

# **MARKETING AUTHORIZATION**

- Every country has its basic legislation concerning medicinal product for human use. The marketing authorisation of the product is granted by the competent health authority. The marketing authorisation of the respective drug is granted and renewed on the basis of the favorable risk-benefit balance which has to maintain throughout the entire life cycle of the medicinal product. The life cycle of the medicinal product can be described as:
  - Development, corresponding to the pre-submission phase
  - Marketing (includes Marketing routine production)
  - Discontinuation of marketing, which may correspond to the expiration of the marketing authorization

- European Union (EU) is a hub of political and economic union of 28 member states (MS) and extensive amount of effort was spent by the EU Commission, the EU parliament, the EMA and the national authorities in updating the EU regulatory environment for pharmaceuticals and granting marketing authorizations within the EU. The primary objective of European Regulation is to safeguard public health, encouraging the development of the pharmaceutical industry of the European Union (EU)
- Prior to marketing a medicinal product in EU a marketing authorization (MA) (product license) must be obtained. The company is responsible (more specifically “Marketing Authorisation Holder”) for placing the medicinal product on the market. A major and important step was taken in 1995 for the evaluation of medicinal products by forming the European Medicines Evaluation Agency, EMA and the establishment of a centralized procedure, leading to a single EU wide evaluation and approval of new medicines

# **PROCEDURES AND APPLICATIONS FOR MARKETING AUTHORIZATION OF MEDICINAL PRODUCTS**

In general there are 4 types of marketing authorization for the drug product to enter into European Union drug market.

A) Initial Marketing Authorization:

1. CENTRALISED PROCEDURE
2. MUTUAL RECOGNITION PROCEDURE
3. NATIONAL PROCEDURE
4. DECENRALISED PROCEDURE

- 1. CENTRALIZED PROCEDURE:
- The 'centralized procedure' for authorizing medicinal products is laid down in Regulation (EC) No726/2004. The centralized 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 authorized 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 procedure is also compulsory for the products which are used as performance enhancers or to increase yields from animals

- I) PRE-SUBMISSION:
- a draft summary of product characteristics;
- Eligibility
- Strength
- Type of application
- Statement of intention to request for accelerated assessment
- Statement of whether Orphan designation is valid or pending
- Proposed invented name
- Request for total or partial fee exemptions

- When an applicant decides to apply to the EMA for the drug product authorization then at least seven months before the submission of application, the applicant should notify the EMEA of their intention to submit an application. So, the applicant will have the opportunity to meet the EMA's product team in person in a PreSubmission meeting where the procedural, regulatory and legal advice will be provided to the applicant
- The applicant's request for eligibility for evaluation via the Centralized Procedure, together with a justification and other documents is presented to all CHMP [Committee for Medicinal Products for Human Use] members. Following discussion at CHMP, the EMEA informs the applicant whether the product is eligible for evaluation via the Centralized Procedure

- Amongst the members of CHMP a Rapporteur and a CoRapporteur will be appointed for the purpose of scientific evaluation and to prepare an Assessment Report for the CHMP on the application. This Assessment report will be submitted to the CHMP and EMA on DAY 80 where a peer review will be done by the members of CHMP for the validity of Scientific/Regulatory conclusions. A list of Questions raised by the CHMP along with the conclusions and review of scientific data will be sent to the applicant on DAY 120. At this point EMA stops the clock for giving time to applicant for responding to the data with proper responses. After receipt of the responses from the applicant, the CHMP adopts a timetable for the evaluation of the responses



- The EMEA ensures that the opinion of the CHMP is given in 90 additional days. After the positive opinion of CHMP, the applicant provides the EMEA with final translations of the necessary documents in all EU languages and the clock resumes from this point. A draft decision will be prepared within fifteen days by the commission on the application, and then the medicinal product will be assigned by a Community registration number which will be placed on product's package if the authorisation is granted. Finally, within 30 days the EMEA transmits the CHMP opinion and other required documents to the European Commission, and the Members of the Standing Committee, and to Norway and Iceland.
- The applicant may go for the other procedures like Mutual Recognition Procedure (MRP) or the Decentralized Procedure (DCP) if the product does not fall within the mandatory scopes of the Centralized Procedure (CP)

