Research Article

Regulatory requirements for registration of modified release dosage forms in European Union

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ABSTRACT

Background: Every country has its basic legislation concerning to protect public health and ensure the availability of high quality, safe, and effective medicinal products. Pharmaceutical products in Europe are tightly regulated to protect public safety and promote European Union (EU) patients access to novel pharmaceutical goods.[1] The European Medicines Agency (EMA) integrates the Member States current research tools for the evaluation, monitoring, and pharmacovigilance of pharmaceutical products for medical and veterinary usage in the EU. **Objectives:** The objective of this study is to depict the initial registration requirements for modified release dosage forms in the Europe and to minimize the error in compiling the dossier by understanding the critical aspects involved in the marketing application for modified release dosage forms. **Discussion:** The EMA uses different marketing authorization paths for authorizing a drug to be marketed in different countries in Europe, and all the procedures require different types of registration process. Pharmaceutical dosage forms can be produced in which the pace and/or position of release of the active substance(s) in contrast with traditional release formulations has been changed in any way. These modifications can have a variety of purposes, such as sustaining long-term medicinal efficacy, minimizing adverse consequences, shielding the active substance from low pH degradation, directing the active substance to a predefined gastrointestinal tract section for local care, or directing the release of active substances at established time points.

KEY WORDS: Marketing authorization, Modified release dosage forms, Procedures

INTRODUCTION[2]

The European Union (EU) is a distinctive economic and political union between 28 countries/EU member states that composed much of the region.

It is the world's largest trading group. It is the world's largest consumer products and services exporter and the main import sector with more than 100 nations.

The EU has two regulatory authorities: The European Medicines Agency and Heads of Medicines Agencies. The Member States of EU are "Austria, Italy, Belgium, Latvia, Bulgaria, Lithuania, Croatia, Luxembourg, Cyprus, Malta,Czechia, Netherlands, Denmark, Poland, Estonia, Portugal, Finland, Romania, France, Slovakia, Germany, Slovenia, Greece, Spain, Hungary, Sweden, Ireland, United Kingdom, Iceland, Liechtenstein, and Norway". This allows them to become part of the EU Single sector.

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Website: jprsolutions.info | ISSN: 0975-7619

Factors Driving Pharmaceutical Market in EU[3]

The research-based pharmaceutical industry is reaching a new age of optimism in medicines/pharmaceutical growth. It aims to turn fundamental research into innovative treatments that are widely available and accessible to patients. Today's, European citizens can expect to live up to 30 years longer than they did a century ago.

The research-based pharmaceutical industry is a key asset of the European economy, as well as guiding medical evolution by studying, creating, and getting in new drugs that enhance well-being and quality of life expectancy for patients worldwide. One of the founding values of the EU was free exchange among its members. Thanks to the Single Market that is necessary. The EU also aims to liberalize international markets outside its boundaries. This is one of the high-tech markets of highest results in Europe.

DISCUSSION

I. Initial procedures and applications for marketing authorization of medicinal products [Table 1].[4]

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Received on: 22-10-2019; Revised on: 16-12-2019; Accepted on: 08-02-2020

There are four procedures for marketing authorization of a drug product in EU, i.e.,

a) Centralized procedure
b) Decentralized procedure
c) Mutual recognition procedure
d) National procedure

Types of marketing authorization applications for EU market are as follows:[4]

Table 1: Legal types of marketing authorization

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, Clinical data	Article 10(a)
"Fixed combination products"	Pre-clinical, Clinical data for combination	Article 10(b)
"Informed consent"	Innovators generic product (Duplicate dossier)	Article 10(c)

Generic Application – Article 10(1)

Application for a generic medicinal product as specified referring to patent drugs is so-called reference medicinal product with a marketing authorization given in a Member State or society. Total functional and safety data, pre-clinical and clinical data are submitted where necessary.

