White Paper

Drug Registration 2022

BlueReg
PHARMA CONSULTING

Hybrid or Mixed Marketing Authorisation Application in the European Union

Introduction

For any medicinal product Marketing Authorisation Application (MAA) in the European Union (EU), 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 paediatric 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 criteria, dossier requirements, pharmacovigilance and paediatric obligations as well as the post authorisation maintainence 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.

Basic EU legislation for medicinal products

Directive 2001/83/EC, regulates the requirements for human medicinal products including marketing authorisation procedures, dossier, types of applications or legal basis.

Legal basis of the application in the EU

The applicant should clearly indicate the legal basis for the submission of their application in the EU Application Form, i.e. select one of the following articles of Directive 2001/83/EC:

Article*	Type of application
8(3)	Full or full-mixed application (complete dossier)
10(1)	Generic medicinal product application
10(3)	Hybrid medicinal product application
10(4)	Similar biologic product application
10a	Well established use application (literature only)
10b	Fixed dose combination (components already authorised separately) application
10c	Informed consent application

***Directive 2001/83/EC**

Hybrid applications

Hybrid applications under Article 10(3) of Directive 2001/83/EC differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary in the following three circumstances:

- where the strict definition of a 'generic medicinal product ' is not met;
- where the bioavailability studies cannot be used to demonstrate bioequivalence;
- where there are changes in the active substance (s), therapeutic indications, strength, pharmaceutical form or route of administration, with regard to the reference medicinal product.

In such cases the results of appropriate tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC as amended by Directive 2003/63/EC.

These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data.

How to present your Hybrid application

Marketing Authorisation Applications for a hybrid medicinal product should follow the structure of the Common Technical Document (CTD) format, as for any other Marketing Authorisation Application. Specific requirements that such applications should fulfil are listed below:

Reference medicinal product

The reference medicinal product is a medicinal product which has been granted a marketing authorisation 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 and to which the application for marketing authorisation for a hybrid medicinal product refers, by demonstration of bioequivalence, usually through the submission of the appropriate bioavailability studies.

Bioequivalence studies performed with a product not authorised within the European Economic Area (EEA) will not be considered acceptable.

Applicants will have to identify in the application form for the hybrid medicinal product the reference medicinal product (product name, strength, pharmaceutical form, MAH, first authorisation, Member State/Union).

Module 1

All Module 1 requirements apply to hybrid application. When certain elements are not included, a justification for its absence should be provided in the respective section.

Applicants should provide in Module 1.5.2 a concise document (up to approximately 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is:

- *A so-called 'hybrid' of a reference medicinal product (Art 10.3). This summary should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.*

Risk Management Plan

The requirements for submission of EU Risk Management Plans for hybrid applications are the same as for any marketing authorisation application, independent of the legal basis of the application. These requirements are described in Directive 2010/84/EU amending Directive 2001/83/EC. However, according to the GVP Guideline for new applications under article 10(3), for changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, the applicant should discuss in RMP whether this results in the addition or deletion of a safety concern. Clinical trial data generated to support the application should be discussed in the RMP, as appropriate.

Paediatric requirements

The paediatric requirements for hybrid application are set out in Articles 7 and 8 of the Paediatric Regulation. Paediatric Investigation Plans (PIPs) are not required for applications following Article 10(3).

Pharmacovigilance system

The requirements for submission of the summary of a pharmacovigilance system are the same as for any marketing authorisation application, independent of the legal basis of the application. These requirements are described in Directive 2010/84/EU amending Directive 2001/83/EC.

Module 2

Module 2 must include the Quality Overall Summary, Non-clinical Overview and Clinical Overview. Nonclinical and Clinical Summaries can be provided, but they are only mandatory if new additional studies have been provided within the documentation.

Module 3

A complete Module 3 should be submitted in accordance to the requirements set out in the Notice to Applicants (NtA).

