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A COMPREHENSIVE STUDY ON THE DOSSIER PREPARATION FOR SUBMISSION OF GENERIC DRUG TO EUROPE IN CTD FORMAT

Sushma A*, Jyothshna Devi K, Umasankar K, Jayachandra Reddy P

Department of Pharmaceutics,
Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati-517605, Andhra Pradesh, India.

ABSTRACT

This research article gives extensive information about regulatory filing requirements to register oral dosage form (tablets) in European agency. For better and clear understanding this thesis explains registration requirements for Tramadol SR 100 mg Prolonged-Release Tablets in European regulatory Agency. The Common Technical Document (CTD) is an internationally agreed format which contains set of specifications for the application dossier submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan. The structure and format of the CTD was agreed in November 2000 within the International Conference on Harmonisation. It provides guidance for the compilation of dossier for applications for European marketing authorisations and is applicable for all types of procedures i.e., national, centralised including mutual recognition and decentralized procedures and for all types of products and for all types of applications. Applicants should consult with the appropriate regulatory authorities for applicability of this format for a particular type of product.

Keywords: CDT, Dossier Preparation, Europe.

INTRODUCTION

Tilodol SR 100 mg Prolonged-Release Tablets manufactured by Sandoz Limited has been selected as reference product for our study [1].

- **Selection of Excipients**

Upon studying SPC of reference listed drug and through experience following excipients are selected for development.

Excipients listed in SPC:
Initial dose layer
Lactose monohydrate
Calcium hydrogen phosphate dihydrate
Maize starch
Cellulose, microcrystalline
Sodium starch glycollate (Type A)
Magnesium stearate
Silica, colloidal anhydrous

Slow release layer
Lactose monohydrate
Hypromellose
Povidone K 25
Magnesium stearate
Silica, colloidal anhydrous
Castor oil, hydrogenated
Colouring agents
Quinoline yellow,
Indigo carmine
Aluminium hydroxide

- **Development Strategy**

Referenced (Tilodol**)** listed tablets description: Flat, round bi-layer-tablet with facet, initial layer white, slow-release layer green with one-sided identification mark "TR/100 R" on one side. From the description it is evident that tablets don't have any score line, so score line is not required for our developing formulation. From the excipients used in the formulation it could be manufactured using wet granulation technique [2].

- **Selection of dissolution method**

As per the USFDA dissolution database following method has been selected for the development and validation for dissolution method in section 3.2.P.5.3 Method validations of submission [3].

Corresponding Author :- **Sushma A** Email:- avulasushma02@gmail.com

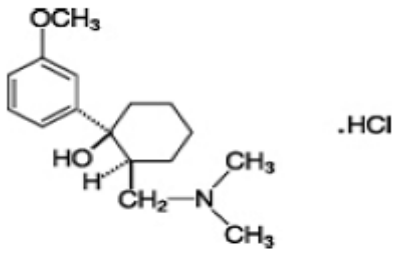
Apparatus: Basket
Media: 0.1 N HCl
RPM: 75
Volume: 900 ml
Time Points: 2,4,8,10,16 hours.

As per the guidelines of EMEA, discriminatory nature of the dissolution media should be presented to the agency during submission. A complete validation report for dissolution media selected however it is adopted from official monograph. The dissolution validation report has to be submitted in the section 3.2.P.5.3-Method validation part.

- **Physical characteristics of Active ingredient**

A narcotic analgesic proposed for moderate to severe pain. It may be habituating. Tramadol is also prepared as a variable release tablets, marketed under the brand name Tilodol.
Category: Opioid Analgesic
Proper name: tramadol hydrochloride
Chemical name: (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride
Molecular formula: $C_{16}H_{25}NO_2$ •HCl
Molecular mass: 299.84

Structural formula:



Physicochemical properties: Tramadol hydrochloride is a white to off-white, crystalline, odourless powder with a melting point between 180-184°C.

BCS Classification of Tramadol HCl:
Class 1: High soluble and High Permeable
pKa: 9.41
logP: 2.4
CAS: 27203-92-5

As per the product is highly soluble dissolution is not the rate limiting step for release. And as we intend to develop controlled release formulation selected a high binding agent to control the release of the drug from formulation. BCS classification details are readily available in below official website http://www.tsrlinc.net/results.cfm

- **Forced degradation studies:**

To derive impurities from active ingredient forced degradation studies has to be conducted on one batch of API and also to know the interaction between the API and excipients forced degradation studies are conducted on the mixture of API and each excipient separately. Usually forced degradation studies are usually conducted for 30 to 45 days at a temperature of 40 to 60 degrees centigrade. 5 to 10% of degradation will be allowed based on the type of drug product [4].

The stress testing should be performed in phase III of regulatory submission process. Stress studies should be done in different pH solutions, in the presence of oxygen and light, and at elevated temperatures and humidity levels to determine the stability of the drug substance. These stress studies are conducted on a single batch. The results should be summarized and submitted in an annual report. However, starting stress testing early in preclinical phase or phase I of clinical trials is highly encouraged and should be conducted on drug substance to obtain sufficient time for identifying degradation products and structure elucidation as well as optimizing the stress conditions. An early stress study also gives timely recommendations for making improvements in the manufacturing process and proper selection of stability-indicating analytical procedures.

- **Setting of Specifications**

As the European pharmacopoeia is not having finished product monographs, it is adopted from USP, where monograph for Tramadol SR tablets are readily available. FP monograph is available in following website www.uspnf.com. From monographs following tests and acceptance criteria are selected for finished product.

Tramadol Hydrochloride Extended-Release Tablets
Definition

Tramadol Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labelled amount of tramadol hydrochloride (C16H25NO2 · HCl).

Identification
A. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

B. Ultraviolet Absorption
Acceptance criteria: The UV absorption spectrum ofthe Sample solution exhibits maxima and minima at the same wavelength as that of a similar solution of the Standard solution [5].

ASSAY
Acceptance criteria: 90.0%–110.0%
Bioequivalance studies (BE):
Mechanism of action:

Tramadol hydrochloride is a centrally acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity to the μ receptor. Other mechanisms which contribute to its

analgesic effect are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Clinical efficacy and safety:

Tramadol hydrochloride has an antitussive effect. In contrast to morphine, analgesic doses of tramadol hydrochloride over a wide range have no respiratory-depressant effect. Also gastrointestinal motility is less affected. Effects on the cardio-vascular system tend to be slight. The potency of tramadol hydrochloride is reported to be 1/10(one tenth) to –1/6(one sixth) that of morphine.

Paediatric population:

Effects of enteral and parenteral administration of tramadol have been investigated in clinical trials involving more than 2,000 paediatric patients ranging in age from neonate to 17 years of age. The indications for pain treatment studied in those trials included pain after surgery (mainly abdominal), after surgical tooth extractions, due to fractures, burns and traumas as well as other painful conditions likely to require analgesic treatment for at least 7 days. At single doses of up to 2 mg/kg or multiple doses of up to 8 mg/kg per day (to a maximum of 400 mg per day) efficacy of tramadol hydrochloride was found to be superior to placebo, and superior or equal to paracetamol, nalbuphine, pethidine or low dose morphine. The conducted trials confirmed the efficacy of tramadol. The safety profile of tramadol was similar in adult and paediatric patients older than 1 year (see section 4.2).

Pharmacokinetic properties

Absorption:

More than 90% of tramadol is absorbed after oral administration. The mean absolute bioavailability is approximately 70%, irrespective of concomitant intake of food. The difference between absorbed and non-metabolised available tramadol is probably due to low first-pass-effect. The first-pass-effect after oral administration is a maximum of 30%. Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 l). Protein binding is about 20%. After administration of tramadol 100 mg prolonged release tablets the peak plasma concentration C_{max} 141 ± 40 ng/ml is reached after 4.9 hours. After administration of tramadol 200 mg prolonged release tablets a C_{max} 260 ± 62 ng/ml is reached after 4.8 hours.

Distribution:

Tramadol passes the blood-brain and placental barriers. Very small amounts of tramadol and its O-desmethyl derivative are found in the breast milk (0.1% and 0.02% respectively of the applied dose).

Biotransformation:

In humans tramadol is mainly metabolised by means of N- and O-demethylation and conjugation of the O-demethylation products with glucuronic acid. Only O-desmethyl-tramadol is pharmacologically active. There are considerable interindividual quantitative differences between the other metabolites. So far, eleven metabolites have been found in the urine. Animal experiments have shown that O-desmethyltramadol is more potent than the parent compound by the factor 2-4. Its half-life t½ ß (6 healthy volunteers) is 7.9 h (range 5.4 - 9.6 h) and is approximately that of tramadol. The inhibition of one or both types of the isoenzymes CYP3A4 and CYP2D6 involved in the biotransformation of tramadol, may affect the plasma concentration of tramadol or its active metabolite. Up to now, clinically relevant interactions have not been reported.

