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Regulatory Requirements for Marketing Authorization of Generic Parentral Product in European Conutries by Decentralised Procedure

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ABSTRACT:

There are three procedures by which a marketing authorisation in EU can be obtained, Centralised Procedure which is compulsory for any novel medicinal products, subject to agreement by Committee on Proprietary Medicinal Products (CPMP), Mutual Recognition Procedure (MRP) which commences only after a marketing authorisation has been issued in a EU member state, which then becomes the Reference Member State (RMS) and the Decentralised Procedure which is applicable in cases where an authorisation does not yet exist in any of the EU Member States. This review article attempts to an insight on the recent regulatory aspects and marketing authorisation procedures in Europe by giving a detailed overview of the decentralised procedure along with the proper timelines to aid various pharmaceutical applicants to make proper marketing applications and place their products in the European Markets. Decentralised procedure came into operation in late 2005. Identical dossiers are submitted in all MS where a marketing authorization is sought. A RMS, selected by the applicant, will prepare draft assessment documents and send them to the CMS. They, in turn, will either approve the assessment or the application will continue into arbitration procedures. Decentralised Procedure involves CMS at an earlier stage of the evaluation than under the MRP in an effort to minimize disagreements and to facilitate the application for marketing authorisation in as many markets as possible.

KEY WORDS: Centralised, Mutual Recognition, Decentralised Procedure, common technical document

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INTRODUCTION [1, 2, 3]:

The European system for the authorisation of medicinal products for human and animal use was introduced in January 1995 with the objective of ensuring that safe, effective and high quality medicines could quickly be made available to citizens across the European Union.

The decentralised procedure, which was introduced with the legislative review of 2004, is also applicable to the majority of conventional medicinal products. Through this procedure an application for the marketing authorisation of a medicinal product is submitted simultaneously in several Member States, one of them being chosen as the "Reference Member State". At the end of the procedure national marketing authorisations are granted in the reference and in the concerned Member States.

Using the decentralized procedure, manufacturer can apply for simultaneous authorization in more than one EU country, that have not yet been authorized in any EU country and that do not fall the mandatory scope of the centralized procedure.

It provides guidance for application of generic drug application and how to seek approval of pharmaceutical dossier in European countries using decentralised procedure.

REGULATORY REQUIREMENTS FOR MARKETING AUTHORIZATION OF GENERIC PARENTRAL PRODUCT IN EUROPE [4, 5]:

Types of procedure for application to Europe:

1. Centralized Procedure
2. Mutual Recognition Procedure
3. Decentralized Procedure

1. Centralised Procedure:

Which is compulsory for products derived from biotechnology, for orphan medicinal products and for medicinal products for human use which contain an active substance authorised in the Community after 20 May 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes. The centralised procedure is also mandatory for veterinary medicinal products intended primarily for use as performance enhancers in order to promote growth or to increase yields from treated animals. Applications for the centralised procedure are made directly to the European Medicines Agency (EMA) and lead to the granting of a European marketing authorisation by the Commission which is binding in all Member States.

2. **Mutual recognition procedure** :

Applicable to the majority of conventional medicinal products, is based on the principle of recognition of an already existing national marketing authorisation by one or more Member States.

3. **Decentralized procedure:**

Using the decentralized procedure, manufacturer can apply for simultaneous authorization in more than one EU country, that have not yet been authorized in any EU country and that do not fall the mandatory scope of the centralized procedure.

Advantages:

1. The applicant need not go through the entire cycle of Dossier filing Queries Reply to queries Approval in all the EU member countries.
2. Approval in multiple countries through single procedure.
3. Time of approval in various EU member countries can be minimized.
4. Costs can be reduced.

Outline of Decentralised Procedure:

(i) Pre-procedural Step

(ii) Assessment step I

(iii) Assessment step II

(iv) National step

TABLE 1: FLOW CHART OF DECENTRALISED PROCEDURE [5]

Pre-procedural Step	
Before Day -14	Applicant discussions with RMSRMS allocate procedure number. Creation in CTS.
Day –14	Submission of the dossier to the RMS and CMSsValidation of the application.
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PrAR),SPC , PL and labeling to the CMSs
Until Day 100	CMSs send their comments to the RMS
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 theRMS and CMSs within a recommended period of 3 months, which could be extended if justified
Day 106	Valid submission of the response of the applicant received. RMS restarts the procedure
Day 106 - 120	RMS updates PrAR to prepare Draft Assessment Report (DAR) draft SPC,Draftlabeling and draft PIL to CMSs.
Day 120	RMS may close procedure if consensus reached. Proceed to national 30 days step For granting MA.

Assessment step II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labeling and draftPIL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
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 and prepare a short report for discussion at Coordination Group
Until Day 205 (Day85)	Breakout Group of involved Member States reaches consensus on the matter
Day 210 (Day 90)	Closure of the procedure including CMSs approval of assessment report, SPC, Labeling and PIL, or referral to Co-ordination group. Proceed to national 30 days step for granting MA.
Day 210 (at the latest)	If consensus 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/CVMP forarbitration in case of unsolved disagreement
National step	
Day 110/125/155/215/	**275** Applicant sends high quality national translations of SPC, labeling and PIL to CMS and RMS
Day 135/150/180/	**240** Granting of national marketing authorization in RMS and CMSs if 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).
Day 300	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).

