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Registering of Super-Generics in Europe

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Abstract

Super generic is the general form of nomenclature for hybrid medicinal product in European Union, which is coined suitably in different regulatory authorities. The Super generic form of the medicinal product is one that considers changes in the form of active substance, therapeutic indications, strength, pharmaceutical form or route of administration. They rely partly of results of pre-clinical tests and clinical trials of a reference / innovator product and some part on new data with appropriate bioavailability and bioequivalence studies. Marketing authorization for Super generics in European Union can be obtained through registration procedures like Centralized, Decentralized, Mutual recognition and national procedure. Additional studies like pharmacokinetics, preclinical and clinical studies are conducted as required by the changes that are made in the Super generic product compared to the innovator product. Antacid Orally Disintegrating Tablets as a part of Super generics have gained considerable attention since last decade. This mode of administration is expected to be beneficial to pediatric, geriatric patients, people with impaired swallowing and psychiatric patients. These products have a significant impact on exhausting marketing authorization trend of conventional dosage forms. In an effort to develop drug products that are more convenient to use and address potential issues of patient compliance, Super generic ODTs have been developed andwith the acceptance by wide range of patients the market for these dosage forms are promising.

Keywords: Super generic, Orally disintegrating tablet, Antacid, Patient compliance

Introduction

The European Medicines Agency is the regulatory agency in Europe. The European Medicines Agency is a decentralized agency of the European Union, located in London. EU consists of 27 countries and 3 European Economic Area (EEA) countries consisting of Iceland, Liechtenstein and Norway. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. For obtaining marketing authorization for any product in Europe, EMA is the regulatory agency for review of the dossier and the related documents.

A license, also referred to as a Marketing Authorization, from the EMA is required before any medicine can be used to treat people in the Europe. Licenses for medicines are granted only when a product meets high standards of quality, safety and works for the purpose intended (efficacy).

There are four types of procedures that applicants can take to obtain a Marketing Authorization. To obtain a marketing authorization in Europe, the applicant may choose any one of the four procedures, viz., Centralized Procedure, National Procedure, Decentralized Procedure and Mutual Recognition Procedure. In these procedures the Centralized Procedure is mandatory for certain types of medicines and optional for others. The Centralized Procedure is administrated by the EMA in London. It consists ofa single application which, when approved, grants marketing authorization for all markets within the European Union consisting of 27 countries and 3 EEA countries. CP is mandatory for Biotechnological Products and New Active substances for which thetherapeutic indication is the treatment of AIDS, Cancer, Diabetes, Neurodegenerative disorder and Orphan products. The decentralized procedure should be used for products that have not yet received authorization in an EU country. Mutual recognition means that EU countries may approve the decision made about a medicinal product by another EU country. In cases where national authorizations are requested for the same medicinal product in more than one Member State and the marketing authorization holder has received a marketing authorization in a Member State, the applicant/marketing
authorization holder shall submit an application in the Member States concerned usingthe procedure of mutual recognition. If no marketing authorization has been granted in the

Community, the applicant may make use of a decentralized procedure and submit an application in all the Member States where it intends to obtain a marketing authorization at the same time, and choose one of them as reference Member State.

To obtain a marketing authorisation in Europe, the generic manufacturer should provide a dossier with quality data, bioequivalence with EU reference product and applicable clinical and non-clinical reports in CTD/eCTD format. In assembling the dossier for application for marketing authorization, applicants shall also take into account the scientific guidelines relating to the quality medicinal products for human use as adopted by the Committee for Medicinal Products for Human Use and published by the European Medicine Evaluation Agency. All data should be submitted following the relevant headings of the EU-CTD according to Notice to Applicants (NTA), Volume 2B.

The safe use of all medicines depends on users reading the labelling and packaging carefully and accurately and being able to assimilate and act on the information presented. The primary purpose of medicines labelling and packaging should be the clear unambiguous identification of the medicine and the conditions for its safe use. So the labeling requirements must have been followed by the applicant while preparing the drug product label.

The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutical quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product. So bioequivalence with reference medicinal product is required for a drug product and the data of bioequivalence should beincluded in a dossier.

For Super generics or hybrid medicinal product (as coined in EU), the bioequivalence studies alone are not sufficient to evaluate the Super generic product and additional pre-clinical and clinical studies are required to consider the Super generic product to be comparable to that of the innovator product.

