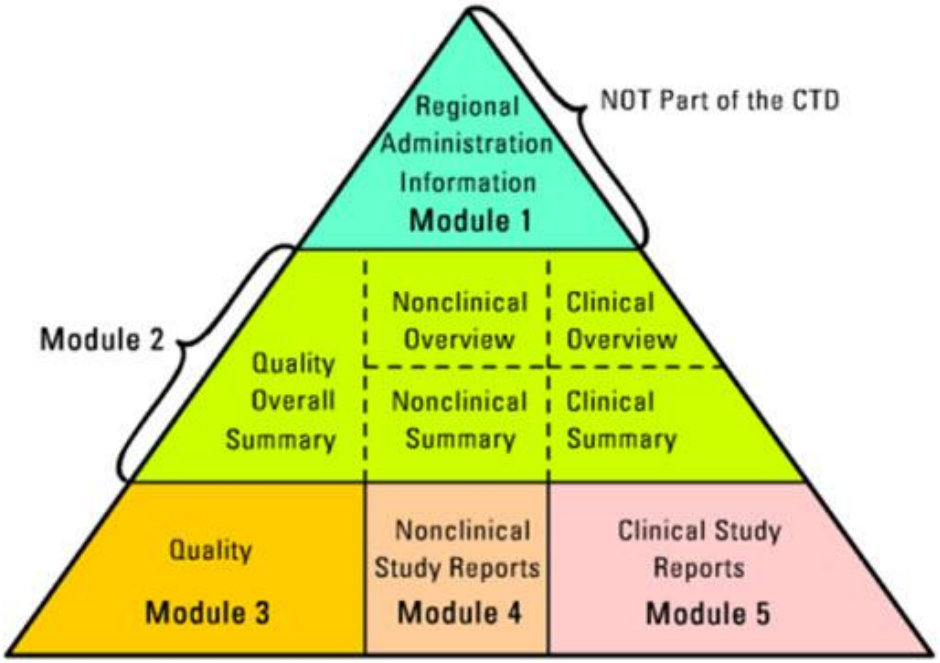


Figure 1CTD Module

Table 1 CTD Module 1.1

Module 1	Administrative Information and Prescribing Information
1.1	Comprehensive table of contents
1.2	**Application Form**
1.3	Product Information
1.3.1	**SPC, Labeling and Package Leaflet**
1.3.2	**Mock-up**
1.3.3	**Specimen**
1.3.4	Consultation with Target Patient Groups
1.3.5	Product Information already approved in other Member States
1.3.6	Braille
1.3.7	Information about the Experts
1.4	Quality
1.4.1	Non-Clinical
1.42	Non- Clinical
1.4.3	Clinical
1.5	Specific Requirements for Different types of Application
1.5.1	Information for Bibliographical Application
1.5.2	Information for generic, 'Hybrid' or Bio-similar Application
1.5.3	(Extended) Data/Market Exclusivity
1.5.4	Exceptional Circumstances
1.5.5	Conditional Marketing Authorization

1.2 Packaging:

1.2.1 Definition as per EU:

Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This Process is done by hand and machine. Packaging is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use. Packaging can be characterized as an organized arrangement of defining merchandise for transport, warehousing, coordination's, deal, and end use. Packaging also refers to the process of designing, evaluating, and producing packages. Packaging can be described as a coordinated system of preparing goods for transport, warehousing, logistics, sale, and end use. Packaging contains, protects, preserves, transports, informs, and sells.[4]

1.2.2 Ideal Requirements of Pharmaceutical Packaging Material:[4]

- Protect the medicinal product from environmental conditions.
- Non-reactive with the product and so does not alter the identity of the product.
- Does not affect tastes or odours of the product.
- Nontoxic.
- FDA approved.
- Protect the dosage form from damage or breakage. For e.g.: During Transportation
- Meet tamper-resistance requirements, For Some Specific Dosage Forms

1.2.3 Types of Packaging:

There are three types of packaging:

A. Primary Packaging
B. Secondary Packaging
C. Tertiary Packaging

1.2.3.1. Primary Packaging:

The material first envelopes the item and hold it. This generally is the littlest unit of conveyance or use and is the bundle which is in direct contact with the measurement structure its self.[4]

e.g.: Blister, strips, pouches, sachets

Advantages:

- It Protects the dosage forms from the Temperature Fluctuation.
- It holds the product highly Which minimize the breakage.

1.2.3.2. Secondary Packaging:

It is done outside of the packaging perhaps used to group primary packages together. It Provides the Multiple dose in one pack and also provide all information regarding the dosage form. It also has the important details such as lot/exp and batch.

e.g.: Cartans, paper drums, Injectable trays.

1.2.3.3. Tertiary Packaging:

It is used for bulk handling, warehouse Storage and transport shipping. Bulk Packaging usually done to transport goods to retail store via supply chain. It should carry enough details when manufacturer export goods to other counting of the globe.

e.g.: Slip Shipment, Intermediate bulk container, Edge Protector

Figure 2 Types of Packaging

1.3 Labeling:

1.3.1 Definition as per EU:

As per Directive 2004/27/EC Labeling includes the contents of the outer and immediate packaging. It is also possible that there may only be the immediate packaging. Label means a display of written, printed or graphic matter like such symbols upon immediate package the wrapper of medicinal product. The information must therefore correspond to the marketing authorisation (MA), the summary of product characteristics (SPC) and the package leaflet, and must always be provided in the three national languages.[5]

The Information given on Label Should be:

- ✓ Accurate
- ✓ Legible
- ✓ Relevant and Adequate

1.3.2 Importance of labeling:

- To fulfil a legal Requirement,
- To ensure the appropriate and safe use of the approved product,
- To Provide consumer with information on the product to enable to take the medicinal dose,
- To Distinguish the products same supplier or different suppliers.

1.3.3 Mock-ups and specimen:

A ' **Mock-ups** ' is a **copy of the flat artwork design in full colour**, presented so that, following cutting and folding where necessary, it provides a replica of both the outer and immediate packaging so that the three-dimensional presentation of the label text is clear. It is generally stated to as a "paper copy" or "computer generated version. Generally, Mock-ups are submitted in full size hard copy and in colour or electronically. A 'specimen' is a sample of the actual printed outer and immediate packaging materials and package leaflet. Mock-ups and specimens of the outer and immediate packaging together with the package leaflet must be submitted by the applicant/MAH to the EMA for review, before commercialisation of the medicinal product.[6]

1.4 Components of label:

There are main three components of label:

A. SmPC (Summary of product characteristics)
B. PIL (Patient information leaflet)
C. Outer label/immediate label

1.4.1 Summary of medicinal Product Characteristics (SmPC)

The SmPC is a legal approved document approved as part of the marketing authorisation of each medicine. The SmPC is the definite of data for human services proficient on the best way to utilize the prescription. Its information is updated throughout the life-cycle of the product as new data emerge if such as addition of new indication or side effects.[7] The SmPC delivers information on a particular medicinal product; therefore, it should not include reference to other medicinal products.[8]

Table 2 Content of SmpC

1	Name of Product	
2	Qualitative and quantitative Composition	
3	Pharmaceutical Dosage form	
4	Clinical Particulars	
	4.1	Therapeutic Indication
	4.2	Posology and method of administration
	4.3	Contraindications
	4.4	Special warnings and precaution for use
	4.5	Interaction with other medicinal products and other forms of indication
	4.6	Fertility, pregnancy, lactation
	4.7	Effects on ability to drive and use machines
	4.8	Undesirable side effects
	4.9	Overdose
5	Pharmacological Properties	
	5.1	Pharmacokinetic Properties
	5.2	Pharmacodynamic Properties
	5.3	Pre-clinical safety data
6	Pharmaceutical Properties	
	6.1	List of Excipients
	6.2	Shelf life
	6.3	Incompatibilities
	6.4	Special Precaution for storage
	6.5	Nature of Contents of containers
	6.6	Special Precaution for disposal
7	Marketing Authorization holder	
8	Marketing Authorization number	
9	Date of First Authorization/renewal of the authorization	
10	Date of Preparation of the text	
11	Dosimetry	
12	Instruction for preparation of radiopharmaceuticals	

Summary of medicinal Product Characteristics (SmPC)

Name of Product:

Article 54(a) of Directive 2001/83/EC requirements related to full name of medicinal Product, its strength, pharmaceutical form and if it is intended for children, adults and babies then it should be in three active substances and the INN (International non-proprietary name).[9]

Qualitative and quantitative Composition:

In this section the packaging need in form of the quantity per unit volume and total quantity per total volume. It is important for safety reasons for the semisolids and injectable. For example, 750 mg, 900 mg, 450 mg, 1000 mg and NOT 1 g. Trailing zeros should not appear (7.5 mg and NOT 7.50 mg).[10]The use of decimal points (or comma) should be avoided where these can be removed (i.e. 750 mg is acceptable whereas 0.75 g is not).

Route of administration:

In this part the negative statements not used., for example, "Not for intravenous use"
Use of only standard abbreviations like i.m, i.v.

Design and layout:

As mention in Article 62 the outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information and other information compatible with the summary of the product characteristics, which is useful for the patient, to the exclusion of any element of a promotional nature.[9] Hues ought to be picked to guarantee a decent complexity between the content and the foundation to guarantee most extreme neatness and openness of the data.[11]

Expiry Date:

The expiry date printed on medicinal products stating only month and year should be taken to mean the last day of that month. Expiry dates should be expressed with the month given as 2 digits or at least 3 characters and the year as 4 digits. E.g.: February 2010, Feb 2010, 02-2010. 16

Name and address of MAH:

Including town, postal code (if available) and country name of the MAH in the language of the text (Telephone, fax numbers or e-mail addresses) may be included.

Language:

The Package pamphlet must be clear, effectively justifiable and elegantly composed. All particulars in the subparagraph shall be amended provided in all the languages used. In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community.[12] The first subparagraph will not keep the bundle pamphlet from being imprinted in a few dialects, gave that a similar data is given in every one of the dialects utilized.

Marketing Authorisation Number:

This is the marketing authorisation number consisting of "EU" followed by a nine-digit number (e.g. "EU/1/96/000/000"). This number must appear on the package, whilst the (national) identification number, if any, can only appear (once) in the 'blue box'. In the Centralized Product.

e.g. EU/0/00/000/001 28 tablets

EU/0/00/000/002 56 tablets

EU/0/00/000/003 100 tablets

Blind and partially- sighted patients:

As mention in Article 56a of the Directive describes the name of the medicinal product including strength and dosage form to be expressed in Braille format on the packaging.[9]

1.4.2 Patient Information Leaflet (PIL)

Patient Information leaflet is a legal approved document as part of dossier.

Following are the content of PIL:

It contains Identification of the medicinal product including the Name, strength and pharmaceutical form. Also contains Information needed before taking the product like contraindications and warnings, precautions for use, children and adolescents and special warnings such as (pregnancy, breastfeeding, driving and using machines). How to take drug its dosage and method and/or route(s) of administration, frequency of administration and duration of treatment, overdose and/or missing a dose, withdrawal effects they are also part of PIL. Medicinal Product's Possible side effects, how to store it and its Storage conditions and expiry date also mentioned in PIL. Contents of the pack and other information includes Pharmaceutical form, physical description, pack sizes, Date on which the PL was approved, Marketing Authorisation Holder (MAH) & Manufacturer details provided in the PIL for patients or healthcare person.

There are six questions in this leaflet:

1. What X is and what it is used for?

Identification of the medicinal product:

- Pharmacotherapeutic group
- Therapeutic indications
- Information on benefits

2. What you need to know before you X

- Information needed before taking the product:
  - contraindications + warnings and precautions for use
  - children and adolescents
  - other medicines and X
  - X with food, drink or alcohol
  - special warnings (pregnancy, breastfeeding, driving and using machines) and excipients warnings, if applicable

3. How to <take><use> X

- Instructions for proper use:

- dosage + method and/or route(s) of administration
- use in children and teenagers
- frequency of administration + duration of treatment
- overdose and/or missing a dose
- withdrawal effects, if applicable

4**. Possible side effects**

- Most serious side effects to be listed first with clear instructions on what action to take. Most frequent side effects to follow - The remainder should be presented on the basis of frequency of occurrence.

5. How to store X

- Storage conditions and expiry date

• Warning against using the product after the expiry date

• Shelf life after reconstitution, if applicable

• Warnings against visible signs of deterioration, if appropriate

6. Contents of the pack and other information

- What X contains

• Full qualitative and quantitative composition of active substance and excipients:

- What X looks like and contents of the pack

• Pharmaceutical form, physical description, pack sizes:

- Marketing Authorisation Holder (MAH) & Manufacturer

- List of local representatives (all or none)

- Date on which the PL was approved

-Information for medical or healthcare professionals, if appropriate

1.4.3 Outer pack/Immediate Pack:

Immediate pack known as Primary pack and Outer pack known as Secondary pack. Immediate packaging. Immediate packaging, it is the material that first envelopes the product and hold it and the container or other form of packaging immediately in contact with medicinal products It contains detailed information of medicinal product on the packaging.

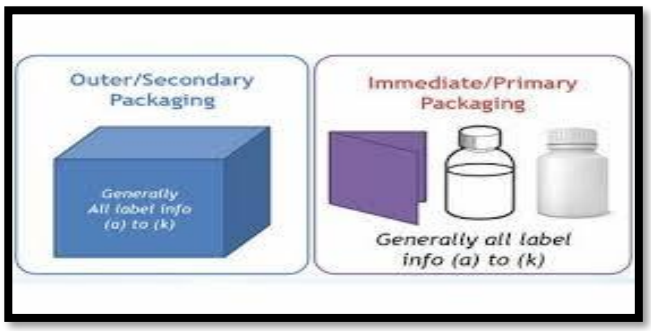


Figure 3 Outer Pack/Immediate Pack

Table 3 Components of labeling

Name of the medicinal product	toremifene 60 mg Capsule
Statement of active substance(s)	60 mg toremifene
List of excipients	This medicinal product contains lactose, sunset yellow (E110) and allura red (E129) [only for 40mg].
Special warning that the medicinal product must be stored out of the sight and reach of children	Keep out of the sight and reach of children
Instructions on use	-
General classification for supply	Medicinal product subject to medical prescription
Special storage conditions	Store in the original package in order to protect from moisture and light.

