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Procedures and Applications for Marketing Authorisation of Medicinal Products in European Union

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Abstract:
The European Union is a confederation of 28 member states that are located in Europe. A single market system has been developed in European Union by the laws, this leads to completely different type of procedures for entering into EU market. European regulation has established and harmonized many aspects of regulating the production, distribution, and use of medicines in the EU. This article discusses the ways and procedures for entering into one of the world's prestigious market. It also describes about the post authorization steps and applications along with fees for obtaining different types of marketing authorization in EU.

Keywords:
EMA, European Union, Marketing procedure, CP, DCP, MRP, Marketing applications.

INTRODUCTION:

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 favourable 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 27 member states (MS) and extensive amount of effort was spent by the EU Commission, the EU parliament, the EMEA 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, EMEA and the establishment of a centralized procedure, leading to a single EU wide evaluation and approval of new medicines.[3]

PROCEDURES AND APPLICATIONS FOR MARKETING AUTHORISATION OF MEDICINAL PRODUCTS:

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

A) Initial Marketing Authorisation:

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

1. CENTRALISED PROCEDURE:

The 'centralised procedure' for authorising medicinal products is laid down in Regulation (EC) No726/2004. The centralised procedure, which is compulsory for products derived from biotechnology, for orphan medicinal products (Fees Exemption will be given in this case) 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. [1]
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 valid or pending

- ✓ Proposed invented name
- ✓ Request for total or partial fee exemptions, etc.

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 Pre-Submission 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 Co-Rapporteur 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. [2]

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). [2] [5]

DAY	ACTION
1	Start of the procedure
80	Receipt of the Assessment Report(s) or critique from Rapporteur and Co- Rapporteur(s) and EMA sends this report to applicant as preliminary conclusions
100	Rapporteur, Co-Rapporteur, other CHMP members and EMEA receive comments from Members of the CHMP (incl. peer reviewers)
115	Receipt of draft list of questions from Rapporteur and Co-Rapporteur, as discussed with the peer reviewers, by CHMP members and EMA
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMA
	CLOCK STOP (for GMP/GLP/GCP inspection)
121	Submission of the responses, including revised summary of product characteristics labelling and package leaflet texts in English, and restart of the clock.
150	EMA sends joint Assessment Report to the applicant making it clear that it only their preliminary conclusions and that it is for information only
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP Members
180	CHMP discussion and decision on the need for adoption of a list of "Outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation
181	Restart the clock and oral explanation (if needed)
181 to 210	210 Final draft of English summary of product characteristics, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMA and other CHMP members.
215	Applicant provides the EMEA with summary of product characteristics, Annex II, labelling and package leaflet and Annex A in the 20 languages
232	Applicant provides EMEA with final translations of summary of product characteristics, Annex II, labelling and package leaflet in the 20 languages, taking account comments received from Member States by Day 229.
By 237	Transmission of Opinion and Annexes in all EU languages to applicant, Commission, and Members of the Standing Committee, and Norway and Iceland.
By 246	Applicant provides EMEA with one final full colour 'worst-case' mock-up of outer and inner packaging for each pharmaceutical form.

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 authorised, since 1 January 1998.

The mutual recognition procedure is used in order to obtain marketing authorisations in several Member States where the medicinal product in question has received a marketing authorisation in any of the Member State at the time of application. [5]

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. [6]

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), labelling and package leaflet. After receiving the reports from RMS, the Concerned Member States will have 90 days to recognise 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).

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
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 CMS(s) 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 labelling to CMSs and RMS.
30 days after close of Procedure	Granting of national marketing authorisations in the CMSs subject to submission of acceptable translations.

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 authorisation by the Reference Member State) and to medicinal products which are not to be authorised in more than one Member State.

4. DECENTRALISED PROCEDURE:

The new Decentralised 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. [5]

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).