- **Mutual Recognition Procedure:** The Regulation for the mutual recognition procedure is laid down in Directive 2001/83/EC. The mutual recognition procedure is mandatory for all medicinal products to be marketed in a Member State other than they were first authorized, since 1 January 1998. The mutual recognition procedure is used in order to obtain marketing authorizations in several Member States where the medicinal product in question has received a marketing authorization in any of the Member State at the time of application.
- **Procedure for Mutual Recognition Procedure (MRP):** An application for this procedure can be sent to one or more Member States. The applications sent should be similar and all Member States must be informed of them. When a Member State decides to assess the application (at this point it becomes the "Reference Member State" RMS), it announces the decision to other Member States (which then become the "Concerned Member States" CMS), to whom applications have also been submitted by the applicant. At this juncture the CMS will suspend their evaluations on the particular application and waits for the RMS's decision on the application

- Usually the procedure ends with the marketing authorization granted by the RMS after the evaluation of the application. In the other case RMS can be the country which had already approved the product; in such a case the RMS updates the existing assessment report in 90 days. The updated report will be sent to all the member states along with the summary of product characteristics (SPC), labeling and package leaflet. After receiving the reports from RMS, the Concerned Member States will have 90 days to recognize the decision made by the RMS on the report and the other documents. Upon the positive decision, a national marketing authorization will be granted in each of the CMS(s)

### **3. NATIONAL PROCEDURE:**

- The national procedure is like the other procedures but in this case only one member state is involved. The documents submitted to an authority are very specific to that particular authority and evaluation of the application is carried out by the same member state. The evaluation time for an application for a national marketing authorization is 210 days from the receipt of the application. But this procedure is stringently limited from 1 January 1998 to the early phase of mutual recognition (granting of the marketing authorization by the Reference Member State) and to medicinal products which are not to be authorized in more than one Member State.

- **4. DECENTRALIZED PROCEDURE:**

- The new Decentralized procedure came into effect in the European Union in 2005 and is regulated by Directive 2004/27/EC. The main purpose of this procedure is to acquire marketing authorizations in several Member States, even though there are no marketing authorization has been granted in the European area.
- Steps involved in Decentralized procedure (DCP): The applicant has to send an application to the respective authorities of each and every member States, where there is plan to attain a marketing authorization. Unlike MRP, here the applicant may assign a country to act as the Reference Member State. This selection can be based on many criteria like workload, previous experience, interests of the applicant and acceptance of the applied dossier by the RMS.

- The RMS will commence the assessment after the application is decided to be complete by both the RMS and all the CMS(s). The RMS then forwards a preliminary Assessment Report on the submitted dossier to the CMS(s) and the applicant in a period of 70 days. The CMS(s) is requested to give comments on the proposed national prescription status and to inform the RMS. On day 105, the RMS will forward all observation and remarks from the CMS(s) to the applicant and stops the clock if necessary, until the applicant prepares a response document for the comments sent. The RMS prepares a Draft Assessment Report on day 120 and may close the procedure if a consensus has been reached between the CMS(s) and the RMS. Otherwise the CMS(s) has 90 more days to approve the Draft Assessment Report, and other documents.
- Authorities of the RMS and the CMS(s) agree to a decision within 30 days after acknowledgement of their agreement to the Assessment Report and other documents. Upon the positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS(s)

- Coordination Group for Mutual Recognition and Decentralized Procedure for Human Medicinal Products (CMDh): When one or more Member States cannot recognize an authorization already granted in an MRP or a final assessment and the product information prepared in a DCP, the disagreement is referred to the Coordination Group for Mutual Recognition and Decentralized Procedure for Human Medicinal Products (CMDh). Within a timeframe of 60 days, Member States shall, within the coordination group, make all efforts to reach a consensus. In case this fails, the procedure is submitted to the appropriate EMEA scientific committee (CHMP or CVMP, as appropriate). The opinion of the EMEA Committee is then forwarded to the Commission, for the start of the decision making process.