Batch number	Lot
Marketing authorization number(s)	For multipacks, clearly indicate the pack content for each marketing authorisation number, e.g.EU/X/XX/XXX/XXX 180 film-coated tablets (2 packs of 90).
Name and address of the marketing authorization holder	To be completed nationally.
Pharmaceutical form and contents	In case of multipacks presentation: On the outer carton or label: "Multipack: 180 (2 packs of 90) film-coated tablets." On the inner carton (without blue box): "90 film-coated tablets. Component of a multipack can't be sold separately.". In case of a treatment initiation pack, "Treatment initiation pack Each pack of 28 film-coated tablets for a 4-week treatment
Method and route(s) of administration	Directions for proper use of the medicinal product, e.g. "Do not swallow", "Do not chew", "Shake well before use". In all cases, and especially if full details cannot be included on the outer packaging itself, a reference to the package leaflet must be made
Expiry date	Expiry dates should be expressed with the month given as 2 digits or at least 3 characters and the year as 4 digits e.g.: February 2007, Feb 2007, 02-2007
Other special warning (s), if necessary	Special warnings on labeling should be reserved to cases where they are considered very important in order to fulfil a risk minimisation objective e.g. "Cytotoxic: Handle with caution", "May cause birth defects", etc

Special precautions for disposal of unused medicinal products or waste materials derived from such medicinal products, if appropriate	The statement(s) should reflect special precautions recommended in section 6.6 or 12 of the SmPC E.g. radiopharmaceuticals, cytostatic
Information in braille	To be completed nationally
Unique identifier	2D barcode
Unique identifier – human readable data	• PC: {number} [product code] • SN: {number} [serial number] • NN: {number} [national reimbursement number or other national number identifying the medicinal product]

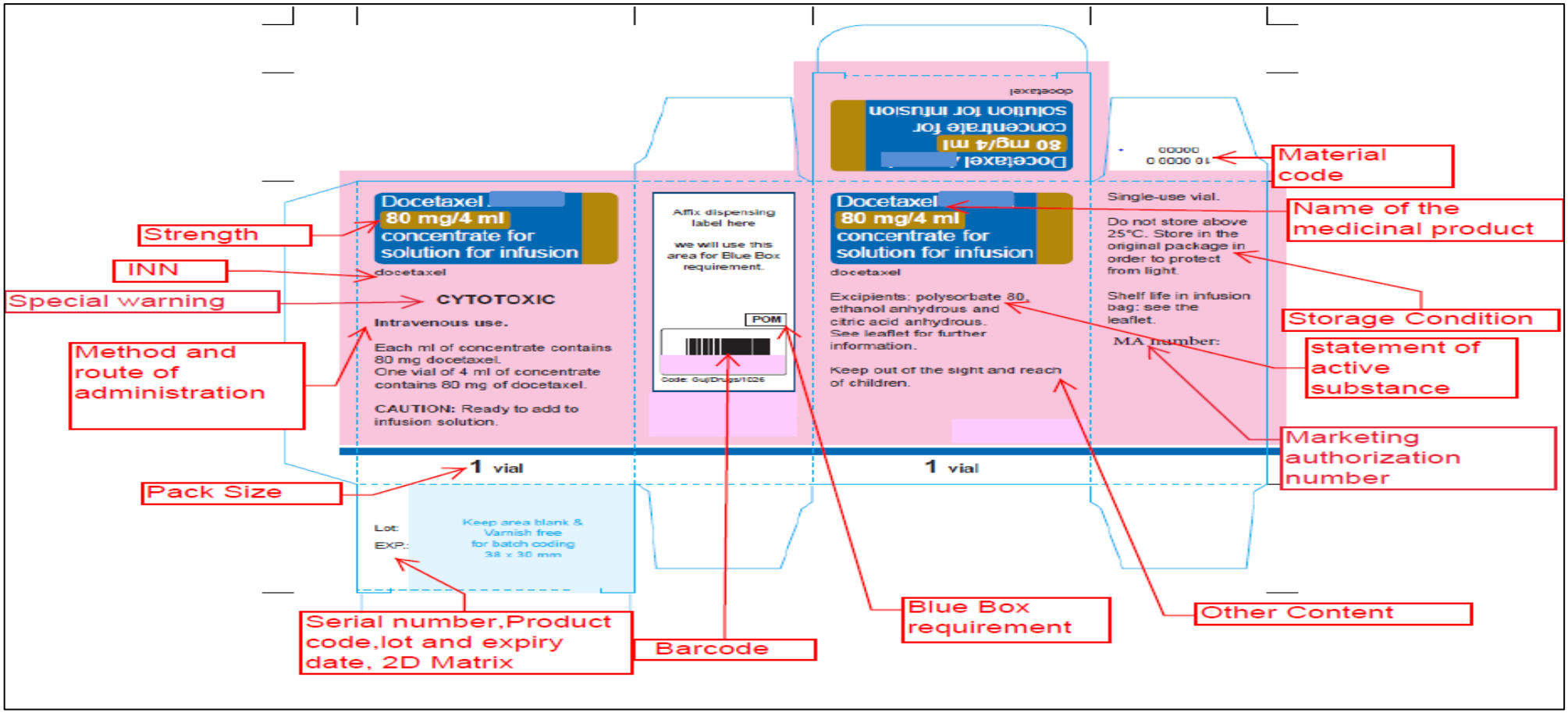


Figure 3 Components of label Mock-ups (Injectable)

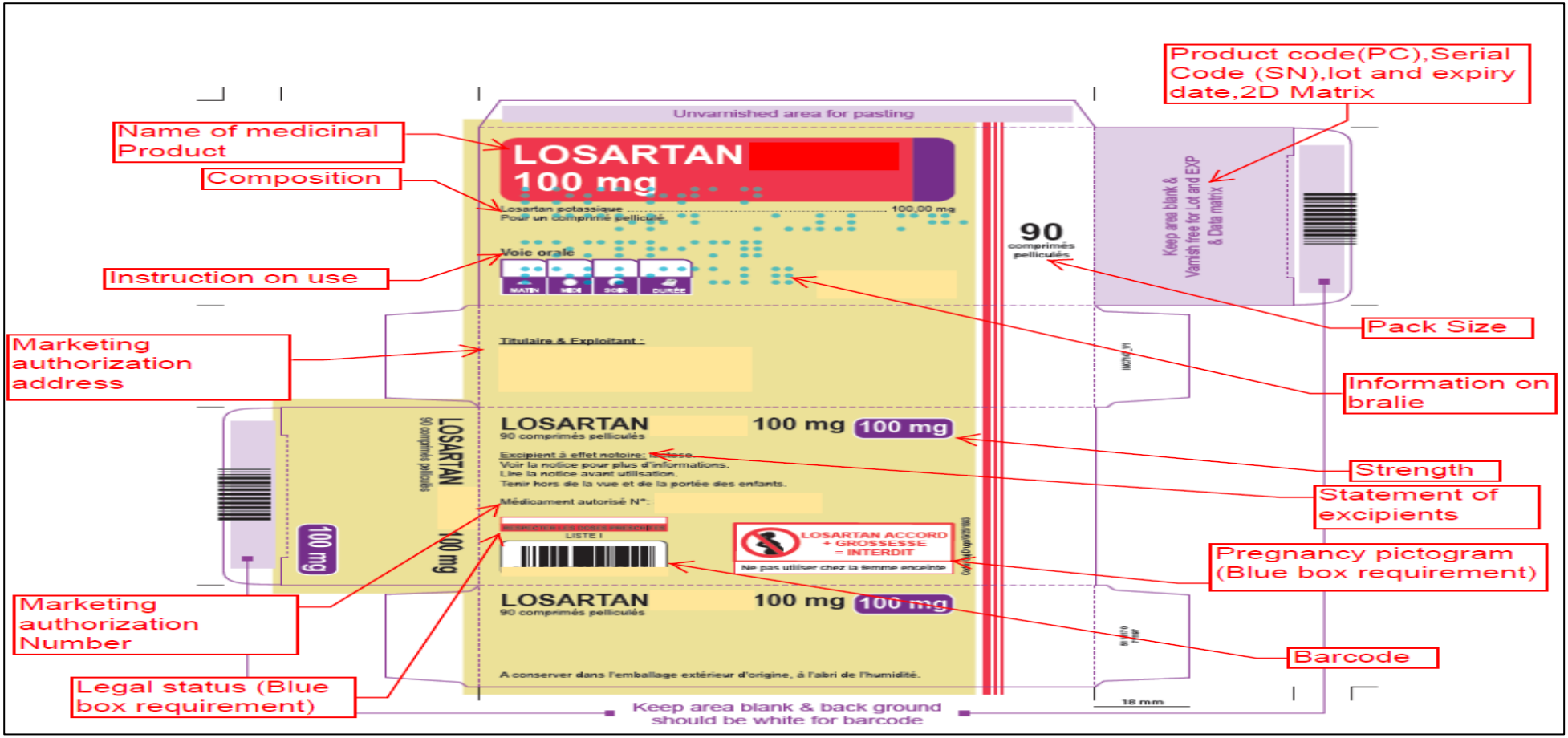


Figure 4 Components of label Mock-ups:(Solid oral dosage)

1.5 Packaging materials with respect to different dosage forms:

A. Solid oral dosage form
B. Injectable

Solid Dosage Forms:

- **Temper Resistance Packaging**

1. Strip package
2. Blister package
3. Bubble pack
4. Film wrappers
5. Shrink seal and bands
6. Sealed tubes
7. Foil paper or plastic pouches
8. Bottle seals
9. Tape seals

Blister package: By heat mellowing a sheet of thermoplastic tar and vacuum drawing the softed sheet of plastic in to shaped shape framed the rankle bundle.[4]

Blister foil contains following information: [13]

- ✓ Name of the medicinal product
- ✓ Name of the marketing authorisation holder
- ✓ Expiry date
- ✓ Batch Number
- ✓ Other

There are two types of blister pack:

1. Plain Blister Pack
2. Cross Perforated Pack

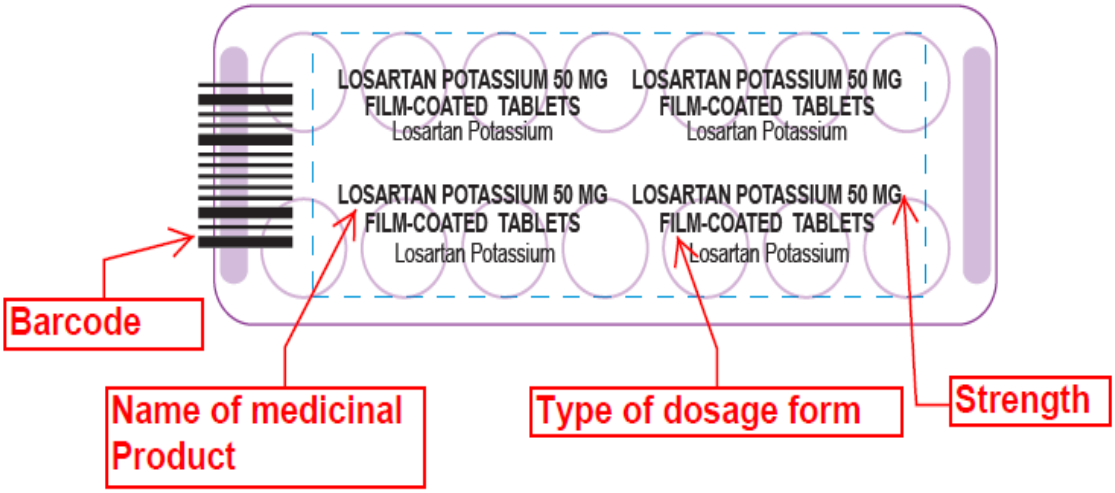


Figure 5 Plain Blister pack (Solid oral)

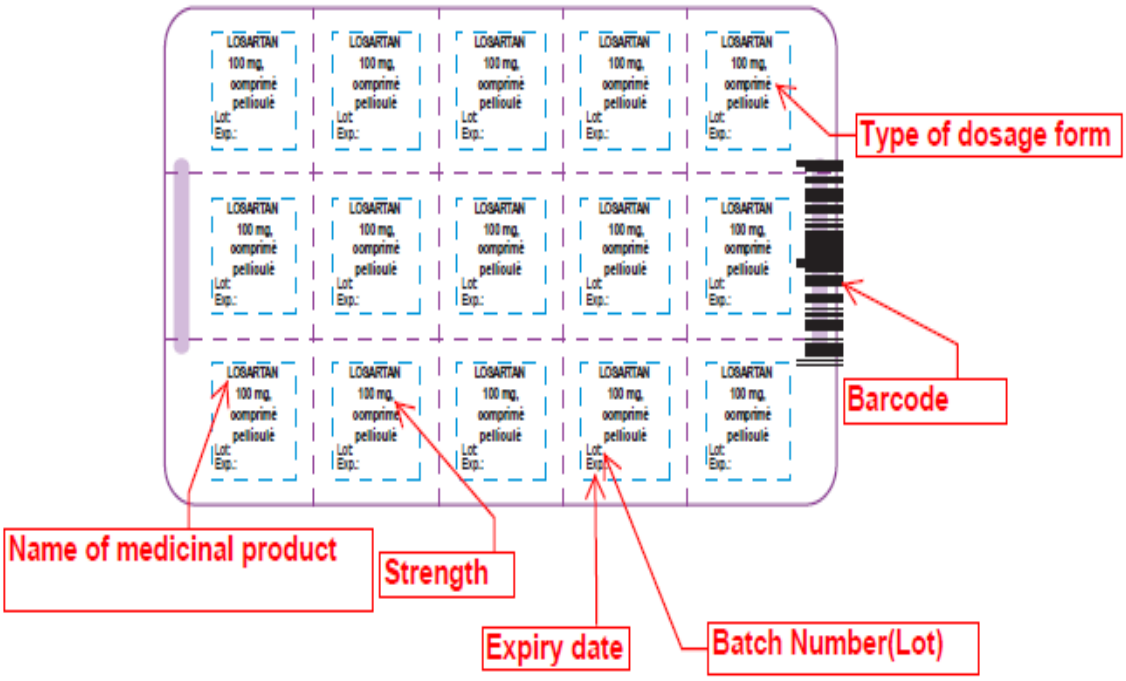


Figure 6 Cross Perforated Pack (Solid Oral)

Injectable

A. Breakable caps

B. FFS Ampule

Vial label contains following information:

- ✓ Name of the medicinal product and route of administration
- ✓ Method of administration
- ✓ Expiry date
- ✓ Batch number
- ✓ Contents by weight by volume, by unit
- ✓ Other

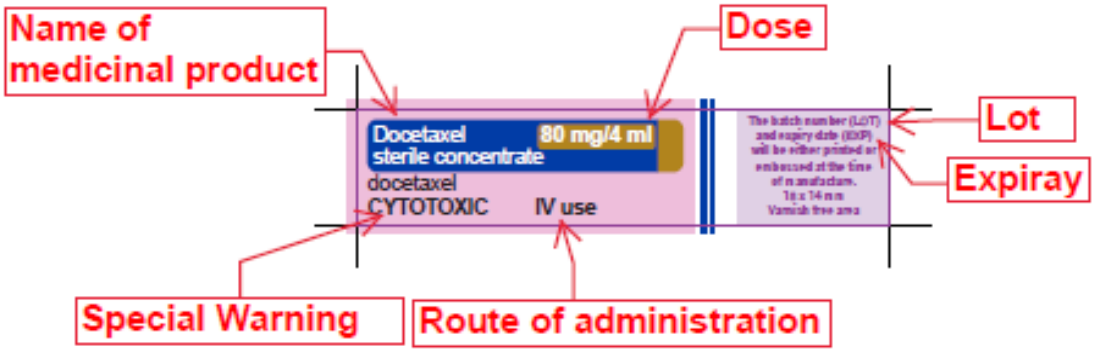


Figure 7 Vial pack (Injectable)

Chapter 2

Aim & Objectives of dissertation work

Aim:

Aim of present work is Regulatory Recruitments and Current Challenges for Labeling and Packaging for medicinal Products in Europe Region.

Objective:

- ✓ To Study Regulatory Requirements for Packaging and labeling for medicinal products in Europe Region.
- ✓ To Study Current challenges related to labeling and packaging in Europe Region.
- ✓ To Study the Cases regarding the variation filing accordance with their Marketing authorization procedures in Europe.