Elimination:

Elimination half-life (t½ ß) is approximately 6 hours, irrespective of the mode of administration .In patients above 75 years of age it may be prolonged by a factor of approximately 1.4. Tramadol and its metabolites are almost completely excreted via the kidneys. Cumulative urinary excretion is 90% of the total radioactivity of the administered dose. In case of impaired hepatic and renal function the half-life may be slightly prolonged. In patients with cirrhosis of the liver, elimination half-lives of 13.3 ± 4.9 h (tramadol) and 18.5 ± 9.4 h (O-desmethyltramadol), in an extreme case 22.3 h and 36 h respectively have been determined. In patients with renal insufficiency (creatinine clearance < 5 ml/min) the values were 11 ± 3.2 h and 16.9 ± 3 h, in an extreme case 19.5 h and 43.2 h, respectively.

Linearity:

Tramadol has a linear pharmacokinetic profile within the therapeutic dose range. The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100–300 ng/ml is usually effective.

Paediatric population:

The pharmacokinetics of tramadol and O-desmethyltramadol after single-dose and multiple-dose oral administration to subjects aged 1 year to 16 years were found to be generally similar to those in adults when adjusting for dose by body weight, but with a higher between-subject variability in children aged 8 years and below. In children below 1 year of age, the pharmacokinetics of tramadol and O-desmethyltramadol have been investigated, but have not been fully characterised. Information from studies including this age group indicates that the formation rate of O-desmethyltramadol via CYP2D6 increases continuously in neonates, and adult levels of CYP2D6 activity are assumed to be reached at about 1 year of age. In addition, immature glucuronidation systems and immature renal function may result in slow elimination and accumulation of O-desmethyltramadol in children under 1 year of age. From the above mentioned pharmacokinetic properties it is clear that interaction with food is in the significant level. Also as we are developing SR tablets, those intends to release drug for prolonged period of time, chance for interaction with food is very possible. Hence as per the reference product SPC and type of formulation, decided to conduct both fast and fed bioequivalence studies between test formulation and reference formulation. Specification limit: Biological

confidence limits should be within 80 to 125%. Any deviation from this range should be considered as fail.

Preparing and Organisation of CTD

The display of information should be unambiguous and transparent, to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Using margins text and tables should be prepared that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text. Acronyms and abbreviations should be defined the first time they are used in each module [6].

Pagination and Segregation

Page numbering should be at the document level and not at the volume or module level. In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document.

Benefits

- It saves time and resources
- It facilitates regulatory review
- It enhances communication
- It facilitates exchange of information between regulatory authorities, applicant and regulatory agency.

Presentation of Application

CTD is divided into 5 modules-

Module 1-Administrative and Prescribing Information
Module 2- Common Technical Document Summaries
Module 3- Quality
Module 4- Non-clinical
Module 5- Clinical

Module 1- Administrative and Prescribing Information

This module should contain documents specific to each region. The content and formatof this module can be specified by the relevant regulatory authorities.This module contains the specific EU-requirements for the administrative data (e.g. the application form, the proposed summary of product characteristics, labelling and package leaflet, etc.).

Module 2- Common Technical Document Summaries-

This modulecontains high level summaries:
2.3 Quality Overall Summary (QOS)
2.4 Non-clinical Overview
2.5 Clinical Overview
2.6 Non-clinical Summary
2.7 Clinical Summary

Module 3-Quality

This module covers Chemical, Pharmaceutical and Biological information

Module 4-Non-clinical

This module contains non-clinical study reports

Module 5- Clinical

This module contains clinical study reports.

Types of Submissions (or) Marketing Authorisation Procedures

There are several alternative procedures for seeking market authorisation of pharmaceutical products –
1. Nationalauthorisation procedure
2. Decentralised procedure
3. Mutual Recognition procedure
4. Centralised procedure

1. National authorisation procedure

Each country within the EU has its own procedures for marketing authorisation of pharmaceutical products.Applicants must submit an application to the competent authority of the Member State. In the UK, this is the MHRA.

- If an applicant wants subsequent market authorisation in more than one EU member states then they go for ***Decentralised and Mutual Recognition***procedure.

2. Decentralised procedure

With the Decentralised procedure, a sponsor can apply for simultaneous authorisation in more than one EU country for products that have not yet been authorised in any EU country and that do not fall within the mandatory scope of centralised procedure.

3. Mutual Recognition procedure

With the Mutual Recognition procedure, a product is first authorised by one country in the EU in accordance with the national procedures of that country and thenfurther marketing authorisations can be sought from other EU countries agree to recognize the decision of the first country.

4. Centralised procedure

In centralised procedure for marketauthorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community.
This procedure results in a marketing authorisation in all EU member states including Iceland, Liechtenstein and Norway.

Centralised procedure is **mandatory**for the following products:

- All biologic agents or other products made using high-technology procedures

- Products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases
- Orphan medicinal products

Centralised procedure is optional for:

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralised procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorisation is in the best interests of patients at the Community level.

Module 1: Administrative and Prescribing Information-

1.0 Cover Letter
1.1 Comprehensive Table of Contents
1.2 Application Form
1.3 Product Information
1.3.1 SPC, Labelling 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 the Member States
1.3.6 Braille
1.4 Information about the Experts
1.4.1 Quality
1.4.2 Non-Clinical
1.4.3 Clinical
1.5 Specific Requirements for Different Types of Applications
1.5.1 Information for Bibliographical Applications
1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
1.5.3 (Extended) Data/Market Exclusivity
1.5.4 Exceptional Circumstances
1.5.5 Conditional Marketing Authorisation
1.6 Environmental Risk Assessment
1.7 Information relating to Orphan Market Exclusivity
1.8 Information relating to Pharmacovigilance
1.8.1 Pharmacovigilance System
1.8.2 Risk-management System
1.9 Information relating to Clinical Trials
1.10 Information relating to Paediatrics

1.0 Cover letter

As an Appendix to the cover letter, a "Notes to Reviewers" document could be provided so that it provides further information in order to facilitate navigation (e.g. on hyperlinking, book marks, notes, volumes presentation etc…). For paper submissions, only the relevant cover letter for the Member State concerned /EMEA should be provided.

1.1 Comprehensive Table of Contents

A comprehensive table of contents should be provided for each type of application, reflecting all module sections submitted as part of the application concerned. For New Applications, all sections should be addressed.

Module 2: Common Technical Document Summaries

2.1 CTD Table of Contents (Module 2 – 5)
2.2 Introduction
2.3 Quality Overall Summary – Introduction
2.3.S Quality Overall Summary – Drug Substance
2.3.P Quality Overall Summary – Drug Product
2.3.A Quality Overall Summary – Appendices
2.3.R Quality Overall Summary – Regional Information
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.6.1 Introduction
2.6.2 Pharmacology Written Summary
2.6.3 Pharmacology Tabulated Summary
2.6.4 Pharmacokinetics Written Summary
2.6.5 Pharmacokinetics Tabulated Summary
2.6.6 Toxicology Written Summary
2.6.7 Toxicology Tabulated Summary
2.7 Clinical Summaries
2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods
2.7.2 Summary of Clinical Pharmacology Studies
2.7.3 Summary of Clinical Efficacy
2.7.4 Summary of Safety
2.7.5 References
2.7.6 Synopses of Individual Studies

Module 3: Quality

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References

Module 5: Clinical Study Reports

5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

1.2 Application Form

It is to be used for an application for a marketing authorisation of a medicinal product for human use submitted to-

(a) The European Medicines Agency under the centralised procedure or

(b) A Member State as well as Iceland, Liechtenstein and Norway undereither a national, mutual recognition or decentralised procedure. Depending on the type of application, the relevant application form has to be included-

- New Applications and Extension Applications
- Variation Applications
- Renewal Applications

1.3 Product Information-

It includes Summary of Product Characteristics (SPC), labelling and package leaflet in their application.

1.3.1 SPC, Labelling and Package Leaflet-

The NCA and the EMEA have published templates in all EU languages including Norwegian and Iceland for the presentation of product information

- **For applications in Mutual recognition or Decentralised procedures**:

For product information, annotated templates are published on the Heads of Agency website where as clean templates are published on the EMEA website.