## **VARIATIONS:**

- Variations are nothing but the modifications requested by the applicant after the grant of a marketing authorization. The submission of variation applications makes sure that the dossier and the Summary of Product Characteristics (SPC) are always kept up to date.
- During the life cycle of a medicinal product, the modifications are repeatedly made to the dossier, which may be simple changes, such as a change in the manufacturing method or a change in a manufacturer (Type 1 variations) and also can be quite complex, such as the application for a new indication, where new clinical and pre-clinical data has to be presented



## **Type IA VARIATIONS (NOTIFICATIONS: “DO AND TELL”):**

- Type IA and Type IAIN: In case of Type IA variations notification shall be submitted within 12 months from the date of implementation and in case of Type IAIN variations notification shall be submitted immediately after implementation. This type of variations does not have serious impact on quality, safety and efficacy of product. [ Type IB: (“TELL, WAIT and DO”)]
- Type IB Variations are processed in an efficient and timely manner. The quality of the submission and supporting documentation is responsibility of Marketing Authorization Holder (MAH)
- This type of variations also does not have any potential effect on the quality, safety and efficacy of product. But, without proper supporting documentation the case may be considered as Type II Variation

# MARKETING AUTHORIZATION PROCEDURES

## **Type II Variations:**

- These types of variations have significant impact on quality, safety and efficacy of product and require prior approval before implementation.
- The 60 and 90-day time frames for evaluation of procedure are maximum time lines thus allowing flexibility for shorter procedures in particular situations. In such cases MAH should contact to the RMS as soon as possible for proposed procedure.

## **Extension of a marketing authorization:**

- A line extension is a change to a marketing authorization that cannot be classified as a variation. Line extension applications are examined in accordance with the procedure for the granting of a new marketing authorization.
- Examples of a line extension are:
  - Application for a product with a new strength
  - Application for a product with a new pharmaceutical form
  - The dossier of the line extension can partially refer to the dossier of the initial product.

The eCTD standard has advantages, which can be summarized as follows:

- For pharmaceutical companies it facilitates changing and reuse of documents
  - Following the changes throughout the lifecycle
- Creating links to other documents

But eCTD is not only an “electronic CTD”, because it covers the content, meta data, and structure of the application within the XML backbone, spans the full product lifecycle, and always provides the current information in context, without having cross-reference and duplicate information manually, it is more definitive - no file can be modified without any control, it stores the version numbers of the documents.

- **Dossier Compilation: T**

- The compilation of a dossier based on the eCTD standard specified the Module 1 contain the region specific administrative and prescribing product information and Module 2-5 as per the ICH specifications. The ICH CTD specifies that Module 1 should contain region specific administrative and prescribing product information. Module 1 is country specific and it contains information as below:
- 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
- 1.3.5 Consultation with Target Patient Groups
- 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 Biosimilar Applications
- 1.5.3 (Extended) Data / Market Exclusivity
- 1.5.4 Exceptional Circumstances
- 1.5.5 Conditional Marketing Authorization
- 1.6 Environmental Risk Assessment
- 1.6.1 Non-GMO
- 1.6.2 GMO
- 1.7 Information relating to orphan market exclusivity (if required)
- 1.7.1 Similarity
- 1.7.2 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 Pediatrics
- 1.11 Responses to Questions
- 1.12 Additional Data.

- Regulatory requirement for the approval of the medicinal drug in European Union was found to be more rigid.
- EU has different types of procedure and different types of applications which will specify the product and time frame required for the approval of the drug which helps in tracking of life of the respective product.
- The retaining of the current marketing authorization systems, DCP together with scope of CP provide a great flexibility of the choice between different marketing authorizations and also allowed to go for the national application of medicinal product.
- To harmonies and fasten the process of medicinal product evaluation, the European Union adopted the eCTD format for the submission.