Chapter 3

Literature review

- Community code regarding to medicinal products for human Use (Directive 2004/27/EC) (31st March 2004) Describes regulatory Requirement for labeling and packaging, also provides the detail information about Summary of Product Characteristics (SmPC) and package leaflet.[14]
- Packaging 'blue- box' requirements and other information on labeling/package leaflet for products authorised via national, mutual recognition, decentralised or centralised procedures (2018) This article provides the Additional country specific information for labeling/ packaging and identification for medicinal products in Europe with in 32 different countries.[15]
- Guidelines on the details of the various categories of variations (2013/C 223/01) this guideline highlighted details of the classification of variations into the following categories of the Variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II.[16]
- Procedures for marketing authorisation (Volume 2A) (June 2018) This Document have covered the types of Marketing Authorization Procedure like Centralised procedure, National procedure, Mutual recognition procedure, Decentralised procedure with their timelines in Europe.[17]
- Guide to Labels and Leaflets of Human Medicines (May2016) The guidance discussed the information on the labels and package leaflets of medicinal products for human use, authorised nationally, through mutual-recognition or through the decentralised procedure. The guidance does not apply to medicinal products authorised through the centralised procedure
- Best practice guidance on the labeling and packaging of medicines (November 2015) These guidance document suggests the design of labeling and packaging components should confirm that the sections are taken into account previous to submission to the Medicines and Healthcare Products Regulatory Agency as any deviations from this guidance may need to be validate where these effect on patient safety. [18]

- Directive 2011/62/EU Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products (8 June 2011) This document describes the falsification of medicinal products is a global problem, requiring effective and enhanced international coordination and cooperation in order to ensure that anti-falsification strategies are more effective, in particular as regards sale of such products via the Internet.[19]
- Guideline on Nordic packages (February 2015) The guidance highlighted the information on the labels and package leaflets of medicinal products for human use in NORDIC Countries (Norway, Finland, Sweden, Denmark, Iceland)
- Checking process of mock-ups and specimens of outer/immediate labeling and package leaflets of human medicinal products in the centralised procedure (August 2014) This guidance documents proposed the detail information about the Labeling and package leaflet requirements, Principles applied to the checking of mock-ups and specimens, the mock-up and specimen checking process, Renewals, Transfer of MAH.[6]
- Recommendations for the implementation of the exemptions to the labeling and package leaflet obligations in the centralised procedure (November 2016) It describes the Principles agreed for granting exemptions to the labeling and package leaflet obligations in the centralised procedure, Orphan medicinal products, generic/hybrid products, Medicinal products not intended to be delivered directly to patients or severe problems in the availability of the medicinal product.[5]
- Directive(2001-83-EC) Article 54 It describes the Name of medicinal Product, dosage form, a list of excipients, method of administration, special warning of medicinal products, storage condition, expire date, name and address of marketing authorization holder and the manufacturers batch number. [20]
- Directive(2001-83-EC) Article 54(a) It describes the name of medicinal Product, its strength, pharmaceutical form and if it is intended for children, adults and babies then it should be in three active substances and the INN (International non-proprietary name).[20]

- Directive(2001-83-EC) Article 55 This article provides the Information on name of the holder of the authorization for placing the product on the market, the expiry date, the batch number.[20]
- Directive(2001-83-EC) Article 56 It needs that the to be involved in the labeling shall be simply, readable, clearly, understandable and indelible.[20]
- Directive(2001-83-EC) Article 56(a) The name of the medicinal product, as mentioned to in Article 54, point (a) must also be stated in Braille format on the packaging. The marketing authorisation holder shall provide that the package information leaflet is made available on request from patients' organisations in formats proper for the blind and partially-sighted.[20]
- Directive(2001-83-EC) Article 57 This article describes the price of the medicinal product, the reimbursement conditions of social security organizations, and the legal status for supply to the patient, in agreement with Title VI (Classification of medicinal products), detection and authenticity.[20]
- Directive(2001-83-EC) Article 58 It allows for the oversight of a package leaflet where all the needs information can be directly taken on the packaging.[20]
- Directive(2001-83-EC) Article 59 This article shall include, for the identification of the medicinal product, the therapeutic indications, description of the adverse reactions, the date on which the package leaflet was last reviewed.[20]
- Directive(2001-83-EC) Article 62 The outer packaging and the package leaflet may involve symbols or pictograms designed to explain certain information and other information compatible with the summary of the product characteristics which is useful for the patient, to the rejected of any element of a promotional nature.[20]
- Directive(2001-83-EC) Article 63 The Package leaflet must be clear, easily understandable and written. The first subparagraph shall not protect these particulars from being indicated in some languages, provided that the same particulars appear in all the languages used. In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community.[20]

- Guideline on QRD for Smpc, labeling, Package leaflet (Version 10, 02/2016) This Guidance provides the detailed information and templets about different sections of summary of product characteristics, Patient information leaflet and different components of label, Blister for medicinal products.[21]

Chapter 4

Regulatory Framework in Europe for packaging and labeling

4.1 Marketing authorization procedure:

Prior to marketing a medicinal product in the EU, a marketing authorisation (product licence) is must. A submission of application to obtain the marketing authorisation (product licence) within the frame of guidance defined by health agencies of EU is called as MA application. Selection of appropriate gateway/channel for submission of MA application is defined as procedure.[22]

There are four types of the Marketing Authorization procedures:

I. National procedure (one-member state only)

II. Mutual Recognition Procedure (MRP)

III. Centralized Procedure (CP)

IV. Decentralized Procedure (DCP)/Repeat wave procedure.

I. National Procedure:

Each European Union Member State has its particular process for the authorization of medicines that fall external the choice of the centralized procedure. Candidates must submit an application to the competent authority of the Member State. Timeline for national procedure is not fixed it varies from agency to agency.[23]

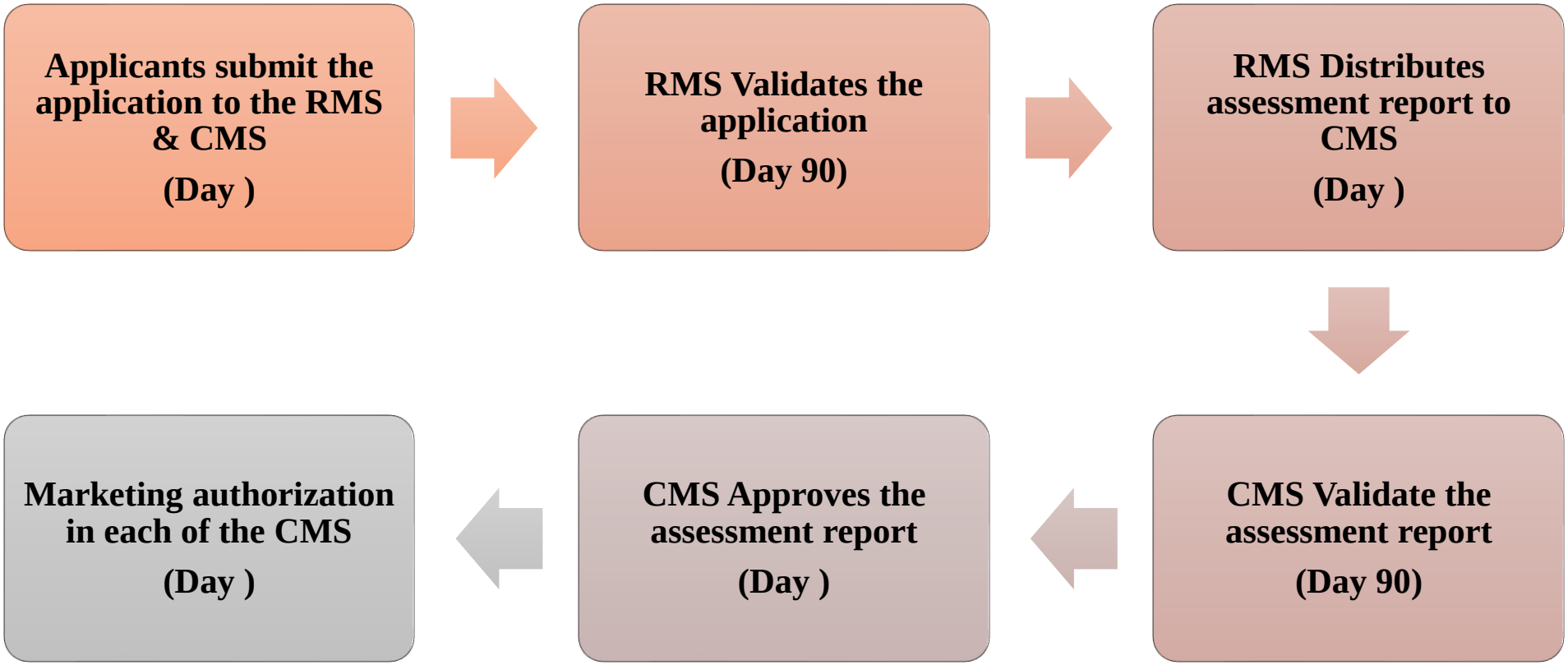


Figure 8 Mutual Recognition Procedure

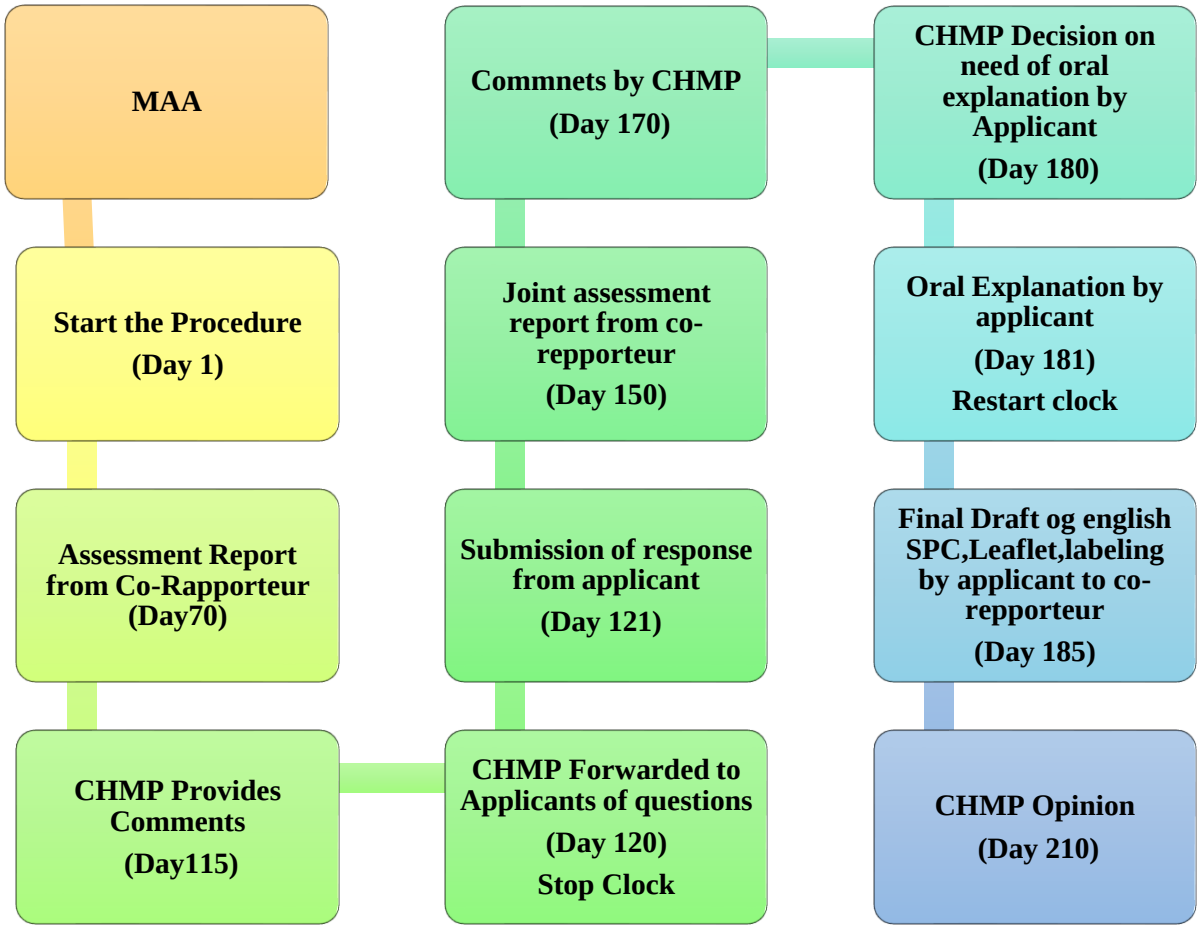


Figure 9 Figure 9Centralized Procedure

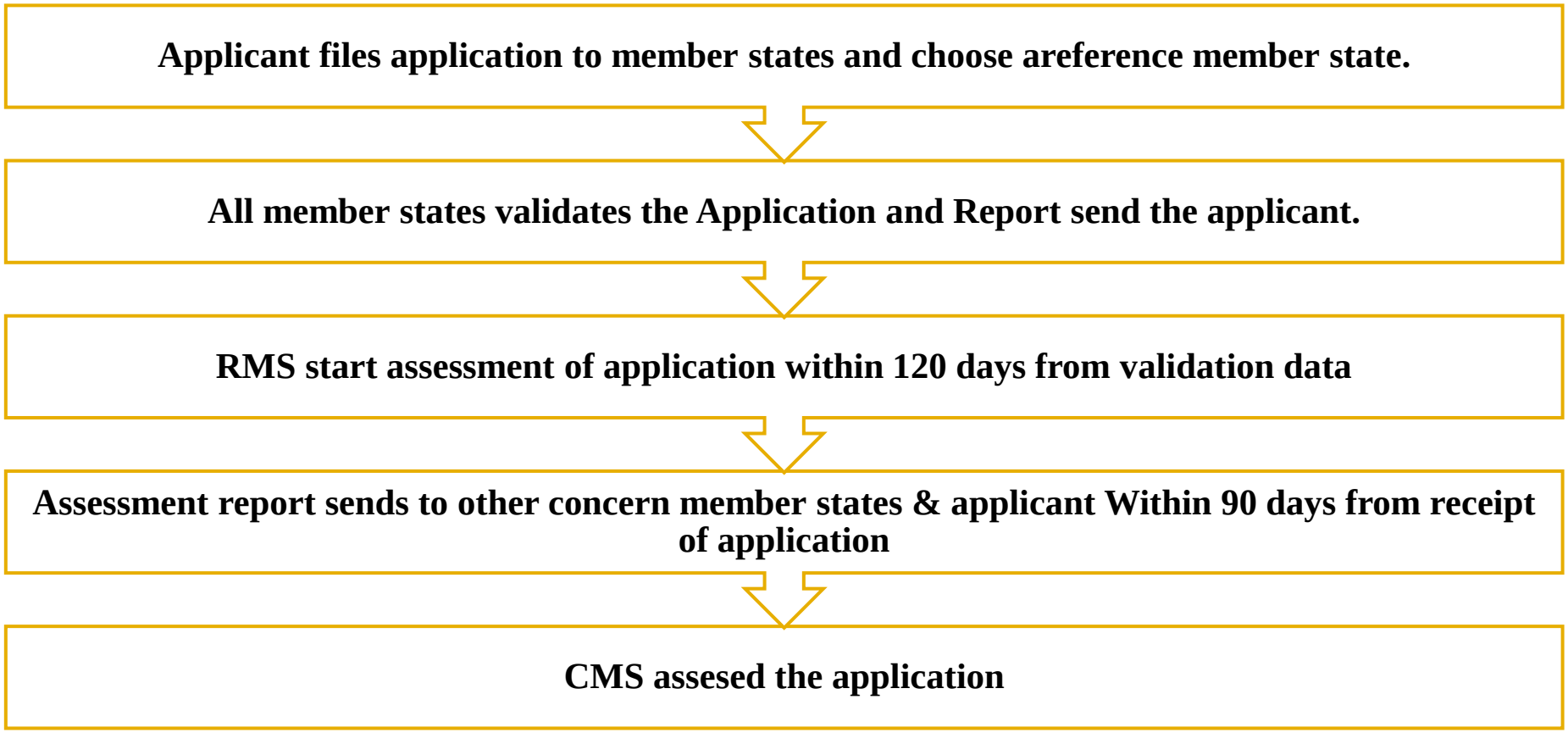


Figure 10 Decentralized Procedure

4.2. Variation:

4.2.1 Definition:

Variation can be characterized as any Modification to an approved licensed product to deal with the Quality, Safety and Potency of the medicinal product. The main purpose of the variations regulations are to build a simple, clearer and more under stable legal framework for the conduct of variations to marketing authorization of medicinal products, while protect a high level of protection of public and animal health.[24] MAH can proceed for any post approval change implementation by filling variation to the agency. This approach can be applicable for all categories of application such as Centralized procedure (CP), National Procedure (NP), Decentralized Procedure (DCP) and Mutual recognition procedure (MRP)[24]

Variation changes are classified in to four types such as

- Administrative
- Quality
- Safety and efficacy
- Pharmacovigilance

Variations can be classified into the following categories as defined in Article 2 of the variation's regulation:

I. Minor variations of Type IA,
II. Minor variations of Type IB
III. Major variations of Type II

1.Type IA variations:

Minor variations have only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation ("Do and Tell" procedure).