Module 4 & 5

For a so-called 'hybrid' of a reference medicinal product (Art 10.3), the results of appropriate preclinical and clinical tests should be provided in accordance to the requirements set out in the Notice to Applicants.

Clinical & Non-clinical data

The new non-clinical and clinical data introduced by the applicant of the hybrid MAA focuses on two aspects. One aspect are bridging studies allowing the applicant to claim certain data from the reference medicinal product. The other aspect is that newly introduced data shall support the proposed differences between the hybrid and the reference medicinal product.

Annex II of Volume 2A, Chapter 1 of the Notice to Applicants specifies the type of additional data that is usually required for hybrid applications, depending on the proposed changes in contrast to the reference medicinal product. For different routes of administration and/or different pharmaceutical forms clinical safety and efficacy data, pharmacokinetic data and non-clinical data (e.g. data on local tolerance) shall be considered.

Taken together, hybrid applications following the legal basis of Article 10(3) are suitable for new pharmaceutical forms of known active substances. In contrast to stand alone-applications applicants are only required to introduce new data to allow a bridging to the reference product and to support the differences between the hybrid and the reference product. However, a hybrid application may not be suitable for products with a complex or innovative new pharmaceutical form especially if they come together with a new indication for the specific substance. In these cases, a potential reference medicinal product may be too different from the new product.

Timetable for Hybrid applications under Article 10(3) of Directive 2001/83/EC

For hybrid applications under Article 10(3), the timetable for a new full application applies for the first evaluation phase (Day 120). For the second evaluation phase, a shortened timetable could be agreed upon on a case-by-case basis.