- **For applications in the centralised procedure**:

For product information, both annotated and clean templates are published on the EMEA website.

Product information must only be presented in the mandatory format and lay-out using the electronic product information templates provided on the EMEA Website. A complete set of SPC/Annex II/Labelling/Package Leaflet texts, as appropriate should be presented per language in alphabetical order.

- **For national procedures other national templates may apply**
- **For the paper submission of product information:**
  - Different language versions should be separated by a tab
  - SPC, (Annex II), labelling and package leaflet should be separated by a tab for submission to CHMP members/Member States, only the relevant language versions are to be provided in addition to the English product information, as required.

The **summary of product characteristics (SPC)** contains the following information

i. Name of the medicinal product
ii. Qualitative and Quantitative composition
iii. Pharmaceutical form
iv. Clinical particulars :

- Therapeutic indications
- Posology and Method of administration
- Contra-indications
- Special warnings and Precautions for use
- Interaction with other medicinal products and other forms of interaction
- Fertility, Pregnancy and lactation
- Effects on ability to drive and use machines
- Undesirable effects
- Overdose

v. Pharmacological properties

- pharmacodynamic properties
- pharmacokinetic properties
- preclinical safety data

vi. Pharmaceutical particulars

- List of excipients
- Incompatibilities
- Shelf life
- Special precautions for storage
- Nature and contents of container
- Special precautions for disposal and other handling

vii. Marketing authorisation holder
viii. Marketing authorisation numbers
ix. Date of the first authorisation or renewal of the authorisation.
x. Date of revision of the text
xi. Legal category
xi. For radiopharmaceuticals, full details of internal radiation dosimetry.
xii. For radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

1.3.2 Mock-up

A "mock-up" is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicinal product. It is generally referred to as a "paper copy" or "computer generated version".

1. The following particulars shall appear on the outer and the immediate packaging:

(a) Name of the medicinal product
(b) Statement of the active substances
(c)List of Excipients
(d) Pharmaceutical form and the contents
(e) Method and Routes of administration
(f) Special warning that the medicinal product must be stored out of the reach and sight of children
(g)Other special warnings, if necessary
(h) Expiry date
(i) Special storage conditions

(j) Specific precautions relating to the disposal of unused medicinal products or Waste materials derived from medicinal products, if appropriate
(k) Name and address of the marketing authorisation holder
(l) Marketing authorisation numbers
(m) The manufacturer's batch number
(n) General classification for supply
(o)Instructions on use
(p) Information in Braille

2. The following particulars at least shall appear on immediate packaging of blister packs -
a) Name of the medicinal product
b) Name of the marketing authorisation holder
c) Expiry date
d) Batch number.

3. The following particulars at least shall appear on small immediate packaging units –
a) Name of the medicinal product and the route of administration
b) Method of administration
c) Expiry date
d) Batch number
e) Contents by weight, by volume or by unit.

1. The following are the particulars shall appear in the package leaflet
(a) For the identification of the medicinal product:
(i) Name of the medicinal product
(ii) Pharmaco-therapeutic group
(b) Therapeutic indications
(c) A list of information which is necessary before the medicinal product is taken:
(i) Contra-indications
(ii) Appropriate precautions for use
(iii) Special warnings
(iv) Interaction with other medicinal products
(v) Interactions with food and drink
(vi) Use by pregnant or breast feeding women
(vii) Effects on the ability to drive or to use machines
(viii) Excipients warnings
(d) The necessary and usual instructions for proper use, and in particular:
(i) Dosage
(ii) Method and Route of administration
(iii) Frequency of administration
(iv) Duration of treatment
(v) Symptoms in case of overdose and actions to be taken
(vi) Actions to be taken when one or more doses have been missed
(vii) Indication of the risk of withdrawal effects
(viii) A specific recommendation to consult the doctor or the Pharmacist as appropriate, for any clarification on the use of the product
(e) Description of side effects
(f) A reference to the expiry date indicated on the label, with:
(i) A warning against using the product after that date
(ii) Special storage conditions
(iii) Where applicable, shelf life after reconstitution, dilution or after first opening the container
(iv) If necessary, a warning concerning certain visible signs of deterioration
(v) Full statement of the active substances and excipients
(vi) Pharmaceutical form, nature and contents of container in weight, volume or units of dosage
(vii) The name and address of the marketing authorisation holder and of manufacturing authorisation holder responsible for batch release, if different
(g) Where the medicinal product is authorised under different names in the member States concerned, a list of the names authorised in each Member State
(h) The date on which the package leaflet was last revised.

1.3.3 Specimen

For paper submissions a separate specimen sample of the actual printed outer and immediate packaging materials and package leaflet should be provided.
For the electronic submission of Module 1, only the list detailing the specimens should be included here, separate from the actual specimens provided.

1.3.4 Consultation with Target Patient Groups

The package leaflet reflects the results of consultations with target patient groups to ensure that it is legible, clear and easy to use, and that results of assessments carried out in cooperation with target patient groups be provided to the competent authority/EMEA.

1.3.5 Product Information already approved in the Member States (where applicable)

1.3.6 Braille

The name of the medicinal product must be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially sighted.

1.4 Information about the Experts

The detailed reports of the high level summaries, Quality, non-clinical study reports and clinical study reports are signed by the experts and a brief curriculum vitae on the educational background, training and occupational experience of the expert is attached. For post-authorisation applications, the relevant expert declarations must be provided. In cases where marketing authorisation holders wish to distinguish such declaration from any previous declarations, the relevant procedure number of the reference member state/EMEA may be included on top.

1.4.1 Quality

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties

QUALITY:

Name of the expert: ……..
Signature:
Address: ……..
……..
……..
……..
Date:

A brief curriculum vitae on the educational background, training and occupational experience of the expert is attached.

1.4.2 Non-Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties

NONCLINICAL (pharmacology, pharmacokinetic, toxicology):

Name of the expert: ……..
Signature:
Address: ……..
……..
……..
……..
Date:

A brief curriculum vitae on the educational background, training and occupational experience of the expert is attached.

This is not applicable for generics.

1.4.3 Clinical

According to his / her respective qualifications the undersigned expert declares hereby to have performed the duties

CLINICAL:

Name of the expert: ……..
Signature:
Address: ……..
……..
……..
……..
Date:

A brief curriculum vitae on the educational background, training and occupational experience of the expert is attached.

1.5 Specific requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications

Applicants should provide here a concise document up to approximately 5 pages summarizing evidence that the constituents of the medicinal product have a well-established use, with an acceptable level of safety and efficacy. The results of pre-clinical tests or clinical trials need not be submitted if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety. In that event, the test and trial results shall be replaced by appropriate scientific literature.

1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications

Generic Medicinal Product-

A medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

The applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised for not less than eight years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. For a 'generic' of a reference medicinal product thesummary should include-

- Qualitative and quantitative composition
- Pharmaceutical form and its safety/efficacy profile of the active substances in comparison to the active substances of the reference medicinal product
- Bio-availability and Bio-equivalence
- The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy.

Hybrid Medicinal Product

- If biostudy is not possible e.g. - locally active products (dermatologicals)
- If criteria for generic are not met e.g. - different strength or form

A 'hybrid' of a reference medicinal product

This summary should include details on the medicinal product

- Its active substance
- Pharmaceutical form
- Strengths
- Therapeutic indications
- Route of administration as appropriate in comparison to the reference medicinal product
- Bio-availability and bio-equivalence

Biosimilar Medicinal Product

A biosimilar medicinal product is a medicinal product which is similar to a biological medicinal product that has already been authorised (the 'biological reference medicinal product'). A 'biosimilar' of a reference biological medicinal product Summary should include details on the similar biological medicinal product-

- Its active substance
- Raw materials and
- Manufacturing process
- Differences with relevant attributes of the reference medicinal product should be included. Any other changes introduced during development which could affect comparability should be highlighted. The comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development programme as appropriate should be defined.

1.5.3 (Extended) Data / Market Exclusivity

The marketing authorisation holder/applicant wishes to claim (additional) data / market exclusivity when applying for a new indication or change in classification, based on the following legal provisions:

- For authorisation of new therapeutic indications representing a significant clinical benefit - 10- year period of marketing protection may be extended by one year. In addition the marketing authorisation holder shall provide a report not more than 5-10 pages, should include:
- Justification of the proposed new indication compared to the therapeutic indications already authorised.
- Details of existing therapies relating to the proposed new indication
- Justification as to why the medicinal product, for which extended marketing protection period is sought.