Minor variation is categorized into two:

Type IA variations requiring immediate notification ('IAIN')
The Classification Guideline specifies which Type IA variations must be notified (submitted) immediately to the National Competent Authorities/European Medicines Agency ('the Agency') following implementation, in order to ensure the continuous supervision of the medicinal product. [25]

II. Type IA variations NOT requiring immediate notification ('IA')

Variations which do not require immediate notification may be submitted by the marketing authorization holder (MAH) within 12 months after implementation. The agency will review the type IA/IAIN Variation within 30 calendar days following repeat. The agency will check the correctness of the application form, the presentence of the required documentation and compliance with the required conditions, in accordance with the Classification guideline.

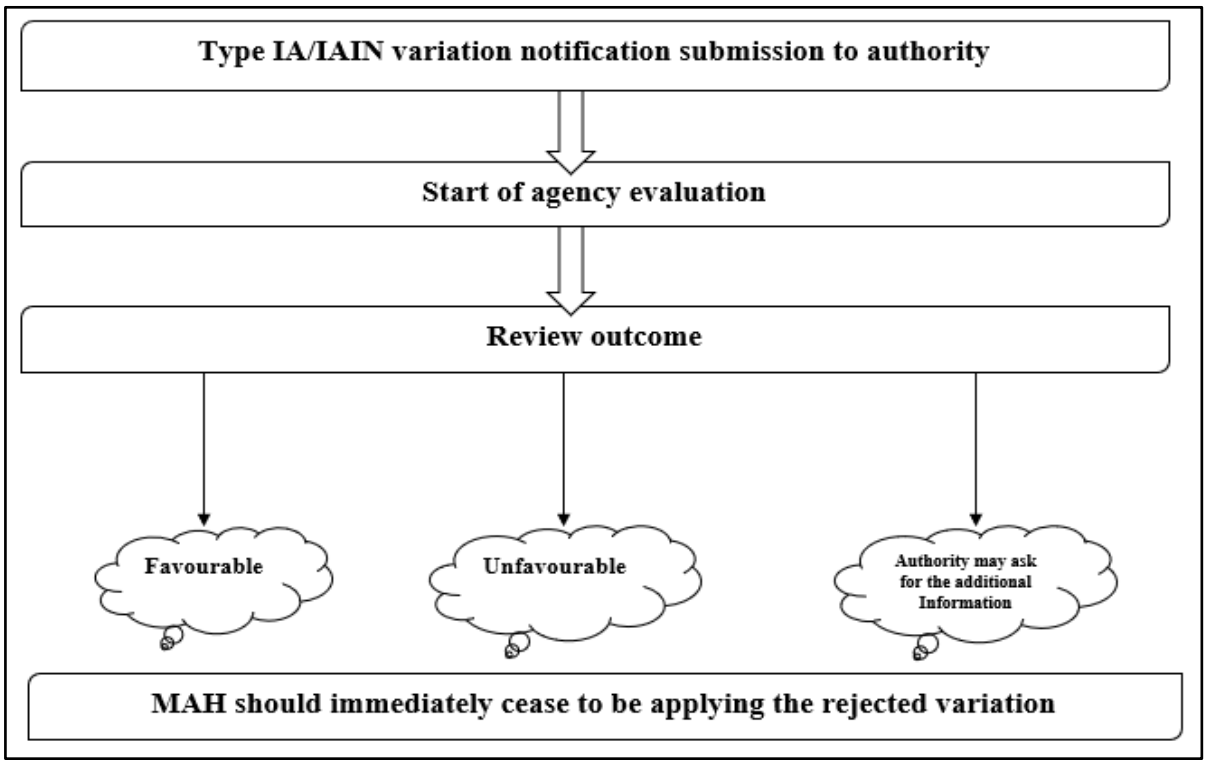


Figure 11 Type IA variations

Such a Common type of Variation:

Type IA_{IN} variations

- Change in imprints, bossings, or other markings, shape, dimensions of the finished product.
- Addition of primary & secondary packaging sites, control or batch release sites.
- Addition of pack size within the range of the currently approved pack size.
- Reduction of shelf-life
- API source addition (CEP source)

Type IA variations

- Batch size addition up to ten-fold.
- Updated CEP from an already approved source
- Deletion of packaging supplier in injectable products.

2. Type IB Variation:

Defines a minor variation of Type IB as a variation which is neither a Type IA variation nor a Type II variation nor an Extension. Such minor variations must be notified to the National Competent Authority/European Medicines Agency ('the Agency') by the Marketing Authorization Holder (MAH) before implementation. However, the MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the National Competent Authority/the Agency before implementing the change ("Tell, Wait and Do" procedure). [23]

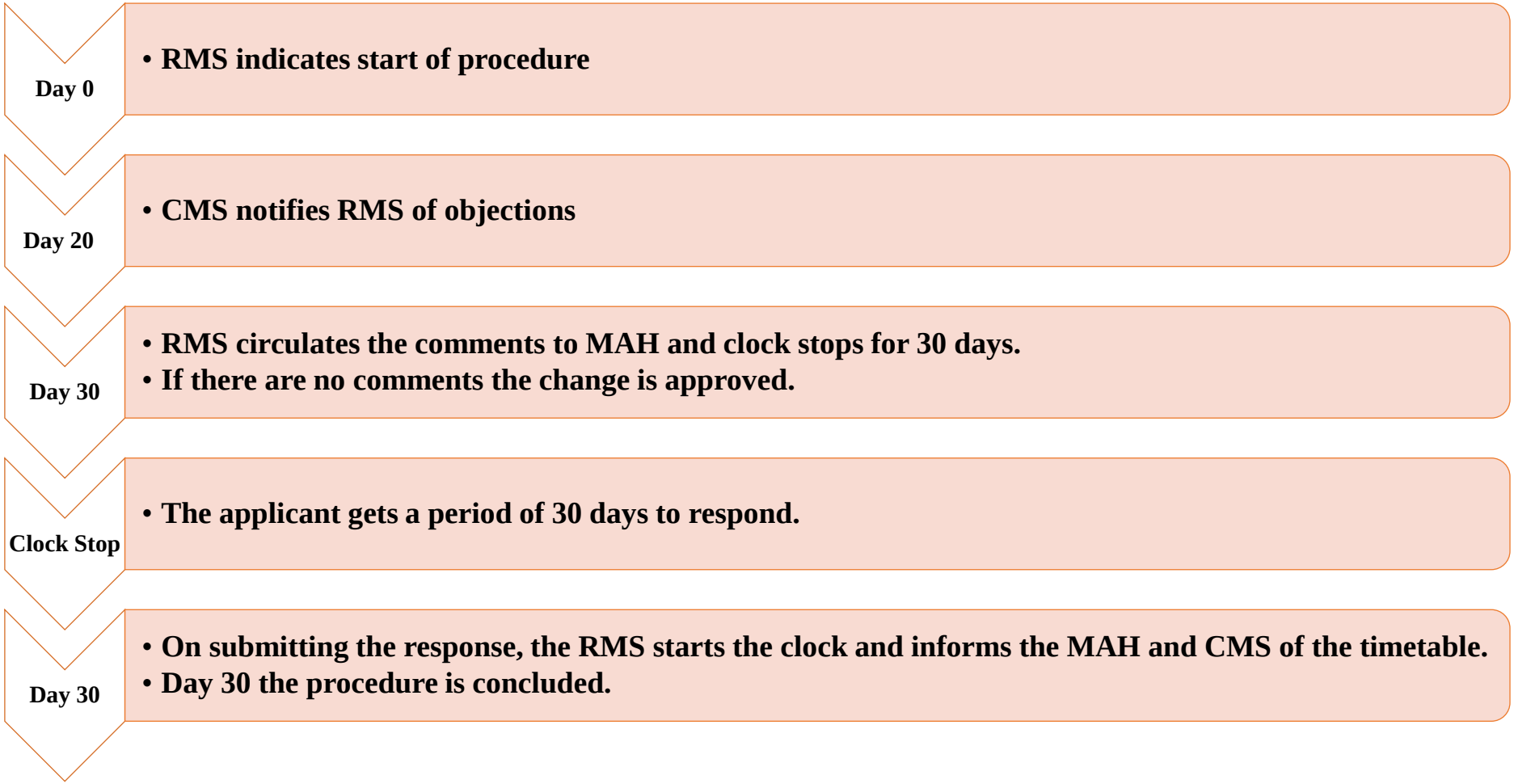


Figure 12 Type 1B Variation

Type IB variations

- Batch size with more than tenfold increase in IR Tablets
- Extension of shelf-life based on stability data.
- Addition of manufacturing site (site transfer).
- Addition of primary packaging site for parenteral products.
- Deletion of therapeutic indication

3.Type II Variation:

- A type II variation is a major variation which is not an extension, and which may have a significant impact on the quality safety or efficacy of a medicinal products.
- Type II Variation require prior approval before implementation.
- Reduced (30days) procedure for type II Variations
- 60-days procedure for Type II Variations
- 90-days procedure for Type II Variations

