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Hybrid or Mixed Marketing Authorization Application in the European Union: Not a Trivial Decision in New Development Programs for Established Drugs

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Abstract

For any medicinal product Marketing Authorization Application (MAA) in the European Union, the applicant needs to indicate the legal basis for the application. This legal basis, laid down in Directive 2001/83/EC as amended, determines the dossier content, the market exclusivity, and the pediatric requirements in a significant way. For new development projects for established active substances, including new strengths, dosage forms, routes of administration, and new indications, the correct choice of legal basis is critical. This article presents the dossier requirements, data protection, and market exclusivity as well as pediatric obligations for mixed MAAs using the Article 8(3) legal basis and so-called "hybrid" applications according to Article 10(3). These legal bases in the European Union are contrasted with applications according to section 505(b)(2) in the United States. A number of case studies are presented to illustrate which factors can determine the legal basis of an MAA.

Keywords

marketing authorization application, hybrid, 505(b)(2), data protection, development plan

Introduction

Problem Statement: When and Why Is the Choice of the Legal Basis an Issue?

Available Legal Bases According to Directive 2001/83/EC

For any medicinal product Marketing Authorization Application (MAA) in the European Union (EU), the applicant needs to define upon which legal basis the application is made. The available legal bases are defined in the European Directive 2001/83/EC,[1] which provides the harmonized basis for the pharmaceutical legislation across the EU member states (Table 1). The required elements of a full application are defined in Article 8(3). In addition, Annex I, Part II.7 of the same Directive specifies that "a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references" may be used to supply these required elements; such applications are called "mixed MAA."[1] All other legal bases represent specific types of derogations to the dossier requirements laid down in Article 8(3) (see also Table 1):

- Article 10(1) and 10(2) for bioequivalent generics
- Article 10(3), known as "hybrid" application, for applications of generics for which bioequivalence cannot be shown or which differ from the originator product (reference medicinal product [RefMP] in EU terms) in therapeutic indication, strength, pharmaceutical form, or route of administration
- Article 10a for bibliographical (so-called well-established use) applications
- Article 10b for fixed combinations
- Article 10c informed consent (ie, duplicate) application dossiers

Hybrid applications are of particular interest for the purposes of this article.

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Table 1. Legal bases for marketing authorization applications in the European Union according to Directive 2001/83/EC as amended.

Article 8(3)	Full dossier	Full application. Data requirements fulfilled by: • Only applicant's own data, or • Applicant's own data and published literature data: mixed marketing authorization application
Article 10(1)	Abbreviated dossier	Bioequivalent generics Full reference to nonclinical and clinical data of reference medicinal product
Article 10(3)	Abbreviated dossier	Hybrid application Full or partial reference to nonclinical and clinical data of reference medicinal product Additional data to establish properties of product
Article 10(4)	Abbreviated dossier	Biosimilar application Partial reference to nonclinical and clinical data of reference medicinal product Additional data to establish properties of product
Article 10a	Full dossier	Well-established use application • Nonclinical and clinical data exclusively from literature • Own data to establish comparability of product to product used in the literature
Article 10b	Full dossier	New fixed combination application • Only data relating to the properties of the new fixed combination required • Can refer to data of the single components
Article 10c	Full dossier	Informed consent application • Duplicate of approved full dossier

The legal basis determines the dossier content, the market exclusivity, and the pediatric requirements in a significant way. However, the legal basis for an MAA is completely independent from the registration route—centralized, decentralized, or national level—and from a number of other characteristics, for example, orphan medicinal product status or approval under exceptional circumstances. There is also no legal basis that provides an easier access to the market; all applications will be held to the same standards of pharmaceutical quality, safety, and efficacy.

The Critical Choice: Full Mixed Dossier Versus Hybrid Dossier

For many applications, the definition of the legal basis is straightforward. However, the legal basis becomes critical for new development projects for established active substances (ie, substances that at the time of application are not protected by a patent, a Supplementary Protection Certificate, or regulatory data protection or that are not under regulatory market exclusivity). When a new dosage form or strength, a route of administration, a new indication, or combinations of these are developed for such a substance, the question will always arise to what degree and how it is possible to rely on data that supported the prior approval of this substance. Reliance on such data is possible either by using a full "mixed MAA" dossier that includes the studies conducted for the new medicinal product supplemented with data from the literature or by using a hybrid application combining one's own study data with *reference* to the approved medicinal product.