1.5.4 Exceptional Circumstances-

A marketing authorisation may be granted based on a reduced development programme (e.g. based only on phase II studies) under so-called "exceptional circumstances". If the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should include a justification in this section, covering the following aspects-

1) A claim that the applicant can show that he is unable to provide comprehensive nonclinical or clinical data on the efficacy and safety under normal conditions of use
2) A listing of the non-clinical or clinical efficacy or safety data that cannot beComprehensively provided
3) Justification on the grounds for approval under exceptional circumstances
4) Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information).
   This is applicable for innovator products not for multisource pharmaceutical products.

1.5.5 Conditional Marketing Authorisation

This is only applicable to applications in the centralised procedure. Where the applicant requests a 'conditional marketing authorisation', the applicant should include a justification in this, covering the following aspects:

- Evidence that the product falls under mandatory scope or optional scope and belongs to one of the following categories:

i. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases

ii. Medicinal products to be used in emergency situations, inresponse to public health threats duly recognised either bythe World Health Organisation or by the Community

iii. Medicinal products designated as orphan medicinal products

- A Conditional MA may be granted when, although comprehensive clinical data have not been provided, all of the following requirements are met:
- Applicant's proposal for completion of ongoing studies, conduct of new studies and/or collection of pharmacovigilance data as appropriate.

1.6 Environmental Risk Assessment

Environmental risk assessment means the evaluation of the risk to human health and the environment. An application for marketing authorisation shall be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment. The requirements in this relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products. For the paper submission of the application, extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

1.7 Information relating to Orphan Market Exclusivity

Where a marketing authorisation in respect of an orphan medicinal product has been granted in all Members States, the Community and the Member States shall not, for a period of 10 years, accept another application for marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product. Where a designated orphan

medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the applicant must submit a report addressing the possible **"similarity"** with the authorised orphan medicinal product.

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

A detailed description of the pharmacovigilance system which the applicant will introduce must be provided. This should include proof that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

1.8.2 Risk-management System

A detailed description of the risk management system which the applicant will introduce should be provided, where appropriate.

The EU-RMP contains 2 parts:

Part I

- A Safety Specification
- A Pharmacovigilance Plan, and

Part II

- An evaluation of the need for risk minimisation activities, and if there is a need for additional (i.e., non- routine) risk minimisation activities:
- A Risk Minimisation Plan

1.9 Information relating to Clinical Trials

Clinical trials carried out outside the European Union meet the ethical requirements together with a listing of all trials (protocol number) and third countries involved.

1.10 Information relating to Paediatrics

With reference to **'Paediatric Regulation'**, this section is required:

- As of 26 July 2008 for all new Applications* for a medicinal product which is not authorised in the EEA
- As of 26 January 2009 for applications* for new indications, new pharmaceutical forms and new routes of administration, for authorised medicinal products which are protected either by a supplementary protection certificate, or by a patent which qualifies for the granting of such a certificate.
- For Paediatric Use marketing authorisation applications (PUMA)

According to **'**paediatric regulation', the competent authority responsible for granting marketing authorisations shall verify whether an application for marketing authorisation, extension or variation complies with the requirements of that Regulation, or whether a PUMA application complies with the agreed Paediatric Investigation Plan (PIP).

Module 2: Common Technical Document Summaries

2.2 Introduction

This should include pharmacological class, mode of action and the proposed clinical use of the medicinal product. This should not exceed one page.

2.3 Quality Overall Summary

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

This should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. This should also emphasise critical key parameters of the product and provide justification in cases where guidelines were not followed. This should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module),including cross-referencing to volume and page number in other Modules.

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

It includes a brief description ofnomenclature, structure and general properties.

2.3.S.2Manufacture

It includes the following information-

- Information on manufacturer
- A brief description of the manufacturing process and process controls that are intended to result in the routine and consistent production of materials of appropriate quality.
- A flow diagram of the synthetic processes
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance
- A discussion of the control of critical manufacturing steps, process controls and process intermediates
- A brief description of process validation and/or evaluation
- A brief summary of major manufacturing changes made throughout development andconclusions from the assessment used to evaluate product consistency.

2.3.S.3 Characterisation

For NCE:

It includes the following information-

- A summary of the interpretation of evidence of structure and isomerism
- When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereo isomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

It includes the following information-

- A description of the desired product and product-related substances
- A summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity)

2.3.S.4 Control of Drug Substance

It includes the following information-

- A brief summary of the justification of the specifications, the analytical procedures, and validation
- A tabulated summary of the batch analyses with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials

It includes the following information-

- A brief description of the reference standards or reference materials used for testing of the drug substance
- A tabulated presentation, where appropriate should be included.

2.3.S.6 Container Closure System

It includes -

- A brief description and discussion of the container closure system including the identity of materials of construction of each primary packaging component and their specifications.

2.3.S.7 Stability

It includes the following information-

- A brief summary of stability studies and its conclusions
- Post-approval stability protocol and stability commitment
- A tabulated summary of the stability results with graphical representation.

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

It includes the following information-

- Descriptionof the dosage form
- Composition, i.e., list of all components of the dosage form, and their amount on aper-unit basis (including overages, if any) the function of thecomponents, and areference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
- Description of accompanying reconstitution diluents
- Type of container and closure used for the dosage form and accompanyingreconstitution diluent, if applicable.

2.3.P.2 Pharmaceutical Development

It includes the following information -

- A brief description of components of drug product
- A brief description of drug product
- A brief description of formulation development
- A brief summary of the justification of any overages in the formulation
- A brief description of physicochemical and biological properties
- A brief description ofmanufacturing process development
- A brief description ofContainer Closure System
- A brief information on microbiological Attributes
- A brief information on Compatibility
- A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles, where relevant.

2.3.P.3 Manufacture

It includes the following information-

- Information on the manufacturer
- A batch formula should be provided
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality
- A flow diagram of process
- A brief description of control of critical steps and intermediates
- A brief description of the process validation and/or evaluation

2.3.P.4 Control of Excipients

It includes the following information-

- Information on specifications
- A summary of analytical procedures and validation
- A brief summary of the justification of the specifications
- A brief description of excipients of human or animal origin

- A brief description of novel excipients

2.3.P.5 Control of Drug Product

It includes the following information-

- Information on specifications
- A summary of analytical procedures and validation
- A brief description of batches and results of batch analyses
- A brief information on characterisation of impurities
- A brief summary of the justification of the specifications
- A tabulated summary of the batch analyses with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials

- A brief information on the reference standards or materials with tabulated presentation, where appropriate should be included.

2.3.P.7 Container Closure System

- A brief description and discussion of the container closure system should be provided.

2.3.P.8 Stability

It includes the following information-

- A summary of stability studies and its conclusion
- A tabulated summary of the stability results with graphical representation where appropriate
- Post-approval stability protocol and stability commitment

2.4 Nonclinical Overview

It provides an integrated overall analysis of the information. It should not exceed about 30 pages. It should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical

2.5 Clinical Overview

It is intended to provide a critical analysis of the clinical data. The Clinical Summary should providea detailed factual summarisation of the clinical information where as the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

2.6 Nonclinical Summary

It is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics and toxicology written summaries in an acceptable format. It is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

2.7 Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarisation of all of theclinical information. This includes information provided in clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for products that have been marketed in other regions. The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

MODULE 3 QUALITY

Introduction

It provides guidance on the format of the chemical, pharmaceutical and biological documentation of a registration application for chemical active substances, biological medicinal products, for radiopharmaceuticals and their corresponding medicinal products. The "Body of Data" indicates where the information should be located. In this neither the type nor extent of specific supporting data has been addressed.

3.1 TABLE OF CONTENTS

A Table of Contents for Module 3 should be provided.

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

It includes information on the nomenclature of the drug substance.

3.2.S.1.2 Structure

NCE:

For NCE the following information should be provided-

- The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.

Biotech:

For biotechnological products the following information should be provided-

- The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications and relative molecular mass.

3.2.S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

It includes the following information on manufacturer-

- The name, address, and responsibility of each manufacturer, including contractors, and each proposed

production site or facility involved in manufacturing and testing.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Information should be provided to adequately describe the manufacturing process and process controls.

3.2.S.2.3 Control of Materials

It includes the following information-

- A brief description of source and materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process.
- A brief information on the quality and control of these materials should beprovided.
- A brief information demonstrating that materials (including biologically-sourcedmaterials, e.g., media components, monoclonal antibodies, enzymes) meet standardsappropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate.
- A brief description of source, manufacture, and characterisation for biologically-sourced materials should be provided

3.2.S.2.4 Controls of Critical Steps and Intermediates

Critical Steps:

Tests and acceptance criteria with justification including experimental data performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

3.2.S.2.5 Process Validation and/or Evaluation

It includes A description of process validation and/or evaluation studies for aseptic processing and sterilisation.