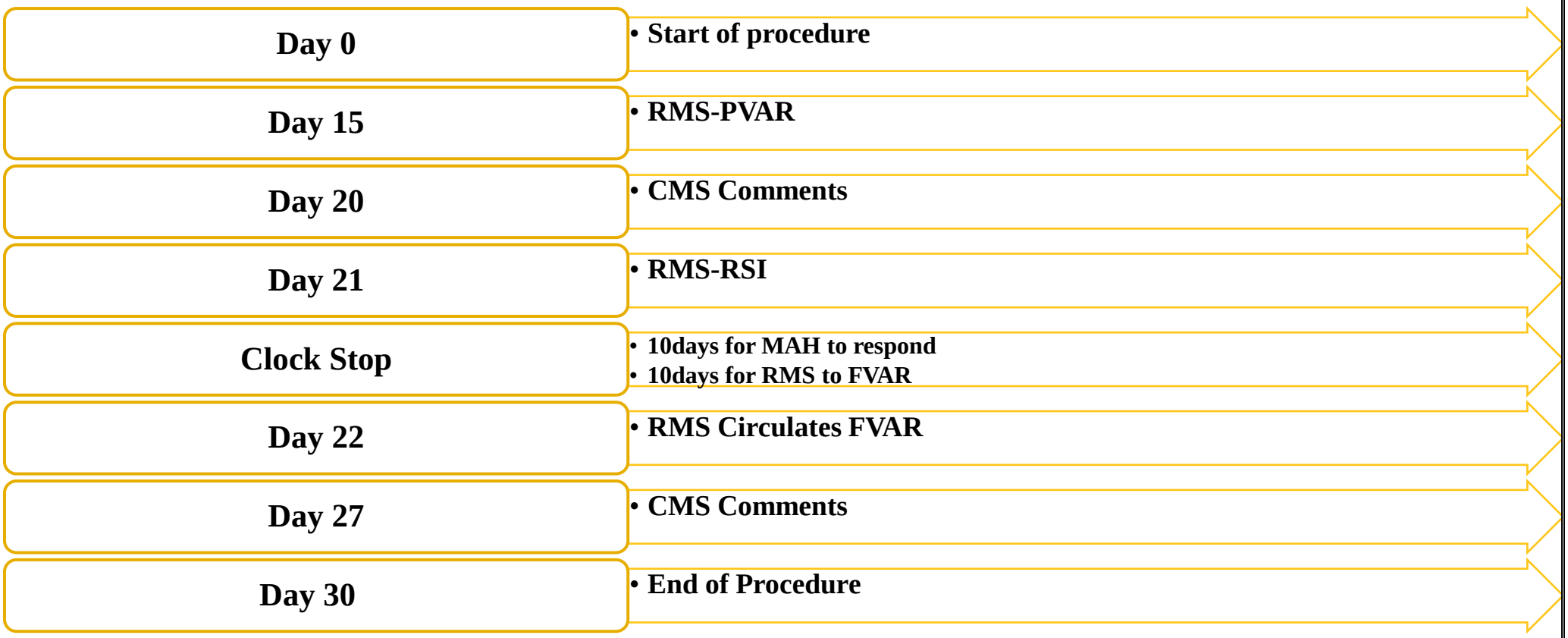


Figure 13 Reduced (30days) procedure for type II Variations

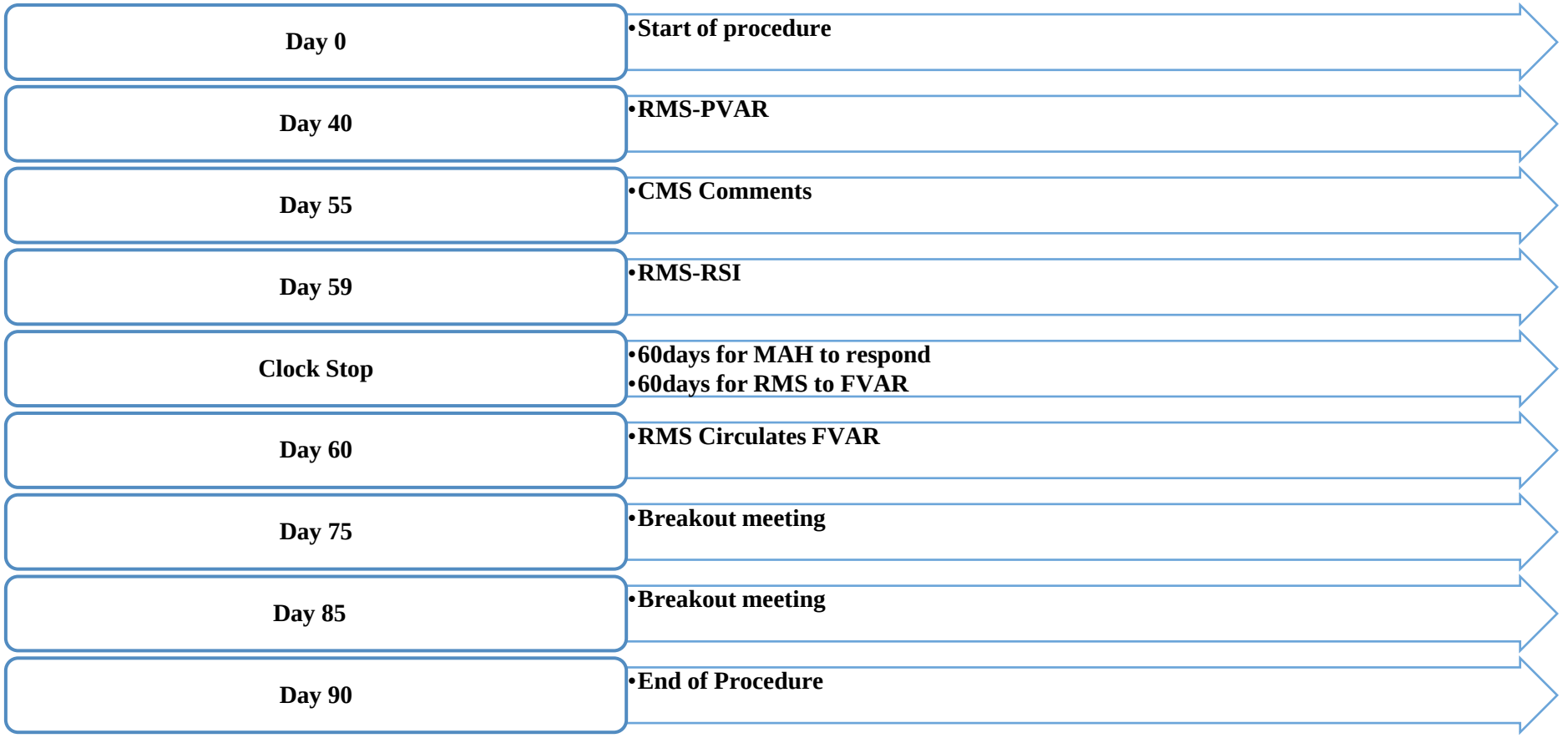


Figure 14 60 Day Procedure for Type II Variation

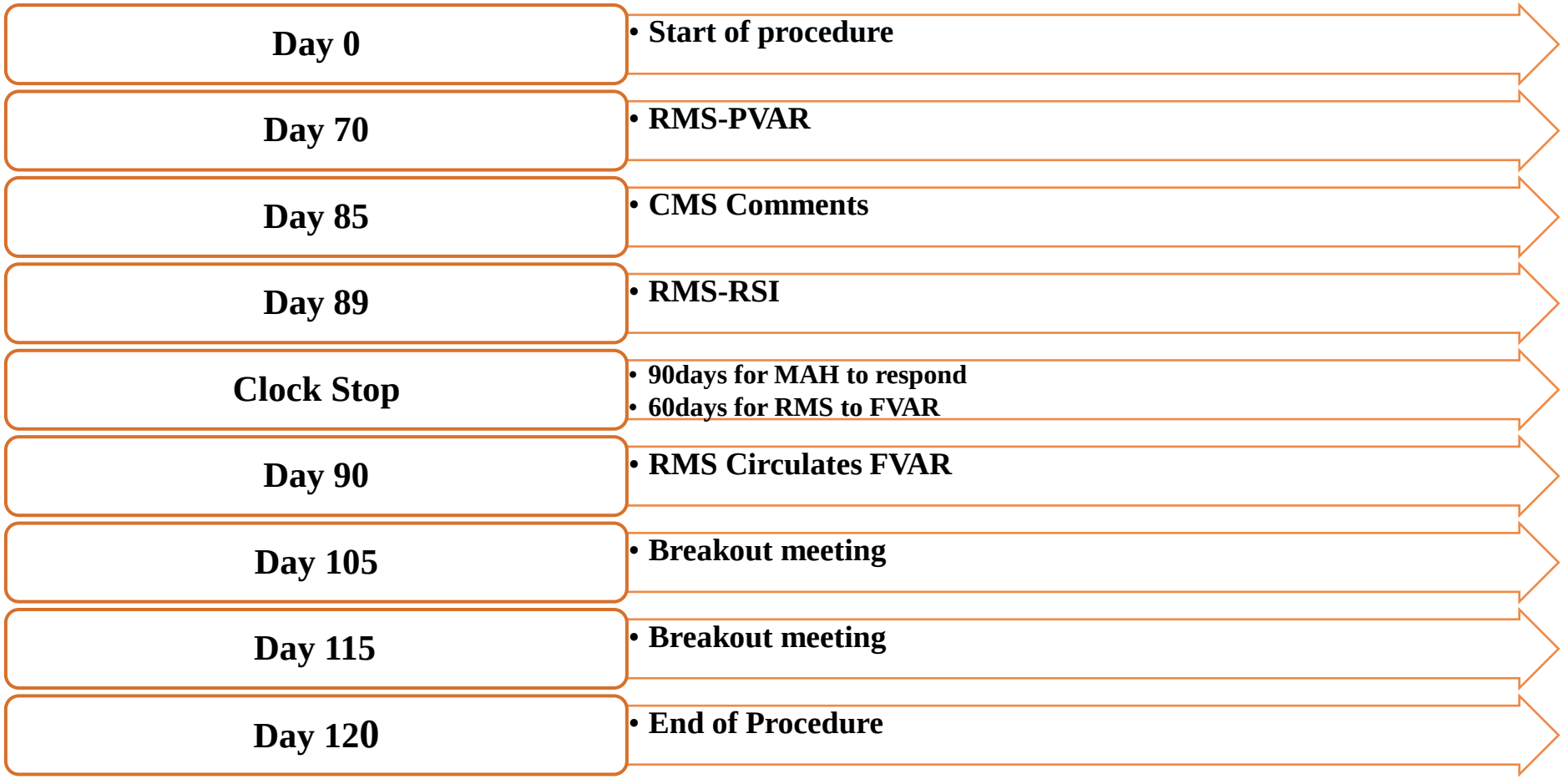


Figure 15 90- Day Procedure for Type II Variation:

Type II variations

- Addition of a new therapeutic indication or modification of an approved one.
- Introduction of a new pharmacovigilance system.
- Extension of retest period based on extrapolation not complying to the ICH.
- Change in coating weight in gastro- resistant dosage forms.

Grouping variation:

Several Type IA and/or IA_{IN} affecting several medicinal products from the same MAH provided that those variations are the same for all medicinal products and are submitted to the same relevant authority.

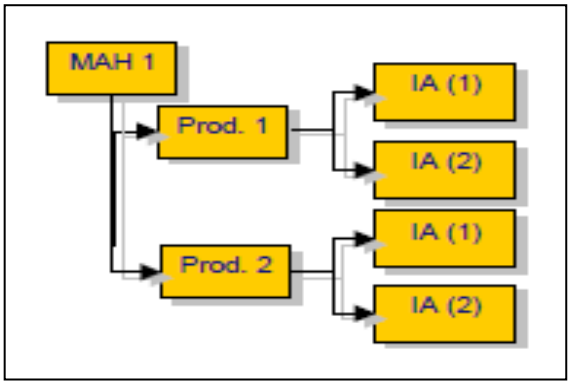


Figure 16 Grouping variation

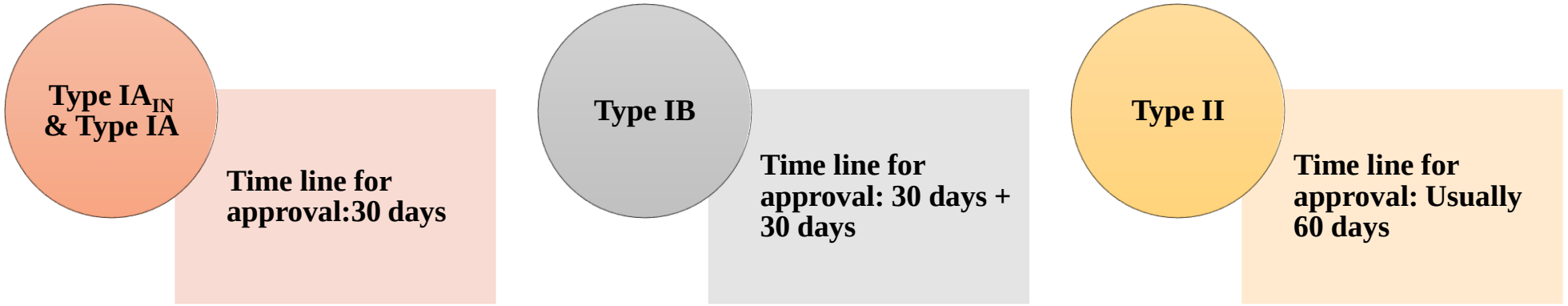


Figure 17 Time lines involved in variations

4.2.1 Case study of variation filing for centralised products:

Case study is the example of product approved centrally in EU region. There are so many updates in labeling rather minor or major, that changes should be updated with in timeline suggested by EU authority and according to guidelines. Here, example is about Type IB variation filing after marketing authorization received in Europe. After receiving any update, it should be filed to authority according to its type (type IA & IB, Type II) and timeline. There was a update in section 4.4(Special warning and precaution for use) and 4.8(Undesirable side effects) of SmPC in order to add new adverse reaction related to respiratory in MAH's safety database, which includes the interstitial pneumonitis, interstitial lung disease and pulmonary fibrosis as a new adverse reaction. The Package leaflet should be updated accordingly. Furthermore, one additional change also included as minor change a condition of Marketing authorization is added Annexure II. Finally, the annexure II is being thought in line with the latest Quality Review Document template version 8.3.

Table 4 Case study of variation filing for centralised products

SR. NO	PRODUCT	MA	TYPE	DATE SENT	DETAILS OF APPLICATION
1	XXX product	CP	IB	25-04-2013	Update section 4.4 and 4.8 of the SmPC in order to add a warning related to respiratory disorders and include interstitial pneumonitis, interstitial lung disease and pulmonary fibrosis as a new adverse reaction observed in the post-marketing setting following a relevant cumulative review of the MAH's safety database. The package leaflet in updated according. Furthermore, and as a minor change, a condition to the MA is added in Annex II in line with respective change for Docetaxel Winthrop at the time of its MA renewal (EMEA/H/C/000808/R/21, EC Decision date 8 March 2012). Finally, the Annex II is being brought in line with the latest QRD template version 8.3

- **Identification of variation type:** Based on the changes made in Smpc and PIL section, came to know that it is type IB variation.

- **Variation Filing:** The product XXX approved through CP procedure (26 countries in EU). In case of CP, needs to follow deadline given by authority to submit variation. MAH can plan variation submission accordingly.

- **Variation text preparation:**
  - Text submitted to authority on day 0.
  - Updated Text submitted to authority on 25-04-2013.
  - Then, query comments come from the authority within 30 days. If no comments then authority gives variation approval. They provide us approved text and variation approval letter.
  - Variation procedure has been closed. Final approval received on 14-06-2013.

- **Update PIL/ Label:** Within time line of 180 days, PIL needs to be updated.

4.3 Labeling and Packaging guidelines as per EMA:

Table 5 Labeling and Packaging guidelines as per EMA

Implementation year	Specific Guideline
August 2014	Checking process of mock-ups and specimens of outer/immediate labeling and package leaflets of human medicinal products in the centralised procedure
February 2015	Guideline on NORDIC Package
Version 10,02/2016	QRD (Quality review of documents) Templates for Summary of Product Characteristics, Package information leaflet (PIL).
March 2018	Packaging 'blue-box' requirements and additional information on labeling/package leaflet

4.3.1 Labeling and package leaflet requirements:

- Title V of Directive 2004/27/EC defines the to be included on the outer/immediate labeling and in the package leaflet.
- The safe and correct use of all medicines depends (amongst others) on users reading the labeling and packaging accurately and being able to understand and act on the information presented.
- The primary purpose of labeling and packaging should, therefore, be the clear unambiguous identification of the medicine and the conditions for its safe use.
- The legal provisions within Article 62 of Directive 2004/27/EC permit the use of images, pictograms and other graphics to aid comprehension of the information, but these exclude any element of a promotional nature.
- As stated in Article 61(1) of Directive 2004/27/EC one or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorising marketing when the marketing authorisation is requested.
- The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.
- In Article 57 of Directive 2004/27/EC, a Member State may ask for additional information to appear on the outer packaging (in a ‘blue box’) concerning identification and authenticity of the product, the legal category for supply and price/reimbursement
- Article 54 of Directive 2001/83/EC requires that the outer packaging must also include a space for the prescribed dose to be indicate

4.3.2 According to directive 2004/24/EC: The mock-up and specimen checking process:

New marketing authorisation applications and extensions applications

Table 6 Mock-ups and specimen Process

Day 120	The mock-ups will subsequently be reviewed in detail by the EMA in parallel to the scientific assessment, and any mock-up comments will be sent together with the PIQ comments on the EN product information by day 120
Day 155	In case of comments or in case the applicant changes the overall design, revised mock-ups should be submitted as part of the answers to the list of questions at day 121. Comments on the (revised) mock-ups will be sent together with the QRD comments (day 155).
Day 165	In case of a QRD sub-group meeting at day 165, EMA could take the opportunity to also discuss the draft mock-ups to complement the product information review.
Day 181	**At day 181, EMA will make sure that any outstanding comments made at Day 155 are solved prior to the opinion**

4.3.4 Submission of Mock-ups and specimens:

- Specimens can be sent to the EMA before the final Commission Decision is granted.
- Applicants should allow sufficient time for the review process of specimens, including any subsequent changes which may exceptionally have to be introduced to the specimens before launch.[6]

Table 7 Mock-up and Specimen Renewals

Mock-ups	**Specimens**
No mock-ups are required at the time of renewal of the marketing authorisation	• At renewal, EMA will perform a new check of the specimens across all marketed product presentations. • As such the EMA will receive and check at least one example specimen of the whole range of marketed product presentations after 5 years, in one submission.

Table 8 Transfer of MAH

Mock-ups	Specimens
• According to point 6 in the Annex to Regulation (EC) No 2141/96 on transfers of centrally authorised medicinal products, mock-ups are to be included in the transfer application. • EMA will review the mock-ups in parallel to the handling of the transfer procedure. • EMA will discuss the best and feasible corrective action with the MAH, taking into account the nature and amount of issues identified. EMA will endeavour to provide such feedback as soon as possible and taking into consideration the production plan of the medicinal product, as applicable.	• Only in case the transfer has an impact on the overall design, relevant revised example specimens should be provided to the EMA by the new MAH, in line with the requirements for new applications and extensions. • If the transfer only affects the MAH details on the packaging and package leaflet without any impact on overall design, specimens are not required

4.4 Requirements as per EMA and as per country specific "blue box requirement"

For EU region, **Identification and authentication of medicine is major**, as there are many countries and their local languages. So that submission of SmPC, patient information leaflet (PIL), outer and immediate label is very important part of dossier. Directive 2004/83/EC by EMA, Article 57 and 62 describes the **Additional information on labeling/package leaflet that required nationally by member states. "Blue box requirement"** published by **Cmdh**, that explains **additional country specific requirements for labeling such as the price, reimbursement, legal status, identification and authenticity, symbols and pictograms.** These requirements apply to products authorised via a different procedure like National, Mutual Recognition or Decentralised Procedure. [15]

Table 9 Blue box requirement for AT-BE-BG-HR15

Section	Austria (AT)	Belgium (BE)	Bulgaria (BG)	Croatia (HR)
Legal Status	For medicinal products subject to medical prescription. ➢ **If the supply is not restricted to pharmacies, this has to be declared appropriately: available only on prescription and only in pharmacies** ➢ For medicinal products not subject to medical prescription. If the supply is not restricted to pharmacies, this has to be declared appropriately-**available only in pharmacies** ➢ Radiopharmaceuticals: available **only on prescription for authorised personnel** ➢ For vaccines and blood derivates official batch release is required. : **Batch released by OMCL** ➢ For vaccines and blood derivatives that usually require official batch release, but have been granted an exemption from this requirement: **Batch marketable.**	The legal status is required on the label: • **In the case of medicinal products that are subject to medical prescription only** ➢ **Medication on medical prescription** ➢ **Prescription** ➢ **On medical prescription** ➢ **Medication on prescription** • **In the case of medicinal products that are not subject to medical prescription** ➢ **Free delivery** ➢ **Free donation** The major narcotic or psychotropic drugs, subject to special medical prescription, require the following labeling: • A number/code assigned by the Minister of Public Health	➢ For pack sizes not intended to be delivered to a single patient but to be used in a hospital environment for several patients /treatment courses: **Hospital pack** ➢ For medicinal products on special medical prescription containing narcotic substances: **Subject to special medical prescription** ➢ For medicinal products on special medical prescription containing psychotropic substances: **Subject to special medical prescription** ➢ For medicinal products on restricted medical prescription for hospital use only: **For hospital use**	The legal status is required on the labeling: ➢ For medicinal products subject to medical prescription: **Medicinal product subject to medical prescription.** ➢ For medicinal products not subject to medical prescription: **Medicinal product not subject to medical prescription**