Under the new medicines legislation which was implemented on 30 October2005, MAs will be valid for five years and then may be renewed on the basis of a re- evaluation of the risk-benefit balance. Once renewed, the marketing authorization will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

The Super generic drug market is growing strongly from last two decades. The essential attribute of Super generic drugs is that they cost less than their original brand equivalents. Drug makers are facing continued patent expirations of leading products, causing many to enter the generics sector. Generics are strong and rising as a means for companies to both increase revenues and achieve economies of scale. Total generic drug sales reached $95b in 2009 and will expand by 7.2% per year through 2014.

Super generic medicines in Europe tend to be 20–80% cheaper than originator medicines and thereby generate substantial savings. Super generic medicine prices tend to vary between European countries. This suggests that prices not only reflect production and distribution costs, but also regulatory environment including registration, pricing, and distribution of original and generic medicines.

The Super generics or hybrid medicinal products are a part of generics which differ from generics in few aspects, Super generics bioavailability studies cannot be used to demonstrate bioequivalence with that of the innovator product, but generics are same as innovator product in every aspect and can be approved through appropriate bioavailability and bioequivalence studies.

Super generics

These are the generic products which rely in part on the results of pre-clinical tests and clinical trials of innovator or reference product and in part on new data through preclinical and clinical studies. In European perspective hybrid medicinal product are considered as Super generics.

Table 1: Comparison of Super generics with generics and New drug application (NDA)

Parameter	New drug application	Generics	Super generics
Preclinical and clinical studies	Required	Not required	Required forcertain parameters
Bioavailability and bioequivalence studies	Not required	Required	Required forcertain parameters
Changes are made in the innovator product	Not applicable	No changes are performed. All theparameters are same as that of the innovator product	Changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration
Data	Submits the dossier based on their data	Uses the data of the innovator product and additional bioavailability andbioequivalence studies data is required	Rely part on the data of the innovator product and part on new studies data
Marketing exclusivity	10 +1 years	5 years	5 years
Registration procedure	Centralized procedure	Centralized or Decentralized or Mutual recognition procedure or National procedure	Centralized or De-centralized or Mutual recognition procedure orNational procedure
Composition and manufacturing method	Experimentally developed	Same as the innovator product	Changes made in composition
Directive	Article 6 of Directive 2001/83/EC	Article 10(1) of Directive 2001/83/EC	Article 10(3) of Directive 2001/83/EC
EU risk managementplan	Required	Not required, same as referenceproduct	Required for the aspects in which changes are made

According to Article 10.3 of the directive 2001/83/EC [1], states that hybrid products under Article 10(3) of Directive 2001/83/EC differ from generic products in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:

- If the definition of a 'generic medicinal product' is not satisfied,
- If the bioavailability studies cannot be used to demonstrate bioequivalence;
- If there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, dosage form, formulation change, dosing regimen change, different active ingredient (ester, ether etc. groups), new combination product compared to the reference medicinal product.

In such cases the results of tests and trials must be consistent with the data contentstandards required in the Annex to the Directive 2001/83/EC as amended by Directive 2003/63/EC. The application for marketing authorization for a hybrid medicinal product is done by demonstration of bioequivalence, usually through the submission of the appropriate bioavailability studies.

Hybrid medicinal products are based on the reference medicinal product which has been

granted a marketing authorization by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC.

Hybrid medicinal product applications of medicinal products authorized via the Centralized procedure have automatic access to the Centralized procedure under Article 3(3) of Regulation (EC) No 726/2004

Hybrid medicinal product applications of medicinal products authorized via the National/MRP/DCP procedure could, at the request of the applicant, be accepted for consideration under the centralized procedure, when the applicant shows that the medicinal product constitutes:

- A significant therapeutic, scientific or technical innovation, or
- The granting of a Community authorization for the medicinal product is in the interest of patients at Community level.

For hybrid applications the legal basis can be found in Article 6 of Regulation (EC) 726/2004 and Article 10 of Directive 2001/83/EC.

Orally disintegrating tablets[2]

Orally Disintegrating Tablet (ODT) is a solid unit dosage form containing drugs that disintegrates rapidly and dissolves in the mouth without taking water within 60 sec or less. Orally disintegrating tablets (ODTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry.

In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and patient populations, pharmaceutical manufacturers have developed products that can be ingested simply by placing them on the tongue.

The products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders).

Advantages

- ODTs have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients.
- ODTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form.
- The primary patients for ODTs are pediatric, geriatric, and bedridden or developmentally disabled patients, patients with persistent nausea, and patients who have little or no access to water.
- From the pharmaceutical industry's point of view, ODTs can provide new dosage forms as a life cycle management tool for drugs near the end of their patent life.
- As the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible.
- The pre-gastric drug absorption avoids the first-pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.