Involved members/groups in DCP:

1. RMS- Reference member state Roles:

- Acts as a link between the applicant (Pharma Company) and the CMSs
- Allocation of procedure number
- Starting the procedure
- Involved in the preparation of preliminary and draft-assessment reports, initial comments on - SmPC (summary of product characteristics), labeling and package leaflets provided in the dossier.
- Stopping and restarting the procedure, before and after clock stop period.
- Closing the procedure if consensus is reached.

2. CMS(s)-Concerned member state(s) Roles:

- Involved in the approval/disapproval of RMS's - preliminary and draft-assessment reports, initial comments on SmPC (summary of product characteristics), labeling and package leaflets
- Involved in earlier stages of DCP to avoid disagreements between CMS and RMS.

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)

CMDh has following responsibilities:

In case of disagreement between the Member States involved in a Mutual recognition or decentralised procedure on the Assessment report, the summary of product characteristics, the labelling or the package leaflet on the grounds of "potential serious risk to public health", the points of disagreement are considered by the CMDh. The CMDh uses its best endeavours to reach agreement on the action to be taken within the 60 day time period foreseen in the legislation.

To lay down, yearly, a list of medicinal products for which a harmonised summary of product characteristics should be drawn up, to promote harmonisation of marketing authorisations across the Community.

The Committee for Medicinal Products for Human Use (CHMP)-

If consensus is not reached at CMDh the points of disagreement will be referred to CHMP.

CTD format [7]:

Dossier is submitted in CTD format
Aim: To harmonize the structure and format of registration documentation.

Benefits:

- Complete, well-organized submissions
- Facilitates electronic submissions
- Easier analysis across applications etc.

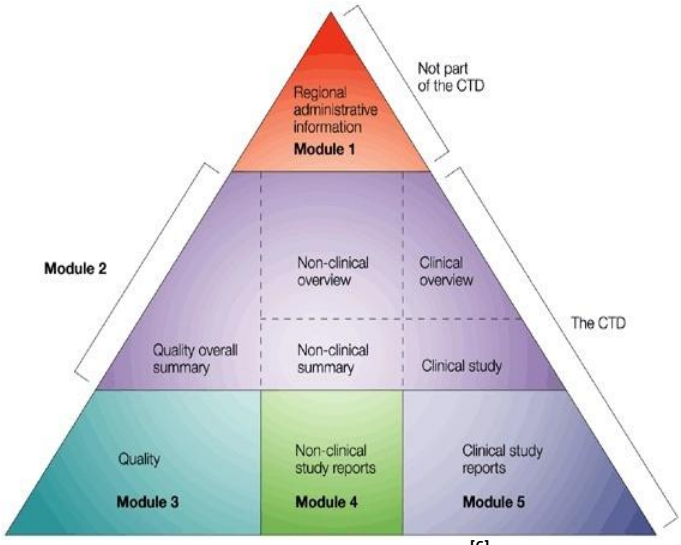

FIGURE 1: CTD TRIANGLE [6]

CTD is organized into five modules:

Module 1 is region specific and Module 2, 3, 4 and 5 are intended to common for all regions.

MODULE 1: ADMINISTRATIVE INFORMATION:

It should contain documents specific to each region e.g. application forms or the proposed label for use in the region.

1.1 Table of contents
1.2 Documents specific to each region (e.g., application forms, priscribing information)

MODULE 2: CTD SUMMARIES

It contains general introduction to the pharmaceutical (its pharmaceutical class, mode of action, proposed clinical use)

2.1 CTD table of contents
2.2 CTD introduction
2.3 Qualities overall summary
2.4 Non-clinical overview
2.5 Clinical overview
2.6 Non-clinical written and tabulated summaries
2.7 Clinical summaries

MODULE 3: QUALITY

3.1 table of contents
3.2 body of data (drug substance, drug product & regional information)
3.3literature references

MODULE 5: CLINICAL STUDY REPORTS

5.1 table of contents of module 5
5.2 tabular listing of all clinical studies
5.3 clinical study reports (BA/BE)
5.4 literature references

Parenteral product does not required BA/BE studies According to guideline “Guideline on the Investigation of Bioequivalence”.

CONCLUSION:

Discussion between industry and regulatory bodies is going on till date regarding the requirements for submission of generic application. EMEA published draft guidance for requirements of parenteral products since long, so as to make it ready to refer regulatory requirements this article has been executed. There were tried to summaries cumulative requirements for parenteral although as it was very well understood after such a long innovation time for that each parenteral products have its own characteristics hence requirements would be differ according to the nature of it.

The aim of this article was to examine how a parenteral product can be approved using a decentralised procedure by Reference Member State (RMS) and concern member states (CMS) and provide general guidance of CTD format In particular, the preparation of Module 1 —Administrative, regional or national information, module 2-CTD summary ,module 3-quality,module 5- clinical study reports.

After all this article will be helpful to understand requirements for the dossier filling by decentralised procedure which can be help to file into different European countries.

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