Section	Austria (AT)	Belgium (BE)	Bulgaria (BG)	Croatia (HR)
Identification and Authenticity	• The EAN code (bar code) is accepted, but not required on the labeling • The marketing authorisation number is required on the labeling (Z.Nr).	➢ **The EAN code (bar code) is accepted but not required on the labeling**. ➢ For reimbursed medicinal products (except containers with oxygen gas) a unique numerical bar code, printed in black with a white background, must appear on the labeling. ➢ An irremovable sticker may be used as well. The unique numerical bar code is required only on products, which are not restricted to hospital use.	The EAN code (bar code) is accepted but not required on the labeling	The EAN code (bar code) is accepted but not required on the labeling.
Symbols and Pictograms	 Caution: This medicine might compromise reactivity and ability to drive."  Radiopharmaceuticals  Recycling symbols are accepted on the labeling, but not required	 external application	➢ Symbols for separate disposal and recycling in compliance with the Law on Waste Management are required on the outer packaging. ➢ **The labeling may include symbols or pictograms as well as other information consistent with the Summary of Product Characteristics and useful for the patient, excluding any element of advertising**	NA

Table 10 Blue box requirements for CY-EL15

Section	Cyprus (CY)	Greece (EL)
Legal Status	The legal status is accepted but not required on the labeling.	➢ Products belonging to List B must be mentioned in red letters **B, to be dispensed with special prescription for narcotics** ➢ Products belonging to the exceptions of list B must be mentioned in green letters ➢ **BΣ, to be dispensed with prescription of Law 3459/2006** ➢ Products belonging to list Γ must be mentioned in red letters **Γ, to be dispensed with special prescription for narcotics** ➢ Products belonging to the exceptions of list Γ must be mentioned in green letters ➢ **ΓΣ, to be dispensed with prescription of Law 3459/2006** ➢ Products belonging to list Δ must be mentioned in green letters **Δ, to be dispensed with prescription of Law 3459/2006**
Identification and Authenticity	The EAN code (bar code) is accepted but not required on the labeling.	All medicinal products must be identified by a safety coded sticker (authenticity sticker) on the outer package. This sticker is of a size of 27mm x 24 mm approx, it is issued by EOF (National Organisation for Medicines) and distributed free of charge to the companies. Information printed : company name, product name, pharmaceutical form, strength, packaging, as well as a product-specific number and a package-specific, unique, serial number (both numbers in both numerical and barcode form). The authenticity sticker is printed on a special paper and carries invisible thread marks as well, so that it is not copied.

Section	Cyprus (CY)	Greece (EL)
		The authenticity sticker requirements apply for all categories of pharmaceutical products, with the exception of the radiopharmaceuticals
Symbols and Pictograms	NA	NA

Table 11 Blue box requirements for CZ-PT-ES-SK15

Section	CZECH REPUBLIC(CZ)	Portugal (PT)	Spain (ES)	SLOVAK REPUBLIC(SK)
Legal Status	The legal status is accepted but not required on the labeling. ➢ For medicinal products subject to medical prescription - **Medicinal product subject to medical prescription** ➢ For medicinal products not subject to medical prescription - **Medicinal product not subject to medical prescription**.	The legal status is required on the labeling for prescription and non-prescription medicinal products. ➢ For medicinal products not subject to medical prescription - **Not subject to medical prescription** ➢ For medicinal products subject to medical prescription - **Subject to medical prescription** ➢ For medicinal products on restricted medical	These statements should be included in a visible place and using big enough font size to ensure adequate readability. The corresponding acronyms (except for 'EFG') should be included in the upper right corner of the package, between the national product number and the symbols. ➢ Medicinal products subject to medical prescription -**Medicinal products subject to medical prescription** ➢ Medicinal products to be used in the hospital -**Hospital use**	➢ **Section 14, medicinal product subject to medical prescription -Medicinal product subject to medical prescription.** ➢ **Section 14, medicinal product not subject to medical prescription-Medicinal product not subject to medical prescription.** ➢ **Section 14, medicinal product subject to special medical prescription.-Medicinal product subject to special medical**

Section	CZECH REPUBLIC(CZ)	Portugal (PT)	Spain (ES)	SLOVAK REPUBLIC(SK)
		prescription -**Restricted use** ➢ For renewed prescription medicinal products -**Medicinal product on prescription which may be renewed** ➢ For medicinal products on special medical prescription containing narcotic substances or psychotropic substances-**Subject to special medical prescription**	➢ Medicinal products for diagnosis performed in hospital - **Hospital diagnosis** ➢ Medicinal products to be used under supervision by a specialized physician -**Special medical control** ➢ Medicinal products with hospital package - **Hospital package. Not to be sold separately** ➢ Medicinal products free samples - **Free sample. Not to be sold** ➢ Generic medicinal products approved on the basis of Directive 2001/83/EC Art. 10.1 **-Generic medical product: EFG** ➢ Medicinal products to be used long term **- Long term treatment**	**prescription with skew blue stripe.** ➢ **Section 14, medicinal product subject to restricted medical prescription-Medicinal product subject to restricted medical prescription.**

Section	CZECH REPUBLIC(CZ)	Portugal (PT)	Spain (ES)	SLOVAK REPUBLIC(SK)
Identification and Authenticity	The EAN code (bar code) is required on the labeling.	A digital code, a bar code and the marketing authorisation number must appear on the label, to identify the medicinal product.	The national product number consists of a code composed of seven digits assigned by the Spanish National Competent Authority (i.e. AEMPS). The national product number or national code should be included in the upper right corner of the package, followed by the corresponding symbols and acronyms.	Identification and Authenticity The GTIN code (bar code) is required on the labeling if the medicinal product is labelled by this code.
Symbols and Pictograms	**NA**	**NA**	For medicinal products subject to medical prescription-◐ For psychotropic medicinal products in list I- IV-◐ For psychotropic medicinal products in annex II- ◑ For narcotic medicinal products-●	Symbols and Pictograms In the case of radiopharmaceuticals an international symbol for radioactivity and the amount of radioactivity should be stated.

Table 12 Blue box requirements for DE-NL-UK-IE-HU15

Section	Germany (DE)	Netherland (NL)	United Kingdom (UK)	Ireland (IE)	Hungary (HU)
Legal Status	➢ In the case of medicinal products that are not subject to medical prescription but are only available in pharmacies : **available only in pharmacies** ➢ In the case of medicinal products that are subject to medical prescription only : **available only on prescription**	➢ If supply is restricted to pharmacy, this has to be expressed in the blue box areas as **-Only pharmacy** ➢ If supply is restricted to pharmacy and chemist's (drugstore), this has to be expressed in the blue box areas as **-Only pharmacy and chemist's** ➢ If supply is restricted to pharmacy, chemist's (drugstore) and general sales, this has to be expressed in the	The legal status is required on the labeling. Labeling must include an indication of the legal status as follows: ➢ Medicines for supply only on the prescription of a medical practitioner - the letters POM in black surrounded by a box: **POM** ➢ Medicines which may be supplied without prescription only under the supervision of a registered pharmacist - the letter P in black surrounded by a box: **P** ➢ Some additional statements are	➢ The non-prescription status of certain medicinal products, containing certain active substances, must be stated. ➢ These active substances include: acyclovir, diclofenac dimethylammonium, diclofenac sodium, famotidine, flurbiprofen, hydrocortisone, hydrocortisone acetate, ibuprofen, ketoprofen, naproxen, nicotine, nicotine resonate, oxathiine and piroxicam, when contained in medicinal products specifically authorised for sale without a prescription. ➢ **The designation "POM" (for prescription-only medicines) is in common use and would be in the boxed area.**	➢ Medicinal product not subject to medical prescription- **Medicines that can be delivered without a prescription** ➢ Medicinal product subject to medical prescription **Medical prescription drug** ➢ Medicinal product subject to restricted medical prescription, intended for outpatients after a diagnosis made by a specialist or in a hospital. -**Medical prescription drug** ➢ Medicinal product subject to restricted medical prescription, requiring special supervision by a specialist throughout the treatment after a diagnosis made by a specialist or in a hospital. – **Medical prescription drug** ➢ Medicinal product subject to special medical prescription written in two copies, likely, if incorrectly

Section	Germany (DE)	Netherland (NL)	United Kingdom (UK)	Ireland (IE)	Hungary (HU)
		blue box areas as **-General sale**	required to appear by law on the labeling and/or the package leaflet for certain medicines. The requirements are set out in current UK legislation. ➢ The additional requirements affect medicines which contain the following substance: ➢ Paracetamol ➢ Applicants whose products contain this substance should refer to UK regulations for detailed requirements.		used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes. -**Medical prescription drug** ➢ Medicinal product subject to special medical prescription written in two copies, containing a substance the activity and/or adverse reactions of which, by reason of its novelty, require further investigation **-Medical prescription drug** ➢ Containing a substance classified as a narcotic or a psychotropic substance subject to special medical prescription written in two copies**. -Medical prescription drug**
Identification and Authenticity	➢ In the case of active substances manufactured by gene technological means, the active substance and the designation of the gene technologically modified microorganism or cell line.	Information regarding the identification and authenticity is accepted but not required on the labeling.	NA	The EAN code (bar code) is accepted but not required on the labeling.	The EAN code (bar code) is accepted but not required on the labeling.

Section	Germany (DE)	Netherland (NL)	United Kingdom (UK)	Ireland (IE)	Hungary (HU)
	➢ In respect of sera, particulars on the type of living organism from which the sera were obtained shall be indicated. ➢ In respect of virus vaccines, particulars of the host system which was used for the multiplication of the virus shall be indicated.	The EAN code (bar code) is accepted but not required on the labeling.			
Symbols and Pictograms	 the official pictogram in case of radiopharmaceuticals	NA	NA	NA	NA

Table 13 Blue box requirements for Nordic Countries15

Section	Denmark (DK)	Finland (FI)	Iceland (IS)	Norway (NO)	Sweden (SE)
Legal Status	no specific requirement	The legal status is accepted but not required	Section: **The legal status is required on the labeling for packages intended for dose dispensing** -For dose dispensing only	Section: **There is no requirement for the legal status to appear on the label except for packages intended for dose dispensing -** For dose dispensing only	The legal status is accepted but not required
Identification and Authenticity	The Nordic number is required on the outer labeling of all medicinal products, except radiopharmaceuticals, certain vitamins and mineral products, homeopathic, herbal and traditional herbal	Nordic article number (VNR)Same as DK	Nordic article number (VNR)Same as DK	The Nordic number is required on the outer labeling of all medicinal products (It is written as “Vnr XX XX XX”. The EAN code (bar code) is accepted but not required on the labeling.	Nordic article number (VNR)Same as DK

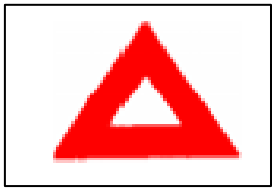
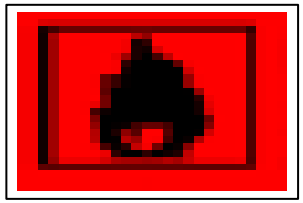
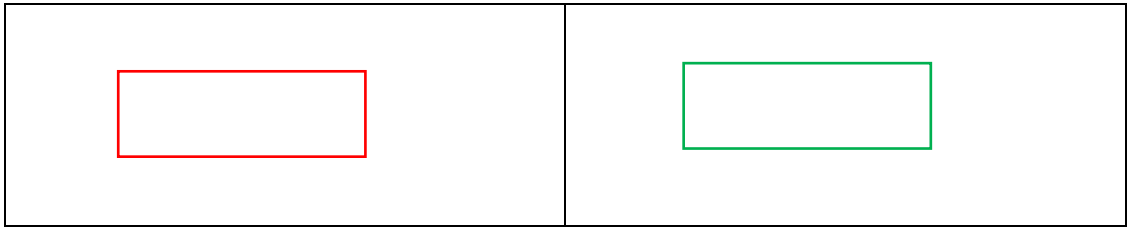
Section	Denmark (DK)	Finland (FI)	Iceland (IS)	Norway (NO)	Sweden (SE)
	medicinal products. It may be written as "Vnr XX XX XX". A bar code is accepted but not required on the labeling.				
Symbols and pictograms	 ➢ **Products which may reduce the ability to drive or operate machines must have a warning triangle.** ➢ **The tip of the triangle points upwards.** ➢ **It is a red triangle on a white background.**	 ➢ **Products containing inflammable material must bear the international warning symbol** ➢ **Warning Triangle same as UK**	➢ **Warning Triangle same as UK**	 Products containing inflammable material must bear the international warning symbol **Inflammable + symbol**	NA

Table 14 Blue box requirements for EE-LT-LV15

Section	Estonia (EE)	Latvia (LV)	Lithuania (LT)
Legal Status	NA	The legal status for supply is required on the labeling	The legal status is required on the labeling.
Identification and Authenticity	NA	NA	The EAN code (bar code) is accepted but not required on the labeling.
Symbols and Pictograms	NA	NA	 Products which may reduce the ability to drive or operate machines can have a warning triangle  Products containing inflammable material can have the international warning symbol

Table 15 Blue box requirements for IT-FR15

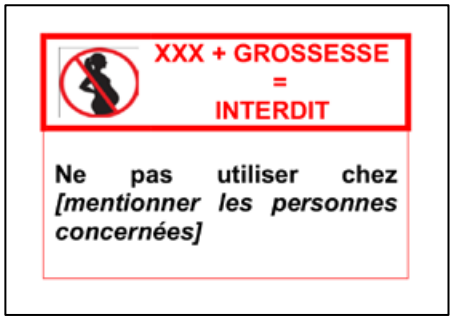
<table>
<tr><th>Section</th><th colspan="2">Italy (IT)</th><th>France (FR)</th></tr>
<tr><td rowspan="4">Legal Status</td><td rowspan="2">For medicinal products not subject to medical prescription (OTC, SOP)</td><td>Medicinal product for self-medication</td><td rowspan="4"><u>1. for all prescription-only products</u>
Active substances are classified in France in 2 categories based on whether or not the supply to the patient may be repeated without a new prescription:
- List I (non-renewable delivery)
- List II (renewable delivery)
This classification must appear on the label with details as follow:
- an empty frame with:
• A red border for list I products
• A green border for list II products
There is no minimum size for the coloured border
  </td></tr>
<tr><td>Medicinal product not subject to medical prescription</td></tr>
<tr><td colspan="2">For medicinal products subject to medical prescription the required Prescription-only medicinal product</td></tr>
<tr><td colspan="2">For medicinal products subject to non-renewable medical prescription required-</td></tr>
</table>

Section	Italy (IT)	France (FR)
	Medicinal product on prescription which may not be renewed	below this frame, written in dark characters on a red rectangular background: **Respect the prescribed dose** • List I or List II • prescription only • **do not swallow (if appropriate)** **<u>2- For products subject to special or restricted prescription</u>** ▪ **2.1 - for medicinal product subject to special medical prescription (narcotics) :** • **narcotic** • **prescription on a specific paper** • **prescription limited to 7x days of treatment** ▪ 2.2 for medicinal products subject to restricted medical prescription:
	For medicinal products on restricted medical prescription, the specification of the restricted authorised has to be added to the general statement on prescription only status- Prescription only medicinal product. Prescription restricted to hospitals or specialists	
	For medicinal products on restricted medical prescription, the specification of the restricted authorised prescriber has to be added to the general statement on restricted	