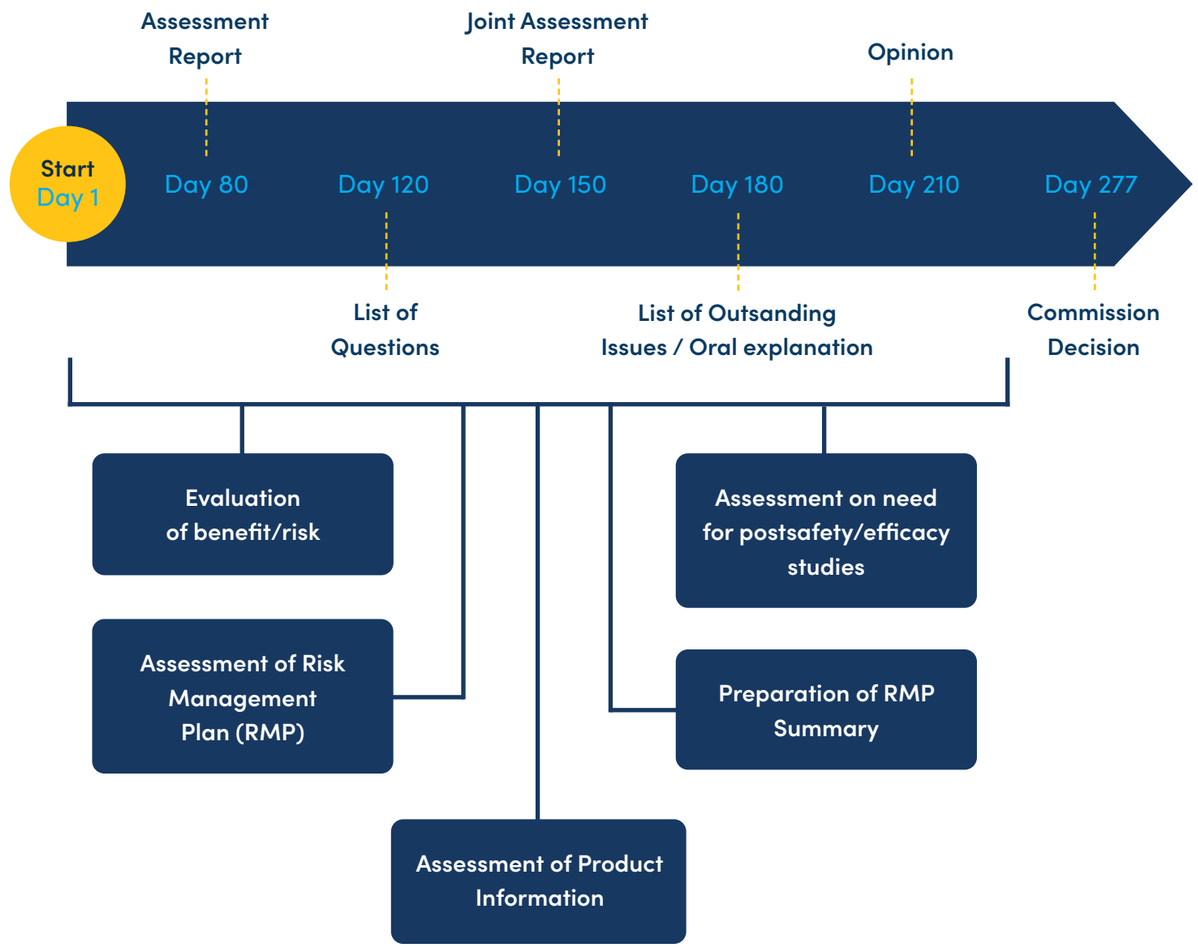

Figure 1. Evaluation overview - CHMP

Post authorisation

Once the MAA is approved, the hybrid MA are maintained in the same way as any other MA,
Any post approval changes to the currently approved hybrid MA can be submitted as variations. For centrally authorised hybrid MA, the administrative and quality changes are generally classified same as mentioned in the EU variation guidelines as for any other MA; exception – variation category A.2 a).
In case of a safety changes, for centrally authorised hybrid of centrally or nationally authorised innovator products, the EMA will provide the MAH of the hybrid product with the exact wording of the reference medicinal product to be implemented and will request the MAH to submit a variation as soon as possible or at the latest within 2 months to implement the changes in the PI as adopted for the innovator.
As for any other MA, the variation regulation lays down the assessment times for the various types of variations. Generally, this assessment time is calculated from the procedure start date to the final decision.

Conclusion

BlueReg has extensive experience in registration of medicinal products in Europe, to provide resources to produce high quality registration dossiers using our multidisciplinary regulatory affairs, scientific writing, and publishing team, and to manage the submission process through to a successful conclusion.

As every project and client situation is unique we provide a tailored package of services to meet the specific needs of the application. Our valuable expertise can assist you by anticipating aspects which could be problematic for the different submissions and procedures, so that potential delays are mitigated against.

BlueReg expertise and high quality submissions will ensure smooth validation and timely progress and smooth running of the procedures. The complexities of European submissions and timelines will be managed, resulting in a close collaboration and development of a strong path to submission and throughout the procedure.

Abbreviations

C

CMD:
Coordination group for Mutual Recognition and Decentralised Procedures

CTD:
Common Technical Document

E

EC:
European Commission

EEA:
European Economic Area

EMA:
European Medicines Agency

EU:
European Union

M

MA:
Marketing Authorisation

MMA:
Marketing Authorisation Application

MAH:
Marketing Authorisation Holder

N

Nta:
Notice to Applicants

P

PIP:
Paediatric Investigation Plan

Bibliography

- https://globi-reg.com/wp-content/uploads/2018/01/Type-of-applications-and-applicants.pdf
- https://journals.sagepub.com/doi abs/10.1177/0092861512443748?journalCode=dijb
- https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-pre-authorisation-procedural-advice-users-centralised-procedure_en-0.pdf
- https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_272_2012_Rev06_2020_03_clean_-_Q_A_on_generics.pdf
- https://www.ema.europa.eu/en/documents/presentation/presentation-centralised-procedure-european-medicines-agency_en.pdf

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Any questions ? **Contact-us.**

- contact@blue-reg.com
- www.blue-reg.com