3.2.S.2.6 Manufacturing Process Development

NCE:

It includes -

- A description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

NCE:

It includes –

- A brief information on confirmation of structure based on e.g., synthetic route and spectral analyses.
- A brief information on the potential for isomerism, theidentification of stereochemistry, or the potential for forming polymorphs.

3.2.S.3.2 Impurities

Information on impurities should be provided.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

The specification for the drug substance should be provided.

3.2.S.4.2 Analytical Procedures

The analytical procedures used for testing the drug substance should be provided.

3.2.S.4.3 Validation of Analytical Procedures

It includes A brief information on analytical validation, including experimental data for the analytical procedures used for testing the drug substance.

3.2.S.4.4 Batch Analyses

Description of batches and results of batch analysesshould be provided.

3.2.S.4.5 Justification of Specification

Justification for the drug substance specification should be provided.

3.2.S.5 Reference Standards or Materials

It includes the following information-

- A description of the manufacture and/or purification of reference materials.
- Documentation of the characterization, storage conditions and formulation supportive of reference materials stability should also be provided.

3.2.S.6 Container Closure System

It includes-

- A description of the container closure systems, including the identity of materials of construction of each primary packaging component, and their specifications that should include description and identification and critical dimensions with drawings, where appropriate.
- A brief information on non-compendial methods with validation, where appropriate.
- A brief description of non-functional secondary packaging components (e.g., those that do not provide additional protection). For functional secondary packaging components, additional information should be provided.

- A brief discussion on choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

It includes-

- A summary on the types of studies conducted, protocols used, and the results of the studies.
- The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

3.2.S.7.3 Stability Data

It includes-

- A tabular, graphical, or narrative description of the results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format.
- A brief information on the analytical procedures used to generate the data and validation of these procedures.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

It includes the following information-

- Description of the dosage form
- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)
- Description of accompanying reconstitution diluents and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

3.2.P.2 Pharmaceutical Development-

It includes-

- A brief information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application.
- A brief description of the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality.
- Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

It includes-

- A discussion of the compatibility of the drug substance with excipients listed in 3.2.P.1.
- A discussion of the physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product.
- For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients

It includes-

- A discussion ofthe choice ofexcipients listed in 3.2.P.1 their concentration, their characteristics that caninfluence the drug product performance relative to their respective functions.

3.2.P.2.2Drug Product

3.2.P.2.2.1 Formulation Development

It includes-

- A brief summary of the development of the drug product taking into consideration the proposed route of administration and usage.
- A brief discussion of the differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1.
- A discussion of the results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) when appropriate.

3.2.P.2.2.2 Overages

It includes-

- A justification of any overages in the formulations described in 3.2.P.1.

3.2.P.2.2.3 Physicochemical and Biological Properties

The following are the parameters relevant to the performance of the drug product should be addressed-

- pH
- Ionic strength
- Dissolution
- Redispersion
- Reconstitution
- Particle size distribution

- Aggregation
- Polymorphism
- Rheological properties
- Biological activity or potency and/or immunological activity

3.2.P.2.3 Manufacturing Process Development

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified. Differences between the manufacturing processes used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed [7].

3.2.P.2.4 Container Closure System

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product.

3.2.P.2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterileproducts and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluents or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

It includes the following information on the manufacturer-

- The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.P.3.2 Batch Formula

It includes-

- A batch formula with a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Critical Steps:

Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

3.2.P.3.5 Process Validation and/or Evaluation

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

3.2.P.4 Control of Excipients [8]

3.2.P.4.1 Specifications

The specifications for excipients should be provided.

3.2.P.4.2 Analytical Procedures

The analytical procedures used for testing the excipients should be provided, where appropriate.

3.2.P.4.3 Validation of Analytical Procedures

It includes-

- A brief information on Analytical validation, including experimental data, for the analytical procedures used for testing the excipients.

3.2.P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate. Justification for the proposed excipient specifications should be provided, where appropriate.

3.2.P.4.5 Excipients of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data).

3.2.P.4.6 Novel Excipients

For excipients used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

The specification(s) for the drug product should be provided.

3.2.P.5.2 Analytical Procedures

The analytical procedures used for testing the drug product should be provided.

3.2.P.5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

3.2.P.5.4 Batch Analyses

A description of batches and results of batch analyses should be provided.

3.2.P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

3.2.P.5.6 Justification of Specifications

Justification for the drug substance specifications should be provided. Reference ICH Guidelines: Q3B, Q6A and Q6B. Justification for the proposed drug product specifications should be provided.

3.2.P.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials". Reference ICH: Q6A and Q6B.

3.2.P.7 Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification.The specifications should include description and identification and critical dimensions, with drawings where appropriate. Non-compendial methods with validation should be included where appropriate. For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

3.2.P.8 Stability [9]

3.2.P.8.1 Stability Summary and Conclusion

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelflife.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

3.2.P.8.3 Stability Data

Results of the stability studies should be presented in an appropriate format (e.g. tabular,graphical, narrative). Information on the analytical procedures used to generate the dataand validation of these procedures should be included.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Biotech:

A diagram should be provided illustrating the manufacturing flow includingmovement of raw materials, personnel, waste, and intermediates in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product. Information on all developmental or approved products manufactured ormanipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated ormulti-use) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

3.2.A.2 Adventitious Agents Safety Evaluation

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

3.2.A.3 Excipients

3.2.R Regional Information

Any additional drug substance/active substance and/or drug product information specific to each region

should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

3.3 LITERATURE REFERENCES

Key literature references should be provided, if applicable.

MODULE 4- NONCLINICAL STUDY REPORTS- Not Applicable

MODULE 5- CLINICAL STUDY REPORTS

This is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5

This is a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

DECENTRALISED PROCEDURE

The DCP came into effect in the EU in 2005. This procedure is used to obtain marketing authorisations in several Member States, when no marketing authorization has been granted in any Member State at the time of application. The procedure to be followed will depend upon whether it is a Member State or the marketing authorisation holder which initiates the decentralised procedure. The DCP cannot be used for products, which have to be authorized via CP, but the DCP can be used for duplicate applications and extension applications ofproducts originally approved by the MRP. In addition it is possible to use the DCP for generic products for which the reference product was authorized via CP. The main difference between the MRP and DCP lies in the fact that the Concerned Member States (CMSs) in a DCP are involved at the onset of the procedure as opposed to waiting for approval before an application is made in the CMS.

The Reference Member State (RMS) grants a Marketing Authorisation which is mutually recognised by the Concerned Member States (CMS).

The decentralised procedure is divided in five steps:

1) Pre-procedural step, including validation phase
2) Assessment step I
3) Assessment step II
4) Discussion at the coordination group level, if needed
5) National Marketing Authorisation step

1) PRE-PROCEDURAL STEP, INCLUDING VALIDATION PHASE

Consultation with RMS

Before submitting an application under the decentralised procedure, the applicant must inform the Member State (MS) chosen as Reference Member State (RMS) of their intention to submit and the month of submission. The applicant has to follow the rules adopted by the MS chosen as the RMS for allocating a timeslot and has to use the common request form in order to ask a MS to be the RMS. At least 2 months before submission of the dossier the applicant should seek regulatory advice or pre-discuss the application with the RMS either during a pre-submission meeting or via a teleconference/e-mail.

The RMS will inform the applicant when the marketing authorisation application could be submitted and will allocate a procedure number to this application. The applicant should discuss with the RMS which form of 'user consultation' of the package leaflet (PL) may be necessary (a full test or a bridging report) and when the results will be available (at the submission of the application or during the clock-off period). If there are different views among MSs on the legal basis of the application, the RMS may discuss this in the meeting of the Co-ordination group for Mutual Recognition and Decentralised Procedures (CMDh) prior to submission of the application but also during the validation phase [10].

Making the application

The applicant submits an application to the National Competent Authorities of each of the MS where a marketing authorisation is to be sought**.** The application shall include a list of all CMSs and the applicant shall designate one Member State to act as "RMS" and to prepare an draft assessment report on the medicinal product. The applicant must give assurance, usually in the covering letter accompanyingthe application, that the dossier as well as the summary of product characteristics, package leaflet and labelling are identical in all Member States.