Section	Italy (IT)	France (FR)
	prescription-only status - Product on prescription which may not be renewed. Prescription restricted to hospitals or specialists **For medicinal products to be used only in hospitals-** Hospital use only, not to be sold to the public **For medicinal products to be used only by specialist -** Medicinal product to be used by specialists only. Not be sold to the public.	➢ In case of medicinal product for hospital use only, the following must be stated: **Medicinal product subject to hospital use only** ➢ In case of medicinal product subject to hospital prescription only, the following must be stated: **Medicinal product subject to hospital prescription only** ➢ In case of medicinal product subject to initial hospital prescription the following must be stated. The duration of the prescription can be specified: **Medicinal product subject to initial hospital prescription only** ➢ In case of medicinal product subject to specialist prescription only, the following must be stated: **Medicinal product subject to specialist prescription only** ➢ In case of medicinal product subject to special supervision throughout the treatment the following must be stated: **Medicinal product subject to special supervision throughout the treatment** ➢ In case of medicinal product restricted to professional use the following must be stated: **Medicinal product subject to professional use only, as referred to article R. 5121-80 of the French Public Health Code**
Identification and Authenticity	National identification Number is required on any part of the	All packaging must include the EAN 128 syntax (combined with ECC.200 data matrix marking) as per the EAN.UC. **for all prescription-only products**

<table>
<tr><th>Section</th><th>Italy (IT)</th><th>France (FR)</th></tr>
<tr><td></td><td>labeling as well as on the peelable sticker.</td><td rowspan="2"><table>
<tr><th>French text required on the labeling</th><th>English translation</th></tr>
<tr><td> 
</td><td>Be careful
Don’t drive before reading the leaflet</td></tr>
<tr><td> 
</td><td>Be very careful
Don’t drive without an healthcare professional opinion</td></tr>
<tr><td> 
</td><td>Warning, danger: do not drive
Don’t drive again without a doctor opinion</td></tr>
</table></td></tr>
<tr><td>Symbols and Pictograms</td><td> 

Doping pictogram: in compliance with the requirements of the Decree of Ministry of Health 19 Maggio 2005 (implementing the Italian Law 14 Dicembre 2000 n 376 as amended);</td></tr>
</table>

<table>
<tr><th>Section</th><th>Italy (IT)</th><th colspan="2">France (FR)</th></tr>
<tr><td rowspan="2"></td><td rowspan="2">Smile pictogram: for medicinal products not subject to medical prescription and for self-medication in compliance with the requirements of the Decree of Ministry of Health 1 Febbraio 2002;</td><td> 
</td><td>XXX + PREGNANCY = DANGER
Do not use for [mention here the concerned population], unless there is no alternative treatment</td></tr>
<tr><td> 
</td><td>XXX + PREGNANCY = PROHIBITED
Do not use for [mention here the concerned population]</td></tr>
</table>

Section	Italy (IT)	France (FR)		
			XXX + PREGNANCY = DANGER Do not use in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective	

Table 16 Blue box requirements for UK-IE-MT15

Section	UK	IE	MT
Legal Status	The legal status is required on the labeling. Labeling must include an indication of the legal status as follows: Medicines for supply only on the prescription of a medical practitioner - the letters POM in black surrounded by a box **POM** ➢ Medicines which may be supplied without prescription only under the supervision of a registered pharmacist - the letter P in black surrounded by a box: **P** ➢ Some additional statements are required to appear by law on the labeling and/or the package leaflet for certain medicines. The requirements are set out in current UK legislation. ➢ The additional requirements affect medicines which contain the following substance:	➢ The non-prescription status of certain medicinal products, containing certain active substances, must be stated. ➢ The designation “POM” (for prescription-only medicines) is in common use and would be in the boxed area.	NA

Section	UK	IE	MT
Identification and authenticity	NA	The EAN code (bar code) is accepted but not required on the labeling	NA
Symbols and Pictograms	NA	NA	NA

Chapter 5
Current Challenges Related to Packaging and Labeling

5. Current Challenges Related to Packaging and Labeling:

➢ Regulatory and Quality Differentiation:

- Europe has different regulatory and quality requirements compared with the United States.
- To meet the labeling compliance which affect the SmPC, PIL and Outer package.
- To minimize risk of Market complaints which affected the identification, readability, and dispensing perspective.
- For example, Identification of medicinal product, readability of the PIL etc.
- Frequent safety update and keep for compliance for supply in given time frame.
- Those safety update in labeling affects the package and supply of goods become challenging as we need to follow time lines.

➢ Compilation to EUFMD along with regulatory compliance:

- To confirm with supply in a scenario of Brexit.

➢ Securing the supply chain and ensuring the traceability:

- With the expanding issue of fake, misbranded, tainted, and occupied medications entering the store network, it is fundamental to guarantee full discernibility of the medication item.
- To comply EUFMD along with regulatory compliance for example other variation filing makes the process complex for manufacturers and also barrier for supply chain.
- In changing scenario, FMD have unique serialization and temper proof evidence on outer package and being an applicant need to update labeling and packaging and to submit regulatory variation to authority and it cost much.

➢ Distribution strategies for the drug product:

- To mitigate risk, cost, and shortening of the supply chain.
- In EU region, there is a trend to acquire tender in different markets, it is challenge for manufacturer to supply with in stipulated time accordingly supply chain strategies product distribution.

➢ Impact of multiple languages on packaging requirements:

- One of the greatest difficulties when entering the European market is the huge number of dialects, which results in a substantial number of related nation explicit pack formats, Within the 28 member states of the EU.
- Different Market / requirement nationally.
- For example, Primary label includes 2D barcode, linear code, unit dose, calendar pack

➢ Complexity of the Supply Chain Throughout the EU:

- Another challenge observed by customer organizations is characterizing their circulation methodology and related item necessities all through the distribution process.
- While appropriating items to target markets, the medication item will confront differing temperature ranges and travel times, so watchful thought should be given to item bundling and conveyance arrangements.
- Variations in nation prerequisites for hostile to falsifying measures likewise adds to store network intricacy.
- For example, the French market requires drug products to have a 2D matrix barcode, incorporating the CIP code and batch and expiry details. Meanwhile in Turkey, each individual saleable unit of drug product must also have a unique serial number, printed both in human readable format and incorporated in a 2D code.[23]

Chapter 6

EUFMD

(European Union Falsified Medicine Directive)

6.EUFMD (European Union Falsified medicine directive)

6.1 Introduction:

To reduce the occasions on which falsified medicines enter the legitimate supply chain. A secure supply chain from excipient suppliers through manufacturers, wholesalers, and pharmacists.[26]

Any medicinal product with a false representation of:

Its Identity including its bundling and naming its name or its creation as respects any of the fixings including excipients and the quality of those ingredients. its source including its maker, its nation of assembling and advertising authorisation holder. its history, including the records and archives identifying with the circulation channels utilized.[26] A meaning of 'falsified medicinal directive should be presented in order to clearly separate falsified medicinal products from other banned medicinal products, as well as from products break the intellectual property rights. Several years ago, Europe worried about the cumulative risk of falsification medicine to the patients with the purpose of safety. Year 2011, European parliament begun the work and revise the directive 2001/838/EC with aim of FMD. The Final phase of the FMD was 9 February 2019. This directive regulation passed by European parliament with the main concern of maximise the manufacturer security and distribution of medicinal products and to safeguard the patient from falsification of medicine which inflowing the supply chain. Falsified medicinal products characterized the one of the most important tasks for global patient safety, and remain a key issue of public health. Under the Directive, every single new pack of professionally prescribed meds set available in Europe from February 2019 onwards should bear two safety features: a one Unique identifier (UI) as a 2D data matrix (scanner tag) and an anti-tampering device (ATD).

6.1 History

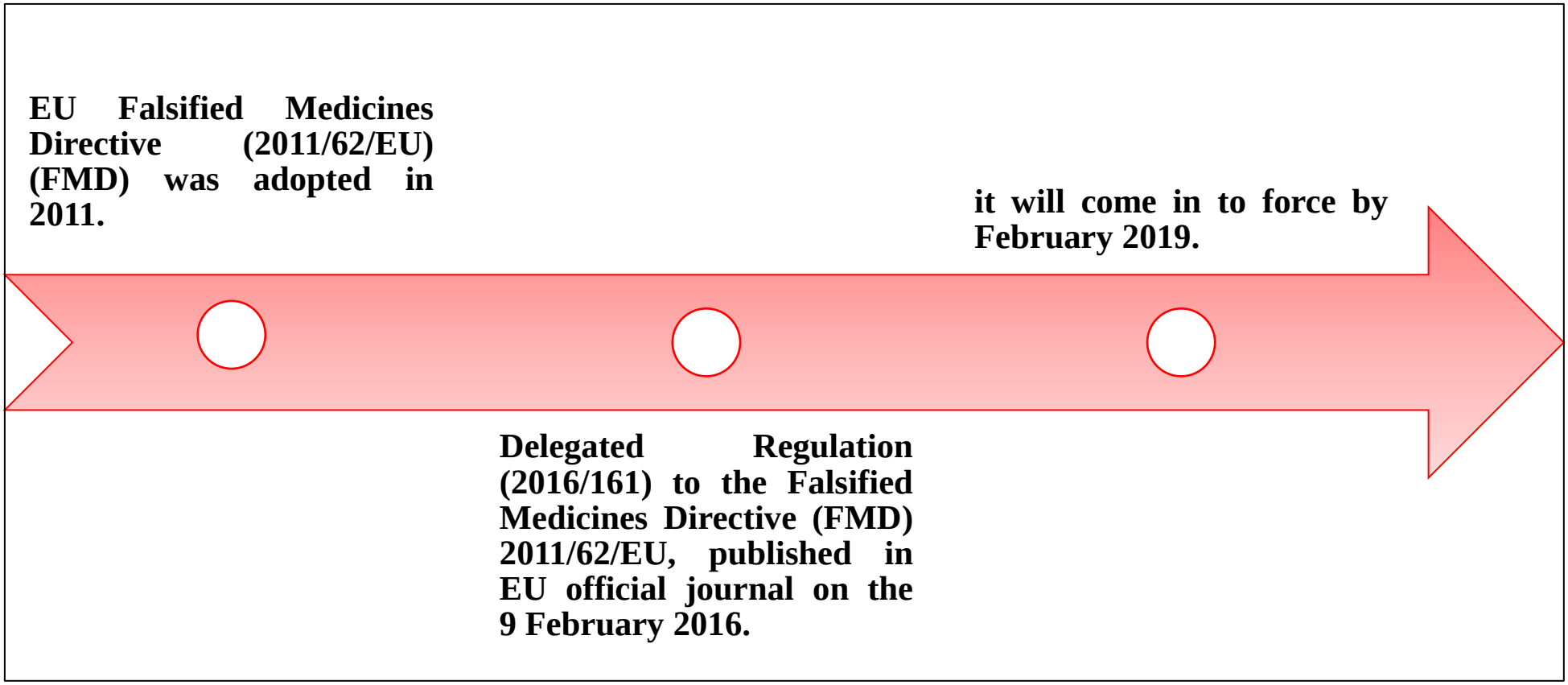


Figure 18 History of EUFMD

6.2 Purpose of EUFMD:

- The FMD is intended to ensure patients by limiting the odds of fake meds going into the built-up drug inventory network crosswise over Europe.
- The main purpose of EUFMD is to acquaint a framework with track genuine prescription from makers to patients.
- It will engage producers, wholesalers; distributers and everyone who supplies to patients to affirm the validity of the helpful things recognize solitary packs. Produces will be obliged to apply wellbeing highlights to each pack: Temper-verification security seal and a 2D scanner tag.
- The scanner tag empowers each pack to be serialized with a one of a kind randomized number, which will be confirmed before apportioning, this recognizable proof information will be put away in a database overseen by the European Medicines Verification Organization (EMVO).
- Producer will register packs with the database and they will be validated, decommissioned or "looked at" in the drug store by filtering the scanner tag.

6.3 Components of labeling

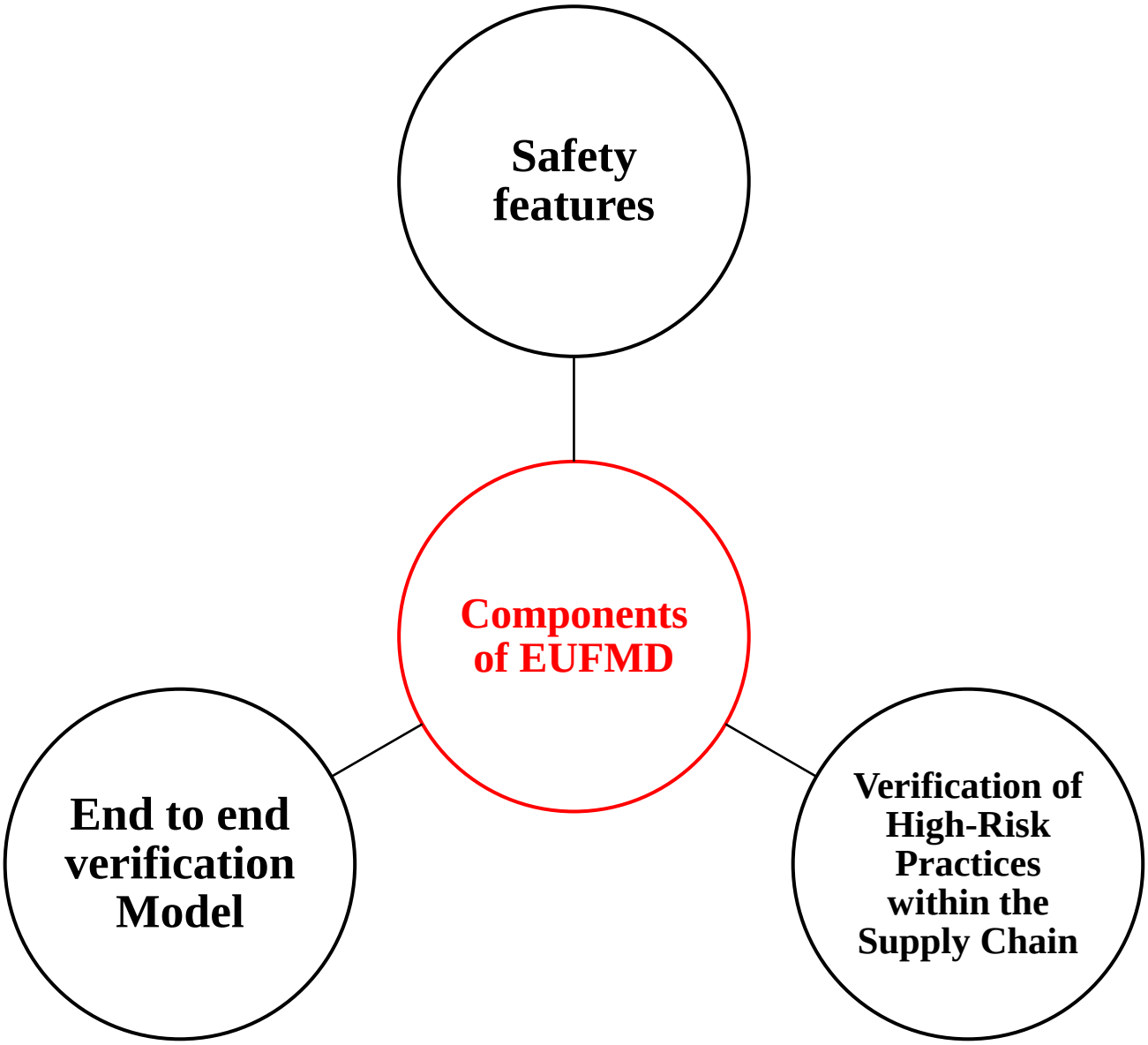


Figure 19 Components of labeling

1. Safety features:

For improve the item security expansion of the sealable units that are two distinctive wellbeing highlights and these security highlights are compulsory. These are a Unique identifier (UI) and a tamper-evident device. The guideline traces rules for the expansion of the UI (usually known as serialization), for coding of item and transfer of information to European vaults or databases. Second one is anti-tampering device. Security Features will enable by discount wholesalers and drug specialists with the worry of to Confirm the legitimacy of the restorative item and Identify singular packs.[27]