Pre-procedural Step	
Before Day -14	Applicant discussions with RMS, RMS allocate procedure number.
Day –14	Submission of the dossier to the RMS and CMSs.
Assessment step I	
Day 0	RMS starts the procedure
Day 70	RMS forwards the Preliminary Assessment Report (PrAR),to 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 and ask applicant to respond to the questions and supplementation to dossier.
Clock-off period	Applicant may send the response document to the RMS 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, draft labelling and draft PIL to CMSs.
Day 120	If consensus reached procedure closed and start of national step.
Assessment step II	
Day 120 (Day 0)	If consensus not reached RMS sends the DAR, draft SPC, draft labelling and draft PL to CMSs
Day 145 (Day 25)	CMSs sends final comments to RMS
Day 150 (Day 30)	If consensus reached procedure close.
Until 180 (Day 60)	If consensus is not reached by day 150, RMS to communicate with applicant and ask for additional information.
Until Day 205 (Day85)	Breakout Group of involved Member States reaches consensus on the matter
Day 210 (Day 90)	Closure of the procedure.
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 decision by Co-ordination Group with referral to CHMP/CVMP for arbitration in case of unsolved disagreement.
National step	
Day 110/125/155/215/275	Applicant sends high quality national translations of SPC, labelling and PIL to CMS and RMS.
Day 135/150/180/240	Granting of national marketing authorisation in RMS and CMSs if no referral to the Co-ordination group.
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.

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. [5]

TYPES OF APPLICATION FOR EU MARKETING AUTHORIZATION:

Legal types of marketing authorization as follows:

CLASS	DETAILS	LEGAL TYPE
Full dossier	Contain complete CTD modules	Article 8(3)
Generic	Pure generic application	Article 10(1)
Generic, additional data	Hybrid	Article 10(3)
Bio similar	Generic biotech products	Article 10(4)
Bibliographic application, Well established use	Pre-clinical and Clinical data	Article 10(a)
Fixed combination products	Pre-clinical and Clinical data for combination	Article 10(b)
Informed consent	Innovators generic product (Duplicate dossier)	Article 10(c)

VARIATIONS:

Variations are nothing but the modifications requested by the applicant after the grant of a marketing authorisation. 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 2 variations).

Type IA VARIATIONS (NOTIFICATIONS: "DO AND TELL"):

Type IA and Type IA_{IN}:

In case of Type IA variations notification shall be submitted within 12 months from the date of implementation and in case of Type IA_{IN} variations notification shall be submitted immediately after implementation. This type of variations does not have

serious impact on quality, safety and efficacy of product. [4]

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.

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.

Variation fees to be paid to the national competent authorities:

Basic fee	267 400 EURO For a single strength associated with one pharmaceutical form and one presentation.
Additional fee	+ 26 800 EURO For each additional strength or pharmaceutical form including one presentation, submitted at the same time as the initial application for authorisation.
	+ 6 700 EURO For each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation.

Application for which a full dossier need not be presented:

Basic fee	172 800 EURO For an application for a marketing authorisation pursuant to Article 10(4) of Directive 2001/83/EC. This fee is for a single strength associated with one pharmaceutical form and one presentation.
Additional fee	+ 10 300 EURO For each additional strength or pharmaceutical form including one presentation submitted at the same time as the initial application for authorisation.
	+ 6 700 EURO For each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation.
Basic fee Article 10(1)	103 800 EURO This fee is for applications for marketing authorisation a single strength associated with one pharmaceutical form and one presentation.
Additional fee Article 10(1)	+ 10 300 EURO For each additional strength or pharmaceutical form including one presentation submitted at the same time as the initial application for authorisation.
	+ 6 700 EURO For each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation.

Extension of a marketing authorization:

A line extension is a change to a marketing authorisation that cannot be classified as a variation. Line extension applications are examined in accordance with the procedure for the granting of a new marketing authorisation. [7]

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.