The choice of the legal basis will depend on the characteristics of the new product, its global development plan, and its desired positioning in the market. Indeed, given these constraints there is frequently no true choice; 1 of the 2 legal bases is imposed, and the development plan is designed to fulfill the requirements of that legal basis. However, with sufficient anticipation, such a situation may be avoided and a development plan can be designed that corresponds to the desired legal basis.

Comparison

Common Requirements

Certain components of full mixed or hybrid MAAs are common among the applications. The following characteristics apply both to full mixed applications and hybrid applications.

Pharmaceutical Data (Module 3)

Full quality (CMC) documentation of the pharmaceutical development and characteristics of the active substance(s) and drug product is required under both legal bases.

Risk Management

For hybrid applications, certain parts of the risk specifications may be omitted if they do not differ from those of the RefMP.

Reference to Data Under Protection

It is always of high importance to consider whether data contained in another application dossier or even in the literature may be covered by regulatory data protection. In this case, reference to these data or their inclusion in dossier is not possible. This notably also applies to data that may have been generated for a different active substance than the one contained in the product for which the application is made. It also applies to

data in approved Summaries of Product Characteristics (SmPC).

Article 8(3)—Full Mixed Dossier

Dossier Requirements

In a mixed MAA, all data elements must come either from one's own studies or from published, preferably peer-reviewed literature. No reliance on prior product approvals is possible, including reliance on publicly available regulatory approval documentation such as European Public Assessment Reports (EPARs) or FDA Summary Bases of Approvals.

The CHMP has further defined the nonclinical data requirements for mixed MAAs in a guideline.[2] Nonclinical investigations are normally not required when there is sufficient well-documented clinical experience to establish all aspects of clinical efficacy and safety. However, additional studies may be required if there are specific identified risks or if there is a lack of available genotoxicity data.

Data Protection and Market Exclusivity

Apart from potential patent protection, mixed MAAs are covered by regulatory data protection for 8 years; that is, for 8 years after approval, no generic MAA may refer to this product. In addition, no generic of the product may be marketed for 10 years after the first approval, providing an additional 2 years of market exclusivity compared with the regulatory data protection. Finally, the 10-year market exclusivity may be extended by 1 year if an authorization is obtained in an additional indication considered to bring a significant clinical benefit compared with existing therapies during the first 8 years after approval. These periods of protection are usually summarized as the 8+2+1 formula.

Pediatrics

According to the pediatric Regulation (EC) No. 1901/2006,[3,4] all mixed MAA application dossiers need to comply with a Pediatric Investigational Plan (PIP) for the product adopted by the European Medicines Agency's Pediatric Committee (PDCO). Depending on the product and the PIP, this may mean the inclusion of pediatric study data, but pediatric development may also be deferred or waived. Indeed, for diseases that do not occur in children or medicines that may be harmful to them, the PDCO has published a list of class and product-specific waivers.[5,6]

Article 10(3)—Hybrid Dossier

Dossier Requirements

As hybrid applications are a type of generic application (and sometimes referred to as "pseudo-generics"), a RefMP approved in the European Union needs to be identified in CTD Module 1.5.2: Information for Generic, "Hybrid" or Bio-similar Applications. This RefMP also needs to be used for comparison purposes if such a comparison is relevant, for example, in relative bioavailability studies or clinical efficacy studies. If the product in development is intended to be bioequivalent or therapeutically equivalent to the RefMP, the RefMP needs be marketed in order for it to be possible to perform comparative studies.

If the product in development is intended to be bioequivalent to the RefMP, comparative quality data and demonstration of bioequivalence following the CHMP bioequivalence guideline[7] are required.

In a hybrid dossier, reference is made to nonclinical and clinical documentation included in the dossier of the RefMP, as well as to its SmPC. Consequently, only data that are specifically required to establish the properties of the new product need to be provided in the application dossier. This is specified in Annex I, Part II.2 of Directive 2001/83/EC[1] and is particularly relevant if there is a lack of published information in the literature and if extensive studies would be required for a mixed MAA. As part of the establishment of the new product's properties, the applicant needs to show in the clinical overview that the proposed use is in line with current medical practice as documented in the literature.