Unique Identifier:

Unique Product Identifier contains following information:

- 2D Matrix (data carrier)
- Global trade item Number (GTIN)-14-digit global product number
- Serial Number
- Lot Number
- Expiry Date
- National Reimbursement No
- Human readable Information

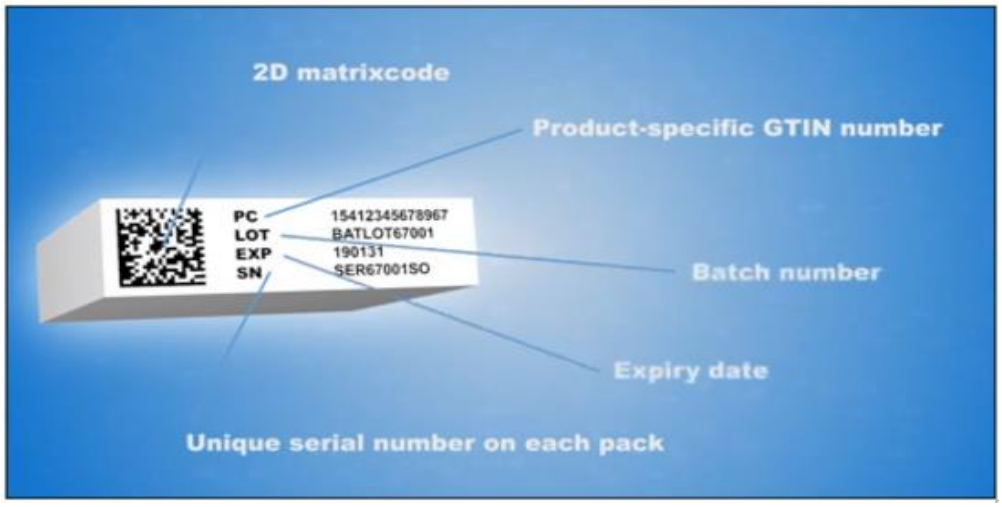


Figure 20 Unique Identifier

2. End-To-End Verification Model:

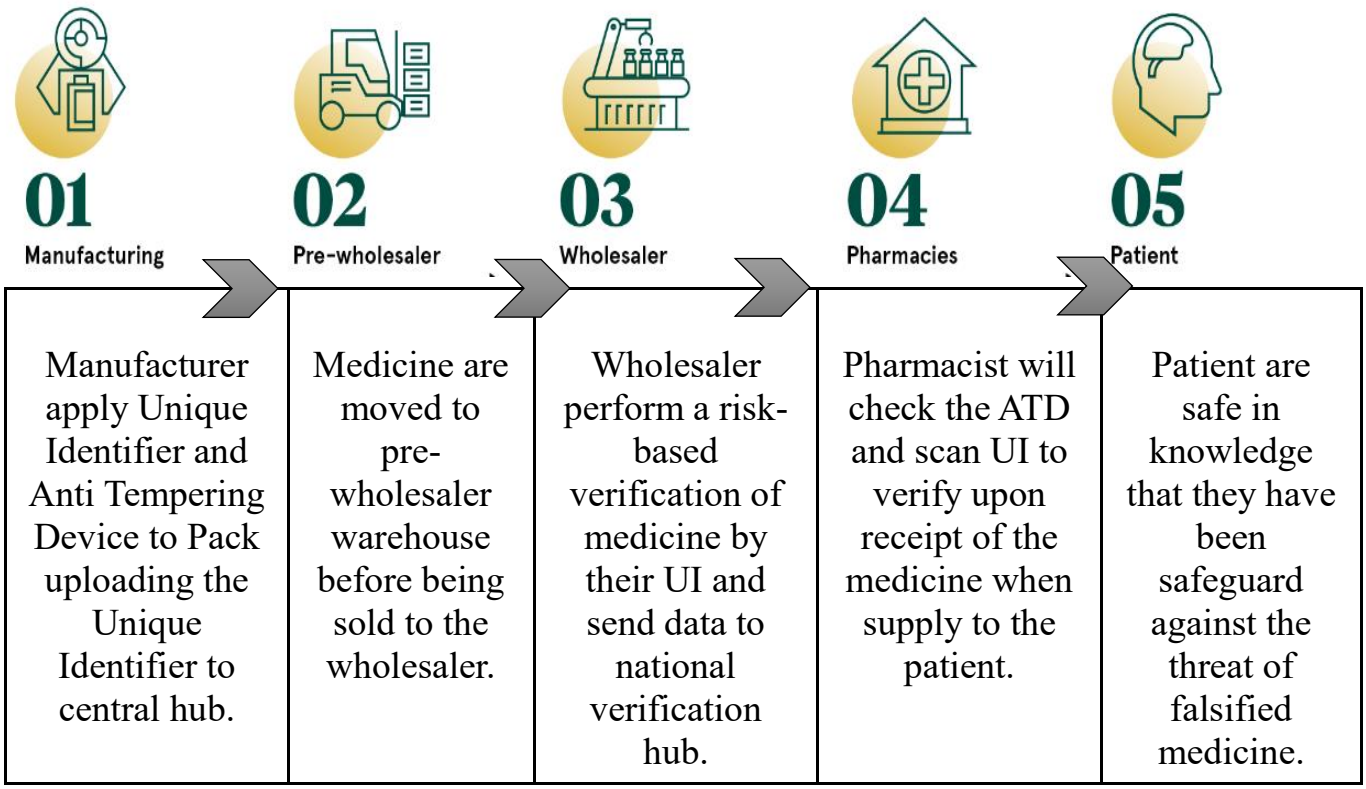


Figure 21 End-To-End Verification Model

The end-to-end serialization model needs the manufacturer apply UI and ATD to pack and uploading the UI to central hub of Eu region. After that the role of pre-wholesaler medicine are moved to the pre-wholesaler warehouse before being sold, he wholesaler. Then, Wholesaler perform risk-based verification of medicine by their UI and send the data to national verification hub. Medicine are passes to pharmacist they will check the ATD and scan UI to verify upon receipt of the medicine when supply to the patient. After scanning the UI Patient are safe in knowledge that they have been safeguard against the threat of falsification medicine. This whole system managed by the European Union Medicine Verification Organization (EMVO)

3.Verification of High-Risk Practices within the Supply Chain:

In expansion to confirmation of the UI at the purpose of administer, the designated guideline likewise distinguishes certain high-chance (of adulteration) forms that should be upgraded. For instance, item came back to a distributer for resale must, later on, be confirmed to even now be substantial in the European storehouses. Item got from a source that isn't assigned by the maker should likewise be checked. Besides, item that isn't bound available to be purchased in the EU must be confirmed and killed in the European stores. Precedents include: tests to administrative organizations, EU item sent to business sectors outside the EU, item for pulverization, and so on. In these examples, the confirmation procedure must incorporate checking both the UI and the alter obvious gadget [28]

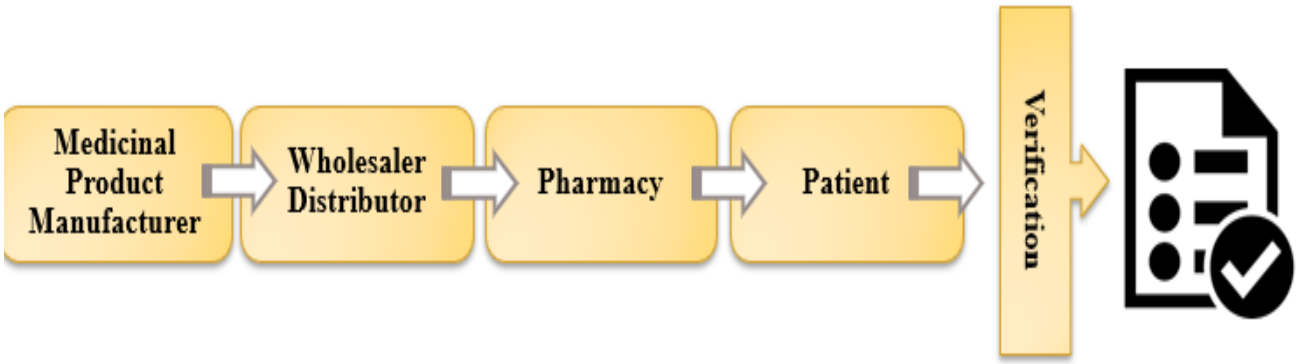


Figure 22 Verification of High-Risk Practices within the Supply Chain

Before EUFMD **After EUFMD**

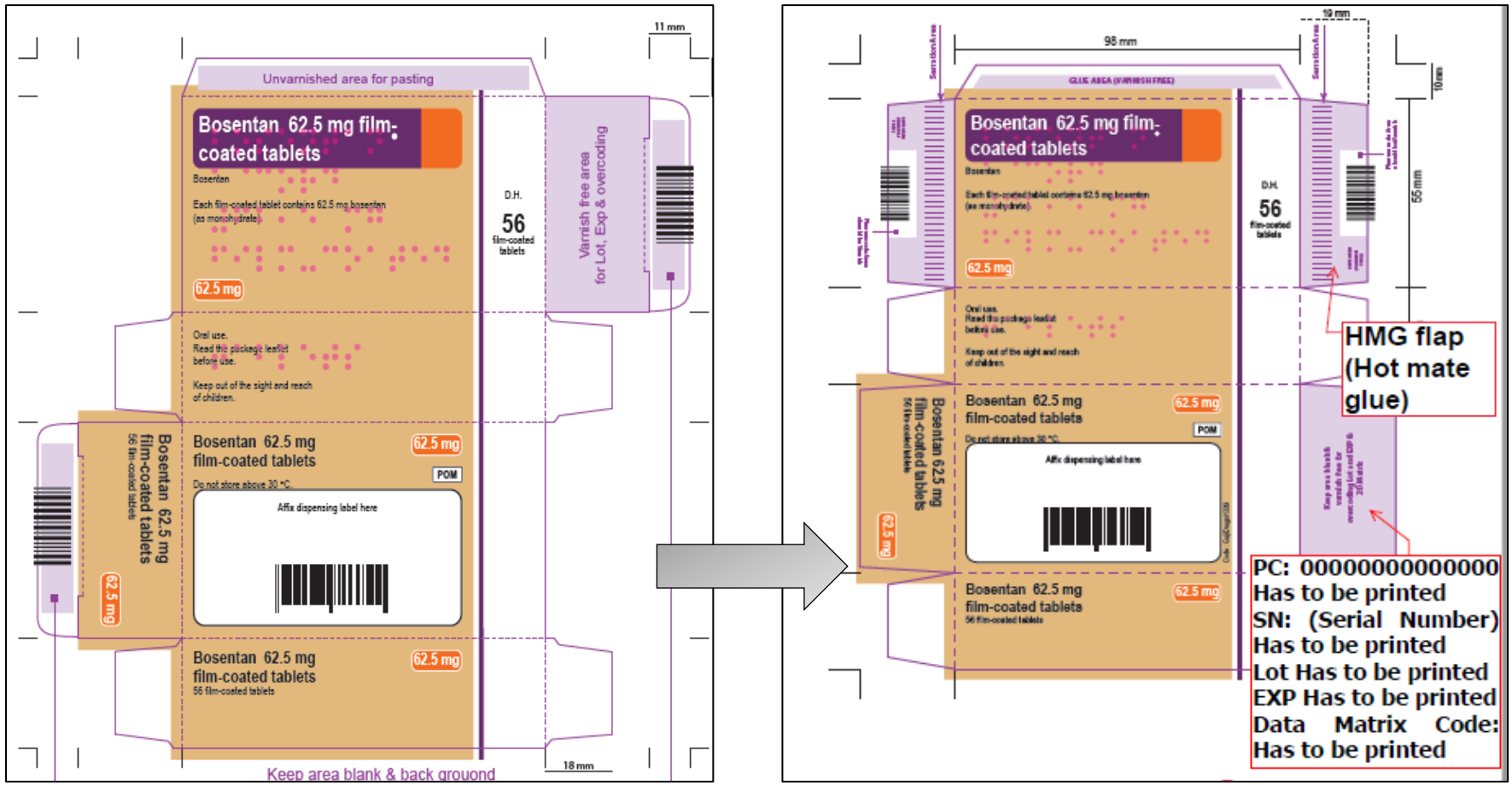


Figure 23 Before-after EUFMD

6.4 Benefits of EUFMD:

- Authentication of the generic product so that patient safeguard to the falsification of the medicinal product and patient get right authentication of the product.[23]
- Prevention of diversion, in this part to stop the falsification of the medicine and patient are prevents from that.
- Patient Compliance this programme conducts with patients which aims to aware from the misbranded and counterfeit drugs.[27]

Chapter 7

Summary

The Common Technical Document format was developed by the ICH to streamline the inconsistency of submission requirement in the Different Countries. EUROPE having a well-established guideline for labeling and packaging. There are guidelines for basic information for labeling and packaging to prepare mock ups, and Also blue box requirement need to be followed nationally to prepare cartons PIL. The main Purpose of the work is to study the labeling and packaging components submitted in module 1.3.1 in European Union Which are Summary of Product Characteristics (SPC), labeling and Package Leaflet. Packaging is the method, Profession and technology of wrapping or assurance of products for transport, storage and use. As packaging of these products are technically complex due to different language and national requirement. [29]Label means to layout of Imprint or graphic matter upon Primary container or the wrapper of medicinal product". According to the labeling there are three elements of the Medicinal Product label: Summary of product characteristics (SmPC) and Patient Information Leaflet (PIL), Outer/Immediate label. For the purpose of safety and efficacy of the product, the medicinal product has been evaluated by the respective regulatory authority of the country. Medicinal product may be approved, if application found suitable by the agency. In Europe region, For the authorization of the medicinal product there are four types of marketing authorization procedure. National, Mutual Recognition, Centralized and Decentralized Procedure. Having well established guidelines by EMA Still it is big challenge for generic manufacturer to watch the all criteria for labeling also to include additional country specific requirement in mock-ups during submission of mock-ups. The main Concern of the variation regulation are to build a simple, clear and more under stable legal framework for the conduct of variation to marketing authorization of the medicinal product. On the basis of the variation categories there are three types of variations. Type IA, Type IB and Type II. For the Identification of Medicinal products by patient is major. Patient detects the summary of product characteristics, Packaging and labeling leaflet of the medicinal products. But as additional requirement for country specific in Europe region that called Blue Box Requirement as mention in Article 57 and 62 of Directive 2004/83/EC. Blue box requirement describes the additional requirement fir labeling like legal status, symbols and pictograms and identification and authenticity of the medicinal product in different 32 countries in Europe region. Europe faces the current challenges

related pack and label that ate to meet the labeling compliance and to minimize the risk of market complaints which affected by the identification, readability and dispensing perspective. In EU region, there is a trend to acquire tender in different markets, it is challenge for manufacturer to supply with in stipulated time. Compilation to EUFMD along with the regulatory compliance and confirm with supply chain in a scenario of Brexit. Europe has been concerned about the growing threat of falsified medicine to the purpose of patient health and safety. Falsified medicine directive regulation is passed by European union parliament, with the main concern is to increase the patient safety and to prevent falsified medicine from entering the supply chain. To improve the patient safety and security, there are main three key components are involved in FMD. Manufacturer should comply with EUFMD before February 2019 to export and distribute medicinal product in Europe Region.

Chapter 8
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