II. Modified Release Dosage Forms

Modified release dosage forms are formulations where the rate and/or site of release of the active ingredient are different from that of the immediate release dosage forms.[5]

1. Prolonged release dosage forms: Prolonged release dosage forms are modified release dosage forms that interpret a prolonged release similar to that of an immediate release dosage form guided down the same path.
2. Delayed release dosage form: After the dose is guided or added, discharge of the active ingredient from these changed release dose formulations is delayed for a certain period. The resulting release is close to that of a treatment type for immediate release.
3. Multiple unit: A type of multiple unit doses consists of a multiplicity of units, for example, pellets or beads each containing excipients that regulate the escape.
4. Single unit: The single-unit dosage forms contains of only one unit.[6]

a) Factors to be considered for the application of modified release dosage forms

1. Pharmacokinetic studies[6]

These studies aim to characterize the modified formulation of the release *in vivo* by investigating:

- The percentage and level of absorption
- Variations in drug absorptions at steady state
- Factors affecting the act of the modified release formulation
- The risk of unanticipated release characteristics (e.g., dose dumping)

2. Dose proportionality[6]

At any time, there are multiple units or when several single strengths can be administered together to attain the desired dosage, dose proportionality for specific strengths/doses of the adjusted release formulations must be sufficiently addressed. Dose proportionality can be tested using a single dose and a multiple grade analysis in the case of product aggregation, where the PK parameters of concern of all the units/dosage are measured later grade change.

3. Factors affecting the act of a modified release drug formulations[6]
   - Food
   - Gastrointestinal functions
   - Unexpected characteristics (e.g., alcohol dose dumping)
   - Special population
   - Impact of site of application on plasma levels
   - Multiphasic modified release products
   - Prolonged residence time in the stomach.

4. Abridged application for modified release dosage forms mentioning to marketed modified release form[6]

Bioequivalence tests with adjusted release formulations are advised for orally administered drugs, by contrasting two formulations (test versus reference) of the same pharmaceutical type.

5. Studies generally required demonstrating bioequivalence[6]
   - A single-dosage fasting study comparing test versus reference drug product
   - A single-dosage fed study using a great fat meal equaling test and reference drug product
   - A multiple dosage study comparing test and reference drug product.

6. Dissolution criteria:

i. General aspects of dissolution testing as related to bioavailability:[7]

A dissolution test is used as a method during the production of a medicinal product to classify formulating factors that affect and may have a critical impact on the drug's bioavailability. As long as the composition and the manufacturing cycle are specified, a dissolution

check is used to ensure all batch-to-batch accuracy in the quality assurance of scale-up and output batches, and the dissolution profiles persist close to those of key clinical trial batches. In addition, a dissolution test may be used in certain instances to waive a study on bioequivalence. Studies of dissolution, therefore, can serve several purposes:

- Testing on product value
- Bioequivalence surrogate inference.

Test methods should be established specific to the product, established on general and/or specific pharmacopoeia necessities. In case, those necessities are shown to be insufficient and/or do not replicate the *in vivo* dissolution, alternative approaches could be deemed to be selective and capable of discriminating between lots of appropriate and unacceptable *in vivo* drug output.

Time points for sampling will be adequate to get accurate dissolution profiles, preferably minimum of every single 15 min. More regular sampling is advised during the time of greatest improvement in the dissolution profile.

If an active drug is deemed showing highly dissolution level, it is fair to assume that it does not cause any bioavailability issues if, however, the delivery form is dissolved rapidly within the physiological pH spectrum and the excipients are proven to have little impact on bioavailability. Conversely, if an active drug is reflected to have minimal or poor solubility, the rate controlling stage for absorption could be dissolution in the dosage type. That is also the case where the excipients monitor the release of the active drug and its eventual breakdown. In such situations, a number of test conditions are required, and satisfactory screening must be carried out.

ii. Similarity of dissolution profiles[7]

Dissolution profile similarity testing and any conclusion drained from the outcomes (e.g., explanation for a bio-waiver) can be reflected effective only if the dissolution profile has been satisfactorily considered by means of enough digit of time points.