Desired characteristics and development challenges of ODTs

Because administration of ODTs is different from administration of conventional tablets, the ODTs should maintain several unique properties,

A. Fast Disintegration:

ODTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 mL) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good

mouth feel and smooth swallowing. The disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

B. Taste of Active Ingredients

Because ODTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept low to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with ODT formulations. If drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the ODT formulations.

C. Drug Properties

For the ideal ODT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of ODTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. The ODT technology should be versatile enough to accommodate unique properties of each drug.

D. Tablet Strength and Porosity

Because ODTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be
soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

E. Moisture Sensitivity

ODTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect ODTs from various environmental conditions.

ANTACIDS[3]

An antacid is a substance which neutralizes stomach acidity. Antacids perform a neutralization reaction, increasing the pH to reduce acidity in the stomach. When gastric hydrochloric acid reaches the nerves in the gastrointestinal mucosa, they send painsignals to the central nervous system. This happens when these nerves are exposed, as in peptic ulcers.

This is because antacids can quickly relieve the symptoms associated with occasional heartburn and indigestion. A number of symptoms, including heartburn, gastritis, and gastro esophageal reflux disease (GERD), can be treated with them.

Antacids contain ingredients such as aluminum hydroxide, calcium carbonate, magnesium hydroxide, and sodium bicarbonate, alone or in various combinations. Antacid products may also contain other ingredients such as simethicone which relieves gas.

Side effects are very rare when antacids are taken as directed. They are more likely when the medicine is taken in large doses or over a long time. Minor side effects include a chalky taste, mild constipation or diarrhea, thirst, stomach cramps, and whitish or speckled stools.

Antacid ODTs have greater advantage over conventional tablets as the ODT platform incorporated in the formulation of antacids ensures to be more advantageous.

METHODOLOGY OF SUPER-GENERIC MARKETING AUTHORIZATION

Procedure for Submission of MA application to EMA[14]

The procedure for submission of marketing authorization application to EMA involves many steps,

Pre-submission meetings

Applicants should notify to the EMA of their intention to submit an application atleast seven months before submission. In that notification applicants should include:

- a draft summary of product characteristics
- a justification of the product's eligibility for evaluation under CP (Centralized procedure)
- an indication on the number of strengths / pharmaceutical forms / pack sizes (if already known)

The applicant's request for eligibility for evaluation via the centralized procedure and justification and summary of product characteristics/product profile from the applicant, will be presented to all CHMP members. Following discussion at CHMP, the EMA will then inform the applicant of the CHMP position as to whether the product is eligible for evaluation via the centralized procedure.

Selection of Rapporteur/Co-Rapporteur

For any scientific evaluation in respects of a procedure a Rapporteur, and if relevant a Co-Rapporteur shall be appointed. The role of the Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP. Where appropriate, the Rapporteur can be supported by a Co-Rapporteur as agreed by the CHMP.

Submission of the application

The date and time of delivery of the dossier to the EMA should be arranged between the applicant and the EMA. If the original indicated submission date cannot be met by the applicant, applicant should inform the EMA, Rapporteur and Co-Rapporteur immediately, since a delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co-Rapporteurs.

The EMA requires from the applicant

- one full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File (ASMF).
- two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labeling and package leaflet in English;
- one electronic copy of module 1 and 2 (at least 2.1-2.5) in word. In addition, applicants must submit the dossier to both the Rapporteur and the Co- Rapporteur in parallel to the EMA.

Data exclusivity and market exclusivity

For applications submitted before 20 November 2005 will be granted withexclusivities like,

- **10 years** for national authorizations granted by the following Member States: Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom, Luxemburg.
- **6 years** for national authorizations granted by the following Member States: Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece, Poland, Czech Republic, Hungary, Lithuania, Latvia, Slovenia, Slovakia, Malta, Estonia, Cyprus and also Norway, Liechtenstein and Iceland.

10 years for all medicinal products authorized through the centralized procedure.

For applications submitted after 20 November 2005 will be granted with exclusivities like,

- Amendment has introduced new rules concerning the periods, from the initial marketing authorization of the reference product, during which no generic productis approved.
- For newer applications the exclusivity period is the same across EU - 10 years / 11 years of both Data Exclusivity and Market Exclusivity. (8 years of Data Exclusivity + 2 years of Market Exclusivity + 1 year of Exclusivity for new therapeutic indication representing significant clinical benefit in comparison with existing therapies).