Validation phase

The procedure for validation of the application starts when the applicant confirms both to the RMS and CMSs the dates of dispatch of the dossier to all Member States. The application should be validated by all CMSs and the RMS. The validation can be made according to the check-in procedure or using any appropriate form.

2) ASSESSMENT STEP I

The RMS has 120 days to prepare a draft assessment report, and comments on draft summary of product characteristics, draft package leaflet and draft labelling. The RMS will start the assessment step I after the applications have been validated by all CMSs and the RMS.

In order to prepare the draft assessment report, the RMS forwards a preliminary assessment report on the dossier to the CMSs and the applicant within 70 days after the start of the assessment step I.

By Day 100 CMSs should communicate their comments on the dossier, the preliminary assessment report and the summary of product characteristics to the RMS within the timeframe set by the RMS.

The RMS shall supply the draft assessment report, summary of product characteristics, package leaflet and labelling to the CMSs and the applicant not later than 120 days after the validation of the application. The draft assessment report would include an appropriate evaluation of any information available upon quality, safety and efficacy. The RMS will notify the applicant when the draft report is available.

The RMS makes the draft assessment report available to the applicant. However, if an Active Substance Master File (ASMF) was submitted, the closed part of the Active Substance Master File as well as any other confidential information would be excluded. Where it is made available to the applicant, the other CMSs will be informed. The letter of access should be included for the information provided in the Active Substance Master File.

3) ASSESSMENT STEP II, INCLUDING DISCUSSION AT CMDH, IF NEEDED

The RMS starts the assessment step II on Day 120 at the latest by sending the Draft Assessment Report (DAR), draft SmPC, draft PL and draft labelling to the CMS and applicant. The start of the assessment step II corresponds to Day 0 of the 90-day period. During the assessment step II, new data/studies (or a delayed Day 106 response) cannot be submitted by the applicant or the ASMF holder. The RMS should clearly indicate in its conclusion if the product is approvable or not.

During the assessment step II period the procedure can be closed at **any time-point** before Day 210 if consensus is reached that the product is approvable. The RMS should circulate its conclusion that the product is approvable together with the final AR, final proposed SmPC/PL and labelling to the CMSs. The RMS should clearly indicate in this, that all remaining comments have been addressed satisfactorily and that the product(s) and SmPC/PL/labelling can now be approved. If necessary a short assessment report can also be added. Each CMS sends its comments to the RMS, CMS and applicant,differentiating between PSRPH and remaining points for clarification no later than Day 145 of the procedure (i.e. Day 25 of 90-day period) and updates the CTS record. Where a CMS is in agreement with the RMS, then a simple e-mail communication would suffice.

It is advised to introduce any major amendments to the SmPC, PL and labelling during an early stage of the procedure in order to allow full discussion in each MS. The CMS should make every effort to send their comments before Day 195 and resolve outstanding issues before Day 205 (i.e. Day 85 of the 90-day period). Only in exceptional cases should changes to the SmPC, PL and labelling be introduced after Day 205. In such cases the RMS should actively inform the CMSs about this. The RMS and CMS have the responsibility to ensure full transparency during the procedure.

If CMSs by Day 210 cannot approve the positive RMS assessment report, SmPC, PL and labelling on the grounds of PSRPH, the CMSs shall notify the RMS, CMSs, the CMDh secretariat at the European Medicines Agency and the applicant at Day 210 at the latest, preferably before 16.00 CET, by using the agreed template for a referral request. The notification shall include a detailed exposition of the reasons for the negative position. This also applies in case the applicant has withdrawn the application after distribution of the DAR in a CMS based on PSRPH raised by this CMS.

Even if CMSs earlier in the procedure have informed that they are of the opinion that there are potential serious risks to public health with the application, they need to confirm their final position on Day 210, so that it is clear to all parties involved, whether the issues have been resolved or not by the applicant's response. It is encouraged to finalise a DCP on Day 210 at 16.00 CET. It is recommended that the CMSs give their final position according to the timelines given above so that the procedure can be closed on Day 210. It is not advisable to have Day 210 on a Saturday or a Sunday.

If a CMS maintains a PSRPH at Day 210, the RMS will refer the matter to the CMDh by circulation of the assessment report, proposed SmPC, PL and labelling and the explanation of the grounds for referral from the disagreeing CMS(s) to all CMDh members, CMDh chair, the CMDh secretariat at the European Medicines Agency and the applicant, within 7 days after Day 210, by using the agreed template for a referral notification. The 60-day procedure in CMDh is described in the CMDh-SOP-Disagreement in procedures-referral to CMDh [11].

Assessment step II:

All CMSs have 90 days to approve the (draft) assessment report, the summary of product characteristics and the labelling and package leaflet. In agreement between the RMS, the CMSs and the applicant the 90 day procedure can be shortened. Day 0 of the 90 days assessment step II corresponds with day 120 of the decentralized procedure. The RMS will update the CTS database with the date of sending of those documents on Day 0. Each CMS should send its comments to the RMS, the other CMSs and the

applicant on the draft assessment report and draft summary of product characteristics, draft package leaflet and labelling according to the timeframe agreed and after receipt of those documents and fill in the CTS database. The applicant will send the response document to the RMS and the CMSs.

Response of Concerned Member States

The RMS will act as the central point between the CMSs and the applicant. All dialogue between the parties involved should be channelled through the RMS. If a CMS considers that there are grounds for supposing that the authorisation of the medicinal product may present a potential serious risk to public health, then this concern should be notified as soon as possible to the RMS, the other CMSs and the applicant. Only objections which present a potential serious risk to public health,shall be presented to the reference Member State, the other concerned Member States and the applicant.

Discussion on the summary of product characteristics, package leaflet and Labeling

At the end of the 90-day period for approval by the concerned Member States, agreement must be reached on the summary of product characteristics, package leaflet and labelling.

Response from the applicant

In response to the objections or questions communicated to the applicant by the concerned Member States, the applicant will provide, if requested, a new proposed summary of product characteristics, package leaflet and labelling in tabular form set against the 120-day draft summary of product characteristics, draft package leaflet and labelling from the reference Member State with the answers to the questions raised by the reference Member State and concerned Member State(s) on the different sections of the summary of product characteristics, package leaflet and labelling.

Break-out sessions

The meetings of the coordination group have been identified as occasions where all Member States can meet. Alongside these meetings, break-out sessions may be organised under responsibility of the reference Member State to discuss applications or to resolve outstanding questions. The reference Member State will inform the marketing authorisation holder if it is considered that representatives from the applicant might be available at the relevant meeting to aid in the resolution of these issues.

Although applicants should be aware that they may not be required to participate in the session they may be asked to agree amendments to the summary of product characteristics, package leaflet and labelling or to answer questions from the Member States. Applicants should ensure that their representatives are able to take decisions on amendments to the summary of product characteristics, package leaflet and labelling being proposed by Member States.

Finalisation of the procedure

All concerned Member States should give their final opinion at latest on day 85 (day 205). On occasion further discussion may be needed around day 85 to avoid a procedure in the coordination group or an arbitration (alternatively a telephone conference or videoconference may be used). Any further changes in the summary of product characteristics, package leaflet and labelling should be agreed on by the reference Member State and all other concerned Member States.

Withdrawal

Where an applicant withdraws an application regarding a medicinal product in one concerned Member State during a decentralised procedure, it is not allowed to submit a national application subsequently. Any such an application will be rejected.

In principle, an application for a marketing authorisation may be withdrawn by the applicant at any time during the decentralised procedure. However, during the assessment step II, once a potential serious risk to public health has been raised to be dealt with by the coordination group and if failed by the CHMP in an arbitration procedure, the opinion of the coordination group and of the CHMP will be given unless all applications and existing marketing authorisations for the product are withdrawn. In such a case, the CHMP may decide either to close or to continue the referral procedure, if there is still is a public health concern.

4) NATIONAL STEP

The National Competent Authority of each involved MS shall adopt a national decision within 30 days after the RMS closes the procedure.

- In case the procedure ended with a decision that the product is approvable, the applicant submits high quality national translations of the SmPC, PL, labelling and mock-ups (if required) no later than 5 days after the procedure is closed. MSs may introduce linguistic changes only to the SmPC, PL and labelling and must ensure their national version of product information is a faithful translation of the final harmonised position. The 'blue box concept' for adequate national information on the label and PL will be permissible.

- In case the procedure ended with a decision that the product is not approvable, all MSs need to take a final decision at national level, unless the applicant withdraws the application.