For modified release products, dissolution similarity may be found using the f_2 statistic as follows,

$$f_2 = 50 \log \left[\frac{100}{1 + \frac{\sum_{t=1}^{t=n} \left[\bar{R}(t) - \bar{T}(t) \right]^2}{n}} \right]$$

Where, f_2 is the similarity factor, n – number of time points, R(t) – mean percent reference drug dissolved at time "*t*" after initiation of the study; T(t) – mean percent test drug dissolved at time "*t*" after beginning of the study. For both the reference and test formulations, percentage dissolution should be determined.

The assessment of the similarity factor is established on the following conditions:

- At least three time points (zero left out)
- The time points must be the same for the two formulations
- Twelve single units for every time point for each formulation
- Less than 1 mean value of greater than 85% dissolved for any of the formulations
- The relative standard deviation or coefficient of variation of any product must be below 20% for the first point and below 10% from the second to last time point.

An f_2 value in between 50 and 100 means that the two dissolution profiles are comparable.

Fees Structure

The fee structure for different articles are provided in Table 2.

Table 2: Application for which full dossiers need not to be presented[8]

Basic fee Article 10(1)	103,800 Euro	This fee is a single strength associated with one pharmaceutical form and one presentation for marketing authorization application.
Additional fee Article 10(1)	+ 10,300 Euro	For through increased intensity of the medicinal form including one presentation provided concurrently with the original authorization submission.
	+ 6700 Euro	For through additional demonstration of the same intensity and prescription type, submitted simultaneously with the original authorization submission.

The regulatory aspects of conventional and modified release systems are given in Table 3.

Table 3: Regulatory aspects of conventional release versus modified release dosage forms

Conventional dosage forms	Modified release dosage forms
Nomenclature of the conventional dosage forms: Tablet name (levonorgestrel Tablet)	Nomenclature of the modified release dosage forms: Tablet name - strength - tablet (gliclazide 30 mg prolonged release tablets)

(*Contd...*)

Table 3: (*Continued*)

Conventional dosage forms	Modified release dosage forms
Strength of the dosage form – single strength	Strength of the dosage form – multiple strength
Excipients – excipients are used to bulk the tablets (e.g.,, lactose)	Excipients – excipients such as hydroxypropyl methylcellulose are used for controlled release of tablets.
Coated tablet (e.g.,, coloring agent and flavoring agent)	Coated tablet – modify the drug releasing time into the blood stream (e.g.,, retarding agent like plasticizer is added to the polymers used as a film-forming agent).
Dissolution time: Single time points but at rare cases more than 1 time point is applicable (e.g.,, nitrofurantoin)	Dissolution time: Multiple time points (minimum of three time points)
Dissolution time: Within 45 min.	Dissolution time: Expressed in hours and typically be determined by the type of modified release dosage form.
f_2 calculation: 85% in 15–30 min	f_2 calculation: Minimum of three time points. Initial time point 20–30%, second time point around 50%, third time to ensure Q = 80%.[5]
pH: 6.8	pH: 4.5, pH: 6.8, pH: 7.4, 0.1 N HCl.
Alcohol dose dumping studies not required	Alcohol dose dumping studies are performed with 5%, 10%, 20%, and 40% alcohol (as indicated) with minimum of 120 min has to be performed.
Buffer: Stomach pH is used (pH in the range 3–5)	Buffer: Acid buffer Basic buffer

SUMMARY

For registration of a product in European Union, eCTD submission format is adopted.

- Modified release dosage forms may have a number of objectives therapeutically, their regulatory requirements differ from conventional systems.
- An *in vitro* dissolution test is established which is able to identify alterations which may have a result on the effectiveness or safety of the product, which is said to be the critical step in regulatory approval.

CONCLUSION

Regulatory requirement for medicinal drug approval has been found to be more rigid in the European Union. The EU has various types of procedures and specific types of applications that define the medicinal product and the timeline needed to authorize the substance that helps monitor the life cycle of the medicinal product involved. This study has put forth the initial submission requirements for the modified release dosage forms in Europe and the possible ways to minimize the error in compiling the dossier by understanding the critical aspects involved in the marketing application for modified release dosage forms.

ACKNOWLEDGMENT

The authors thank Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, for supporting to the study.

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Source of support: Nil; Conflicts of interest: None Declared