Data Protection and Market Exclusivity

Medicinal products approved based on hybrid applications have no data exclusivity or market protection, as they are legally assimilated to generics. However, it is not possible to register a generic of a hybrid product, because only medicinal products approved based on a full dossier can serve as RefMP. Any copy of a hybrid product will have to repeat the development of the existing product. Interestingly, this implies that a competitor may have to perform studies comparing its product to the existing hybrid product if that product has become the standard of care.

In case the newly developed product is a designated orphan medicinal product, a 10-year market exclusivity applies, and no copy of the hybrid product can be registered in the same indication during this period. However, according to Article 8 of Regulation (EC) No. 141/2000 on orphan medicinal products, this exclusivity can be revoked if a similar but clinically superior product receives approval in the same indication.[8]

Pediatrics

According to Article 9 of the Pediatric Regulation (EC) No. 1901/2001,[3] no approved PIP is required as part of a hybrid dossier, even if the product is intended for a pediatric use. However, an application for a Pediatric Use Marketing Authorization (PUMA) for medicinal products that are exclusively developed for the use in children can use a hybrid dossier (Article 30.3 of the Regulation), but in this case a PIP is required.

PUMAs benefit from access to the Centralized Procedure and protection according to the 8+2+1 rule.

EU Hybrid Application Versus US 505(b)(2)

Comparison of Scopes

Both the European mixed MAA and the hybrid dossiers share similarities with US NDAs that are covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic (FD&C) Act.[9] This section covers the type of "application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference." [9] Such information for which the applicant has not obtained a right of reference may only be

1. published literature and/or
2. FDA findings of safety and effectiveness of an approved drug ("reference product").

Despite this similarity, a closer look at the applicable FDA guidance[10] shows that the correspondence is not straightforward.

Literature-based 505(b)(2) applications, that is, applications that include some key data from literature, are quite clearly equivalent to mixed MAAs in the European Union. Interestingly, in the United States the question of whether any key data come from the literature determines the choice between the legal bases of applications: if any element of the key data is from the literature (or from another source to which the applicant does not have a right of reference), section 505(b)(2) applies rather than section 505(b)(1). There is no comparable distinction in the European Union.

Any 505(b)(2) applications relying on the FDA's previous finding of safety and/or effectiveness for a drug will likely be similarly acceptable as hybrid applications in the European Union, if the drug in question is registered in the European Union, that is, if an EU RefMP exists. Comparability to that EU RefMP in terms of quality and bioavailability may have to be shown; it is not sufficient to demonstrate comparability to a US-sourced medicinal product.

Establishing the legal "right of reference" to the raw data of published literature or the FDA's previous finding of safety and/or effectiveness is critical in determining the applicability of a 505(b)(2) NDA application. Right of reference is defined per 21 CFR 314.3(b) as "the authority to rely upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigations for FDA audit."[9] Thus, to be eligible for 505(b)(2) NDA, the applicant must not have obtained any legal right to the raw data from the referenced investigations (whether published literature or a reference product), or a full 505(b)(1) NDA would be applicable.

There are also cases where US 505(b)(2) applications will be considered completely differently in the European Union. Prodrugs (here, inactive molecules that are metabolically converted into known active substances after administration) may be approvable by the FDA under 505(b)(2) by relying on prior demonstration of safety and efficacy of the active moiety as simple drug. In the European Union, such new prodrugs are considered different molecular entities and will require full MAAs according to Article 8(3). Furthermore, 505(b)(2) applications may be made for drugs with a change in an active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety. In the European Union, such changes are accepted for "regular" generic applications according to Article 10(1) and (2). Also, new fixed combinations of 2 or more active substances fall under 505(b)(2) applications in the United States, whereas they fall under the specific Article 10b of the Directive in the European Union.

The US generic application (Abbreviated New Drug Application, ANDA) route according to section 505(j) may, upon permission from the FDA, be used for drugs with a similar active ingredient or whose route of administration, dosage form, or strength differs from that of the reference listed drug. Such changes have to be minor, for example, the change from an immediate release tablet to a capsule or the addition of an intermediary strength. Such changes will usually have to be submitted as a hybrid application in the European Union. However, changes to the active substance as described above, and changes from one immediate-release oral dosage form to another, fall under Article 10(1) and (2) and are treated as "regular" generic applications.