Table 2: Review procedure of hybrid medicinal product dossier

DAY	ACTION
1*	Start of the procedure
80	Receipt of the Assessment Reports from Rapporteur by CHMP members and EMA. EMA sends Rapporteur Assessment Reports to the applicant making itclear that it only sets out their preliminary conclusions. The so-called Day-80 assessment reports in no ways bind the CHMP and are sent to the applicant for information only.
90	Adoption of GxP Inspection Request
100	Rapporteur, other CHMP members and EMA receive comments from Membersof the CHMP
115	Receipt of draft list of questions (LoQ) from Rapporteur, including the CHMP recommendation and scientific discussions, by CHMP members and EMA (If applicable)
120	Adoption CHMP Opinion + CHMP Assessment Report unless "major" objections, GxP Inspection issues or questions on the restricted part of the ASMF are identified. Adoption of a timetable for the provision of translations.
DAY	**ACTION**
121*	Submission of the responses
Restart of the clock	
DAY	**ACTION**
150	Circulation of the Joint Response Assessment Report (so-called Day-150 Assessment Report). EMA sends this joint Assessment Report to the applicant making clear that it is sent for information only and does not yet represent the position of the CHMP
170	Comments from CHMP Members to Rapporteur, the EMA and other CHMP members
180	Adoption of CHMP Opinion + CHMP Assessment Report unless "major" objections are identified to be addressed in writing or during an Oral explanation and/or outstanding GxP issues. Adoption of a timetable for the provision of translations
Clock stop in case of Oral Explanation	
181	Restart of the clock. Oral explanation and circulation of the final GxP Inspection Report
Beforeday 210	Adoption of CHMP Opinion + CHMP Assessment ReportAdoption of a timetable for the provision of translations

CASE STUDIES

1. Pfizer goes Super-generic[15]

Pfizer is dealing with Biocon to sell generic insulin in emerging markets. Biocon makes generic versions of bestselling drugs from Novo Nordisk, Eli Lily, Sanofi-Aventis. Most of the growth in next year will be from the sale of super-generic drugs in emerging markets. Biocon based in Bengaluru, India, will be responsible for developing and manufacturing diabetes treatments and for new drug approvals. Pfizer has been expanding its business in field of super-generics in emerging markets.

2. Super-generics key to HalcyGen's future[16]

Melbourne, Australia-based firm HalcyGen is expecting its so-called Super-generics to expand its share of the market which added the company's partnership arrangements with local firm Mayne Pharma would be key to its success. HalcyGen's strategy is to develop value-added formulations for Super-generic compounds that are off-patent but which have a newly-established intellectual property position through improved delivery and formulation. It then hopes to market these Super generics as a low-risk option to drugmakers looking for new opportunities in niche markets.

3. Generic drugs market to reach $358 billion by 2016 [17]

The Super-generic drugs industry is facing a period of unprecedented growth to 2005, according to a new report from Datamonitor, entitled: the Super-generics Industry in 2005; a New Threat to Pharma. The loss of patent protection on $100 billion of drug revenues (based on 1999 turnover) by 2005 will fund the expansion of generics companies into fully-fledged pharmaceutical concerns. And, says Datamonitor, this will present a significant competitive threat to research-based companies, particularly those lacking innovative portfolios.

4. Manufacturers to Increase Focus on Super Generics to Drive Revenues [18]

Research has released its research article titled "Generic Growth Strategies - Manufacturers to Increase Focus on Super Generics to Drive Revenues". It provides a comprehensive overview of the generic drugs market, analysis of upcoming noteworthy patent expirations, and trends and issues facing the generics market. Many changes have structured the generic drugs market in the last 30 years; and the reason behind the players' urgency in developing and implementing generic growth strategies. The report also contains impact analysis of the regulatory landscape in the major geographies pertaining to the Super-generic drugs market. Major strategies adopted by the leading companies in the generic drugs market have been analyzed in much detail, along with an elaborate company portfolio and strategic analysis of leading generic players. GBI Research has found that the pharmaceutical industry in general and the Super-generics sector in particular have turned out to be highly competitive of late. There is rampant consolidation; novel business models are developing, such as hybrid models between Super-generic and innovator companies; and generics companies partnering with third- party sales teams to increase growth. The benefits from these partnerships are wide ranging for the Super-generics companies, from higher access to research and development capabilities and innovator drugs' access to wider penetration in new markets.

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