Validation [12]

The first step of the review process is for the EMEA to assess the MAA to determine whether the reviewers require additional information, data or clarification in order to conduct the review. Once the MAA is deemed valid, the CHMP establishes the timetable for scientific evaluation.

Positive outcome of the validation

In case of a positive outcome, the EMEA shall notify the applicant accordingly in writing that the validation has been successfully completed, together with the names of CHMP members to whom full or partial copies of the dossier should be sent (including any additional information supplied during the validation phase). The timetable for evaluation adopted by the CHMP will be attached to the letter confirming the positive outcome of the validation.

The EMEA, CHMP members and the appointed experts, who have received full or part dossiers, are required to fully protect the confidentiality of the data submitted to them. The EMEA will publish the International Non proprietary Name (INN) of Orphan Medicinal Products when a marketing authorization application is submitted, as well as the designated orphan indication and the name of the sponsor.

Negative outcome of the validation

Failure to provide the data, information or clarification requested, failure to adhere to the EUCTD format will result in a negative validation, of which the applicant shall be informed in writing. The applicant will be invited to either collect the dossier or have it destroyed by the EMEA. Individual arrangements should be made with the Rapporteur and Co-Rapporteur concerning copies in their possession. The applicant will be required to submit a new dossier to the EMEA should a new application be initiated in the future.

Payment of fees

The EMA will issue an invoice on the date of the notification of the administrative validation to the applicant and fees will be payable in EUROS within 45 days of the date of the said notification. The invoice will be sent to the billing address indicated by the Applicant and will contain clear details of the product and procedures involved, the type of fee, the amount of the fee, the bank account to where the fee should be paid and the due date for payment.

Need for samples and sample analysis

At the time of submission of the application there is no need of samples for testing the proposed medicinal product. During the assessment of the application the CHMP may, however, request the testing of samples of the medicinal product and/or its ingredients. In this case the Rapporteur and/or Co-Rapporteur will specify a test protocol (type of samples, number of samples, number of batches, testing to be performed and methods and specifications to be used) and agree with the EMEA which Official Medicines Control Laboratory (OMCL) or other laboratories designated for this purpose by the Member States will carry out the required testing. Sampling and testing will be co-ordinated by the EMA in collaboration with the European Directorate for the Quality of Medicines and Healthcare (EDQM).

PRE-AUTHORISATION INSPECTIONS (GMP, GCP AND GLP)

Inspections requested in connection with an application for a marketing authorisation must be adopted by the CHMP. It should be pointed out that pre authorisation inspections, where requested by the CHMP, should be carried out within the 210 days set out in the legislation for the scientific evaluation of the application and that applicants therefore are required to ensure that the sites to be inspected (manufacturing and quality control sites and/or nonclinical study sites and/or clinical trials sites) are ready for inspection from the time of submission of the application.

Inspection Team

The team required to perform the inspection will be proposed and co-ordinated by the EMA Secretariat. The team will be drawn from the inspection services of the Supervisory and other competent authorities of the EEA. On the advice of the Rapporteur and/or Co-Rapporteur the Inspection Team may include scientific experts and/or a Rapporteur for the Inspection.

Type of inspection:

GMP Inspections: Inspections may be carried out to verify compliance with European Community Good Manufacturing Practice principles and guidelines and/or to cover product or process related issues arising from the assessment of the application.

GCP Inspections: routine inspections are carried out as a routine surveillance of GCP compliance, and not all applications would necessarily give rise to a routine GCP inspection.

The applications, clinical trials and sites are selected to cover a range of different situations (e.g. size of sponsor company, origin of pivotal data, target population etc.).

The assessment of the dossier may however identify a need for a specific GCP inspection(s) (triggered inspection). These triggered inspections should be given priority due to their nature of investigating an established concern.

GLP Inspections: these are normally study related audits that are requested when it is necessary to assess in retrospect specific issues related to the assessment of the application. Exceptionally, a general GLP inspection covering general GLP compliance could be requested to verify compliance with Good Laboratory Practice Principles and Guidelines.

Validation

Detailed information on the documentation that will be reviewed from a GMP and GCP perspective during validation.

Timetable for Inspections

Inspection request(s) may be adopted by CHMP at any stage of the assessment. However, they are usually requested for adoption by CHMP at Day 90 or at the latest by Day 120. In the case of GCP inspections, they will always be addressed in the List of Questions, except in those situations when a GCP inspection is requested later in the procedure. For inspections covering specific aspects of the application, issues to be checked during the inspection will be detailed in an attachment to the Day 80 assessment report(s) or discussed with the assessors.

Inspection Reports

Inspectors will send the draft Inspection Report to the manufacturer within fifteen days of the Inspection for comments on major factual errors, point of disagreement or remedial actions. Where necessary, the manufacturer should respond within a further fifteen days to provide comments and, if necessary, an action plan with a timetable for implementation. This will be considered during the finalisation of the Inspection Report and, if necessary, attached to it.

Oral (or written) explanation

The CHMP will discuss the joint-assessment report and comments of other CHMP members. The CHMP may identify additional issues which the sponsor must address in writing or during an oral explanation. If a sponsor wishes to make an oral presentation, it usually has one month to prepare.

POST APPROVAL CHANGES

Variations

Variations are any change to the licensed details following approval in any Member State. The current variations regulation came into force on 01 January 2010. At present, there are three main types of variations detailed in the regulation:

Type IA variations

These "minor" variations generally refer to changes in the name/address of the Marketing Authorisation Holder or a change to the manufacturer's name and address, a minor change to the batch size, submission of a Certificate of Suitability for the drug substance, amongst others. These 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).

There are two types of Type IA variations

1. Type IA variations requiring immediate notification ('IAIN')

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

1.Type IA variations requiring immediate notification ('IAIN')

These 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.

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

Variations which do not require immediate notification may be submitted by the marketing authorisation holder (MAH) **within 12 months** after implementation, or may be submitted earlier should this facilitate dossier life-cycle maintenance or when necessary e.g. to ensure that the latest product information is reflected in Certificates of Pharmaceutical Products.

The 12 months deadline to notify minor variations of Type IA allows for an 'annual reporting' for these variations, where a MAH submits several minor variations of Type IA which have been implemented during the previous twelve months.

Most of these Type IA variations do not impact on the product information. However, in case of an upcoming submission of a variation, extension or other regulatory procedure which will affect the product information, the MAH should also include any Type IA changes affecting the product information, in order to keep the product information up-to-date and to facilitate document management.

The timetable for approval of a Type IA variation is 30 days.

Type IB variations

These "minor" variations generally refer to a change in the name of the product, minor changes to the method of manufacture for the drug substance or drug product, swapping one excipient for a comparable excipient, changes to batch size, change in shelf life of the drug product, etc. Type IB is the default variation type for variations not listed in the Regulation. 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 by the Marketing Authorisation Holder (MAH) before implementation, but do not require a formal approval. Upon acknowledgement of receipt of a valid notification, 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).

The timetable for approval of a Type IB variation is 30 – 90 days.

Type II variations

These "major" variations are any variations that are specifically listed in the Regulation and they require prior approval before they can be implemented. They often require clinical, non-clinical and/or quality expert statements or justifications, depending on the change. These variations are not an extension and which may have a significant impact on the Quality, Safety or Efficacy of a medicinal product. These major variations require prior approval before implementation ('Prior authorisation' procedure).

The timetable for approval is 30 – 90 days, although the usual time is 60 days.

Table 1. Dissolution Specifications as per dissolution method 1 of USP

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 15
2	4	10–40
3	8	50–85
4	10	65–95
5	16	NLT 80

Table 2. Dissolution Specifications as per dissolution method 2 of USP

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	NMT 15
2	4	10–30
3	8	47–72
4	10	60–85
5	16	NLT 80

Table 3. Dissolution Specifications as per dissolution method 3 of USP

Time Point (i)	Time (h)	Amount Dissolved (%)	
		100 mg/Tablet and 300 mg/Tablet	200 mg/Tablet
1	2	NMT 40	NMT 35
2	4	45–75	32–62
3	8	NLT 70	NLT 70
4	16	NLT 85	NLT 85

Table 4. Impurities

Name	Relative retention time	Relative response factor	Acceptance criteria NMT (%)
Desmethyl tramadol (impurity D)[a]	0.57	1.0	0.20
Tramadol related compound A [b]	0.84	1.0	0.2
Tramadol hydrochloride	1.00	-----	------
1,6 Olefin [c]	2.78	3.0	------
1,2 Olefin [d]	3.28	2.2	------
Individual unspecified impurity	---	1.0	0.20
Total impurities	---	-----	0.60

[a]3-{(1RS,2RS)-2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl}phenol; [b]RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride; [c]1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-6-ene hydro-chloride (identified and reported as an individual unspecified impurity if present); [d]1-(3-Methoxyphenyl)-2-(dimethylaminomethyl) cyclohex-1-ene hydro-chloride (identified and reported as an individual unspecified impurity if present).

