IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Orphan Drug Development Guidebook

Building Block E108

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
Building Block (BB) Title	Conditional marketing authorization (CMA)
References	https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
Description	The CMA allows a fast access to medicines for patients, which fulfill an unmet medical need. It enables the marketing authorization of medicines for which there is sufficient evidence to suggest the presence of a positive benefit/ risk profile for patients with an unmet medical need, but it would be technically not feasible to confirm such positive profile in a time frame compatible with the medical need of the product. In these conditions, the benefit to patients of immediate availability outweighs the risk of an initial authorization therefore less comprehensive data than normally required. The procedure allows patients earlier access to medicines for rare and ultra-rare conditions, for which obtaining full confirmatory evidence before product authorisation would be problematic due to the presence of a significant unmet patient's need. The procedure 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.
Category	Regulatory Building Block
Geograp	European Union

hical scope	
Availability	Any applicant developing medicines for rare and non-rare diseases.
Scope of use	The provision may be applied for by the developer at the time of the Marketing Authorization Application (MAA), or may be imposed by CHMP if the developer has applied for a full authorisation. The MAA should include all the relevant documentation for applications according to Directive 2001/83/EC. Medicines for human use are eligible if they belong to at least one of these categories: • aimed at treating, preventing or diagnosing seriously debilitating or life-threatening diseases; • intended for use in emergency situations (also less comprehensive CMC and non-clinical data may be accepted for such products); • designated as orphan medicine
Stakeholders	• EMA • Medicine developers
Enablers / Requirements	The CMA may be granted if all the requirements are met: • the benefit-risk balance of the product is positive; • it is likely that the applicant will be able to provide comprehensive data (if not, consider applying for authorization under exceptional circumstances); • unmet medical needs will be fulfilled; • the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to need for further data.
Output	Authorization to market new medicines for unmet needs well before a definitive set of evidence is available which can be due to technical constraints such as difficult enrollment in trials, long duration of studies required, etc.
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 7 months before MAA.
Expert tips	– Consider this possibility at the beginning of drug development – If CMA potentially applicable, plan to include a specific question on applicability as early as possible into your interaction with the Agency – If CMA is due to the 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 at the time of initial MAA, in order to devise a risk-based strategy for data collection and gap filling after CMA. 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 adequate value assessment and prompt access to the treatment after initial marketing authorization – Pro-actively request CMA as part of your MAA. – Consider also the request for accelerated PROs: • Faster access of medicine to patients CONs: • It is a "temporary" authorization, therefore requires commitment to complete pivotal development with the risk of having the product withdrawn from the market in case of negative outcome of confirmatory study/-ies. • The co-presence of product available in clinical practice and of clinical trial(s) may generate issues or limitations in terms of possible designs of the confirmatory study/-ies (e.g. acceptability of placebo) and "competition" between the two settings (e.g. preference of patients for normal clinical use rather than being part of a cumbersome trial). • It "certifies" the intrinsic limitations of the clinical data package also in front of stakeholders other than the EMA (e.g. HTA bodies), who might prefer to wait for the generation of additional data before enabling access to the treatment, thus vanishing the meaning of the provision. • 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.