Level I:

Basic fee (Level I)	80 300 EURO
Additional fee Add.Strength/Potency	+ 20 100 EURO
Add Pharm Form	+ 6 700 EURO

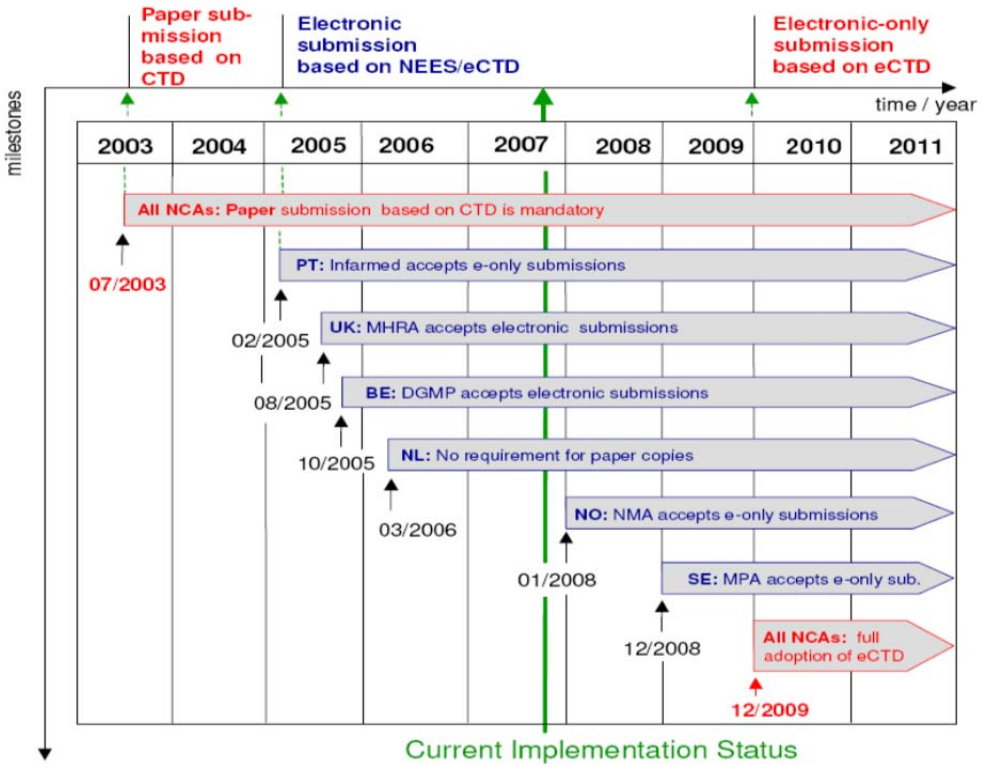
Level II:

Basic fee (Level II)	60 200 EURO
Additional fee Add.Strength/Potency	+20 100 EURO
Add Pharm Form	+ 6 700 EURO

Basic fee (Level III) Extension in Pediatric	80 300 EURO
Additional fee Add.Strength/Potency	+ 20 100 EURO
Add Pharm Form	+ 6 700 EURO

Level III:

eCTD Implementation:



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.

On the other hand the eCTD standard has an impact on current regulatory practise, especially within multi-national marketing applications based on the MRP or DCP.

Therefore, in the following section, the impact of the eCTD standard is determined considering issues such as "Dossier Compilation", "Submission Management", and "Lifecycle Management".

This analysis will be conducted using the following case scenario:

- ✓ Medicinal product with the trade name "Prontofer" comprising three different pharmaceutical forms such as oral solution, oral drops, solution, and film-coated tablets.
- ✓ All pharmaceutical forms have one strength only
- ✓ It is intended by the applicant to receive a marketing authorization from 10 Member States for all pharmaceutical forms following either the MRP or the DCP.
- ✓ A second wave covering four additional Member States is also planned. [7]
- ✓

Dossier Compilation:

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 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
1.6.1 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 Paediatrics
1.11 Responses to Questions
1.12 Additional Data.

CONCLUSION:

- 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.

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