Table 5. Flow chart for the mutual recognition procedure

Approx. 90 days before submission to CMS	Applicant requests RMS to update Assessment Report (AR) and allocate procedure number.
Day -14	Applicant submits the dossier to CMS. RMS circulates the AR including SPC, PL and labelling to CMSs. Validation of the application in the CMSs.
Day 0	RMS starts the procedure
Day 50	CMSs send their comments to the RMS and applicant
Day 60	Applicant sends the response document to CMSs and RMS
Until Day 68	RMS circulates their assessment of the response document to CMSs.
Day 75	CMSs send their remaining comments to RMS and applicant. A break-out session can be organised between day 73 – 80)
Day 85	CMSs send any remaining comments to RMS and applicant.
Day 90	CMSs notify RMS and applicant of final position (and in case of negative position also the CMD secretariat of the EMEA). If consensus is reached, the RMS closes the procedure. If consensus is not reached, the points for disagreement submitted by CMSs are referred to CMD(h) by the RMS within 7 days after Day 90.
Day 150	For procedures referred to CMD(h): If consensus is reached at the level of CMD(h), the RMS closes the procedure. If consensus is not reached at the level of CMD(h), the RMS refers the matter to CHMP for arbitration
5 days after close of procedure	Applicant sends high quality national translations of SPC, PL and labeling to CMSs and RMS.
30 days after close of procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

Table 6. Flow Chart of the Decentralised Procedure

Pre-procedural Step	
Before Day -14	Applicant discussions with RMS RMS allocates procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSs Validation of the application. Positive validation should only be indicated in CTS, not via e-mail.
Assessment step I	
Day 0	RMS starts the procedure. The CMS are informed via CTS.
Day 70	RMS forwards the Preliminary Assessment Report (PrAR) (including comments on SmPC, PL and labelling) on the dossier to the CMSs and the applicant
Until Day 100	CMSs send their comments to the RMS, CMSs and applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments
Until Day 105	Consultation between RMS and CMSs and applicant. If consensus not reached RMS stops the clock to allow applicant to supplement the dossier and respond to the questions.
Clock-off period	Applicant may send draft responses to the RMS and agrees the date with the RMS for submission of the final response. Applicant sends the final response document to the RMS and CMSs within a period of 3 months, which can be extended by a further 3 months.
Day 106	RMS restarts the procedure following the receipt of a valid response or expiry of the agreed clock-stop period if a response has not been received. The CMS are informed via e-mail and CTS will be updated accordingly.
Assessment step II	
Day 120 (Day 0)	RMS sends the DAR, draft SmPC, draft labelling and draft PL to CMSs and the applicant
Day 145 (Day 25)	CMSs send comments to RMS, CMSs and the applicant. It may also be sufficient for the CMS to indicate in CTS only in case there are no additional comments.
Day 150 (Day 30)	RMS may close procedure if consensus reached Proceed to national 30 days step for granting MA
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate outstanding issues with applicant, receive any additional clarification, prepare a short report and forward it to the CMSs and the

	applicant
Day 195 (at the latest)	A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues
Between Day 195 and Day 210	RMS consults with the CMSs and the applicant to discuss the remaining comments raised.
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SmPC, labelling and PL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus on a positive RMS AR was not reached at day 210, points of disagreement will be referred to the Co-ordination group for resolution
Day 270 (at the latest)	Final position adopted by Co-ordination Group with referral to CHMP for arbitration in case of unsolved disagreement
National step **5 days after close of procedure**	Applicant sends high quality national translations of SmPC, labelling and PL to CMSs and RMS
30 days after close of the procedure	Granting of national marketing authorisation in RMS and CMSs if outcome is positive and there is no referral to the Co-ordination group. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).
30 days after close of CMD referral procedure	Granting of national marketing authorisation in RMS and CMSs if positive conclusion by the Co-ordination group and no referral to the CHMP/CVMP. (National Agencies will adopt the decision and will issue the marketing authorisation subject to submission of acceptable translations).

DISCUSSION AND CONCLUSION

Drug development to commercialization is highly regulated. Every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality. These standards are set by regulatory authorities of their respective countries such as EMEA in Europe. Regulation affects all aspects of the pharmaceutical world, from independent innovators and pharmaceutical companies to regulatory and administrative bodies and patients also. Regulatory department is crucial link between company, products and regulatory authorities whose positive or negative standpoint foster the insight of the regulatory authority into the industry, for good or for bad. So, the better the scientific precision, the greater will be the chances for a product to come to the market within the expected time. Licences for medicines are granted only when a product meets high standards of safety and quality and works for the purpose intended. The regulatory system also imposes rigorous standards on medicines manufacturers and wholesale dealers who trade in them.

A licence, also referred to as a marketing authorisation, from the EMEA/concerned state authority is required before any medicine can be used to treat people in the Europe.

To begin the process, companies and/or researchers must apply to the EMEA/concerned state authority for permission to test drugs through clinical trials, if these trials are to be conducted in the Europe. In order to receive permission to run a trial, they must first satisfy the EMEA/concerned state authority that they have met strict safety criteria. All the test results from these trials on how well the medicine works and its side effects, plus details of what the medicine contains, how it works in the body, and who it is meant to treat, are then sent to the EMEA/concerned state authority for detailed assessment. The assessment team is made up of experts from different relevant specialties, each of whom has undergone additional training in medicines assessment. The length of the assessment process depends on the type of medicine as well as the quality of the initial information supplied by the manufacturer, how much further detail is required, and how soon queries can be resolved. In the past, all this information used to be supplied in paper format; now it is supplied electronically, to minimise procedural delays. The EMEA/concerned state authority also has to comply with strict timeframes and performance targets for the licensing of medicines.

Once the EMEA/concerned state authority is satisfied that the medicine works as it should, and that it is acceptably safe, it is given a marketing authorisation or product licence. The pharmaceutical company and any wholesalers must also be able to satisfy the MHRA that the manufacture, distribution, and supply of the medicine meet the required safety and quality standards.

Most new types of medicine are licensed by the EMEA, to ensure that it is available to, and used in the same way, across all the member states of the European Union (EU). In my thesis, I explained in detail about the regulatory requirements for a generic drug to get marketing authorization in Europe.

EMEA is responsible for the scientific evaluation of applications for European Union (EU) marketing authorisations for human and veterinary medicines in the centralisedprocedure. Under the centralised procedure, pharmaceutical companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised marketing authorisation is valid in all European Union (EU) Member

States, as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. By law, a company can only start to market a medicine once it has received a marketing authorisation.

In the European Union (EU), medicines can be authorised by the centralised authorisation procedure or national authorisation procedures.

Centralised authorisation procedure

The European Medicines Agency is responsible for the centralised procedure for human and veterinary medicines. This procedure results in a single marketing authorisation that is valid in all European Union countries, as well as in Iceland, Liechtenstein and Norway.

The centralised procedure is compulsory for:

- human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases;
- veterinary medicines for use as growth or yield enhancers;
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- Officially designated 'orphan medicines' (medicines used for rare human diseases).

For medicines that do not fall within these categories, companies have the option of submitting an application for a centralised marketing authorisation to the Agency, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorisation would be in the interest of public or animal health. Applications through the centralised procedure are submitted directly to the Agency. Evaluation by the Agency's scientific committees takes up to 210 days, at the end of which the committee adopts an opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the EuropeanCommission, which has the ultimate authority for granting marketing authorisations in the EU. Once a marketing authorisation has been granted, the marketing-authorisation holder can begin to make the medicine available to patients and healthcare professionals in all EU countries.

National authorisation procedures

Each EU Member State has its own procedures for the authorisation, within their own territory, of medicines that fall outside the scope of the centralised procedure. Information about these national procedures can normally be found on the website of the national medicine authority in the country concerned. There are also two possible routes available to companies for the authorisation of these medicines in several countries simultaneously:

- **Decentralised procedure**: companies can apply for the simultaneous authorisation in more than one EU country of a medicine that has not yet been authorised in any EU country and that do not fall within the mandatory scope of the centralised procedure;
- **Mutual-recognition procedure:** companies that have a medicine authorised in one EU Member State can apply for this authorisation to be recognised in other EU countries.

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