Data Protection

Data protection periods apply for data referenced in US 505(b)(2) applications, similar to the data protection periods discussed for the European Union above. 505(b)(2) applications themselves have 3 years of data protection if clinical studies have been conducted. A mixed MAA thus has a longer exclusivity than a 505(b)(2) application, whereas a hybrid application has unlimited but indirect protection.

Case Studies and Examples

Following are a number of examples to illustrate which legal basis has been used for the registration of newly developed products using established active substances, drawing upon publicly available information and our own experience.

From the Centralized Procedure

An MAA for PecFent® (fentanyl nasal spray) was granted to Archimedes Development Ltd., for a new dosage form and strength of fentanyl in the same indication as previously approved products.[11] Archimedes used a hybrid application including pharmacokinetic bridging studies to a centrally approved fentanyl oral lozenge formulation as RefMP. PecFent was not bioequivalent to the RefMP, and Archimedes provided data from a substantial clinical program (two phase 3 studies).

Nycomed used a hybrid application for Controloc Control® (pantoprazole), an identical dosage form and strength of the RefMP, to introduce a new, more limited indication and at the same time switch from prescription to nonprescription (OTC) status.[12] Interestingly, the RefMP was Nycomed's proprietary pantoprazole: the company effectively created a pseudo-generic to its own product, with a view to positioning both products differently on the market.

A mixed MAA for Pedea® (ibuprofen solution for injection) was submitted by Orphan Europe for a new, intravenous formulation of ibuprofen indicated for the treatment of patent ductus arteriosus in newborn premature babies.[13] Orphan Europe submitted a number of clinical efficacy and safety studies that it had conducted but also bridged to literature data generated with an existing intramuscular ibuprofen lysinate formulation used off-label by the intravenous route. For this purpose, bioequivalence was demonstrated in a healthy volunteer study. Despite this bioequivalence, the simultaneous changes in active substance (ibuprofen vs ibuprofen lysinate), route of administration (intravenous vs intramuscular), and indication made this dossier unsuitable for a submission as a hybrid application.

From the Author's Experience

A company has developed a sustained release dosage form of an approved product, introducing a new dosage form and new strengths, while keeping the indication unchanged. The company conducted a substantial pharmacokinetic and phase 3 study program and targeted a mixed MAA to obtain market exclusivity. In this case, clinical and nonclinical data were available in the literature to address all data requirements. Had this not been the case, a hybrid application would have been a possibility and indeed would still be viable alternative approach as the production process is secured by intellectual property and proprietary technology.

For use in a new indication, a company developed a new strength of an existing product while keeping the dosage form and route of administration unchanged. To support the new indication, a significant pharmacokinetic and phase 3 study program is ongoing. The company is aiming at a mixed MAA, again to obtain market exclusivity as there is no strong patent protection for this new use. In addition, significant data important for the definition of the dose are taken from published literature.

A different case is presented by a different, newly developed strength of an existing product, for which the company cannot claim intellectual property. This product is intended to be used in combination with recently approved medicinal products, and important data on the combined use are contained in the dossiers of these products and are under data protection. This precluded a largely literature-based mixed MAA, leaving a hybrid application referring to a RefMP with the targeted indication as the only option. As this product is an orphan medicinal product, orphan exclusivity will provide the essential market exclusivity regardless of the legal basis of the application.

Conclusions

Each product development is different, and each has its particular set of constraints. A thorough analysis must be made early in the development process to decide on the appropriate legal basis for an EU MAA, as this choice dictates the dossier content and hence the development plan in a significant way. The decision should not be treated as a box-ticking exercise before the submission of the dossier!

In many cases, there will not be a true choice, but if there is, the most advantageous legal basis needs to be chosen carefully. The decision as to which legal basis is the most advantageous one will be driven by the available published data and their quality, the available budget for one's own studies required to close data gaps in the literature, the desired data protection and market exclusivity, the competitive environment, and the key market regions (European Union vs United States). Last but not least, the status of the development of the product is an important factor, as prior decisions in the development plan may have already narrowed the available options. Therefore, the selection of the legal basis for an MAA should be considered early in product development and revisited as major milestones are achieved and the product evolves toward the MAA.

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