

Orphan Drug Development Guidebook

Building Block E109

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

| ITEM | DESCRIPTION |
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| Building Block (BB) Title | Marketing Authorization Under Exceptional Circumstances (MAUEC) |
| References | <p>https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-procedures-granting-marketing-authorisation-under-exceptional-circumstances-pursuant/2004_en.pdf</p> <p>Pre-authorisation guidance</p> <p>https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance</p> |
| Description | <p>The MAUEC enables the marketing authorization of medicines for which the applicant would otherwise be unable to provide comprehensive data on the efficacy and safety under normal conditions due to reasons of extreme rarity of the condition, technical impossibility to generate comprehensive knowledge, or ethical constraints.</p> <p>This provision of the EU legislation makes possible to develop drugs in situations when only a few patients are available to take part in clinical trials and thus comprehensive efficacy and safety data cannot be generated, neither during the development phase nor in a post-marketing setting. This procedure allows access to medicines for patients with low prevalence conditions.</p> <p>The application for the provision does not envisage a dedicated process and therefore does not have a time duration. The evaluation of applicability is part of the MAA review and therefore follows the expected timeline for drug approval in EU. After the marketing authorization is granted, its validity is of five years but it is subject to an annual reassessment of the benefit/ risk profile. Such procedure of yearly reassessment has a variable duration from submission to completion.</p> |

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| Category | Regulatory Building Block |
| Geographical scope | European Union |
| Availability | Applicants developing medicines for rare diseases. |
| Scope of use | <p>The provision is applied for by the developer at the time of the Marketing Authorization Application (MAA). The MAA should include all the relevant documentation for applications in exceptional circumstances according to Directive 2001/83/EC, Annex I, Part II. CHMP can propose an approval under exceptional circumstances, even if the applicant has not requested it.</p> <p>This provision is applicable to cases in which the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:</p> <ul style="list-style-type: none"> • The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive data on the efficacy and safety under normal conditions of use or • Collection of full information is not possible, or • It would be contrary to generally accepted principles of medical ethics to collect such information. |
| Stakeholders | <ul style="list-style-type: none"> • EMA • Medicine developers |
| Enablers/ Requirements | <p>The MAUEC is granted if all the requirements are met:</p> <ul style="list-style-type: none"> • The Applicant can show the impossibility to provide comprehensive non-clinical or clinical data on the efficacy and safety • The Applicant agrees on conducting specific procedures/ obligations after approval, including an annual reassessment of the benefit/ risk ratio. |

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| Output | Marketing authorization license that enables patient access to new medicines that would be otherwise not available due to the technical or ethical impossibility for the developer to generate comprehensive pre-clinical or clinical data at any time before or after the initial approval. |
| Best time to apply and time window | Although the formal request to the Authority to apply the provision occurs at the time of MAA, the best time to start thinking about this possibility is at the very beginning of development, as this strategic and technical decision has a significant influence over the development of the drug. Any interaction with the EMA during development in the form of Scientific Advice/ Protocol Assistance are expected to include a discussion on the applicability of this provision and its justification. The topic should be discussed at the pre-submission meeting, to be run by procedure at least 6 months before MAA. |
| Expert tips | <ul style="list-style-type: none"> – Consider this possibility at the beginning of drug development – If MAUEC potentially applicable, plan to include a specific question on applicability as early as possible into your interaction with the Agency – If MAUEC is due to the extreme rarity of the condition, consider application as Orphan Designation as one of the first regulatory steps – Design your development plan around the information that you consider impossible to gather, in order to devise a risk-based strategy for data collection and gap filling. Discuss gaps with the Agency during development interactions. – Explore the possibility to engage in dialogue also with payers, physicians, and patients in order to ensure the accuracy of your justification for UEC and to discuss their information needs in such extreme situation – Pro-actively request MAUEC as part of your MAA – Pro-actively propose post-authorization measures based on your knowledge gaps (e.g. a disease and product registry, post-approval studies, etc.) – Consider also the request for accelerated assessment <p>PROs:</p> <ul style="list-style-type: none"> • It enables development and approval of drugs otherwise “non-developable” in the EU. This is of particular relevance when the disease is ultra-rare and when a global development of the product is not pursuable. • Differently than the Conditional Marketing Authorization, it is not a “temporary” license subject to confirmation and there is a clear understanding that a larger development is impossible/ unfeasible. |

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| | <p>CONS:</p> <ul style="list-style-type: none"> • To be pursued, it requires appropriate due diligence of the disease or the development condition in order to provide a solid and long-standing justification of its applicability. • After approval, it requires continuous development and regulatory effort by the developer in order to fulfill the Specific Obligations (proposed by the Applicant or imposed by the EMA) and conduct the Annual Reassessment. • It “certifies” the intrinsic limitations of the clinical data package also in front of stakeholders other than the EMA (e.g. HTA bodies) |
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