Drug Repurposing Guidebook

Building Block E146

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	Engaging with HTA
References	https://health.ec.europa.eu/health-technology-assessment_en https://health.ec.europa.eu/health-technology-assessment/key-documents_en Palkmets O, Nagda N, Sear R. Early HTA Advice In European Countries: Scope And Associated Costs. Value in Health 2017; 20 (9): A695.
Description	The HTA is procedure for assessing the added value of new medicines and medical devices. In Europe, pricing and reimbursement decisions on the drugs are a national/regional responsibility, and are made based on a process of appraisal by national Health technology Agencies (HTA) that includes value assessment and economic considerations, amongst others. Regional and national HTA bodies provide recommendations on medicines and other health technologies that can be financed or reimbursed by the healthcare system in a particular Member State or region. The assessment criteria used by HTA bodies differ between Member States, in accordance with regional and national legislation. At the request of Sponsors, Regional and national HTA bodies can provide recommendations on the data to be submitted at the time of application for pricing, funding or reimbursement of medicines and other health technologies by the healthcare system in a particular Member State or region.

	National advice can be sought by sponsors during clinical development of new drugs and repurposed ones, in order to advance which will be the likely criteria for value assessment that will drive the price and reimbursement decision, and whether the data collection that has been planned by the sponsor for pivotal trials will be appropriate and sufficient to inform the process. The advice received can be used to timely implement changes to the clinical development plan to ensure that all the required information is available at the time of authorization, so that any delays in access due to lack of data can be avoided. However, the current systems fail to account to distinguish between products developed de novo and "repurposed" drugs, Development costs would typically not be accounted for when assessing value, but could be regarded by the decision-makers during the deliberative process and pricing negotiations. Early engagement with HTA bodies is then of paramount importance to set correctly the scene and inform the evidence generation. The process of National Scientific Advice with HTA bodies is applicable to any kind of product, thus not restricted to rare diseases, nor to "de novo" drugs but may be especially relevant for repurposed drugs intended for rare diseases with anticipated low market volume and high prices per treatment, because substantial differences may occur across countries in the criteria for appraisal and the need for a health economic assessment due to differences in standards of medical and social care, as well as in the affordability of high prices for new drugs.
Category	Regulatory and HTA engagement
Type of BB	HTA and reimbursement
Geographical scope	Europe
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	As per the traditional drug development of "de novo" products, clinical development is mainly focused on regulatory approval of marketing authorization applications, and the criteria for approval of orphan drugs in Europe is applied at an Europeanlevel (i.e., mandated centralized procedure for orphans). However, the competence for pricing and reimbursement decision in Europe relies on National authorities. While European countries share regulatory criteria, they diverge in wealth, economic systems and healthcare models, so that funding and public coverage may be substantially different. Because reimbursement is arranged at a national level, despite a common positioning may be reached from supranational consultation through coordinated procedures

	involving many HTAs, it may still be required to gather opinions on particular requirements for a given country. National advice would allow for timely planning of data collection (I ex: related to different clinical practices in a given country) and/or specific studies (I ex: comparison to different standards of care) that might be required by the HTA in order to appraise the new product. Similarly of the "de novo" drugs, the BB is to be used by sponsors in preparation of the post-authorization process of pricing and reimbursement, in order to anticipate that all the relevant data needed to support application for pricing and reimbursement is collected timely and appropriately, in order to satisfy the HTA procedures for value assessment and criteria for drug appraisal.
Stakeholders	• Sponsors of products intended for marketing authorization application and future application for pricing and funding/reimbursement. • National Health Technology Agencies receive the applications and issue opinions on the questions raised by the Sponsors.
Enablers/ Requirements	The Sponsor of a given clinical development of any kind of drug should identify the strategic need or convenience of a national scientific advice with HTA, and the best moment for consultation. This is relevant also for the repurposed drug under development. The Sponsor contacts the HTA for requirements, prepares documentation and submits application. The HTA reviews the materials and prepares answers. The format of consultation can be in writing or in the form of a face to face meeting, depending on HTA internal procedures.
Output	The HTA issues opinion in writing or in the form of a face-to-face meeting, depending on HTA internal procedures. The opinion is generally kept confidential.
Best time to apply and time window	The tool can be used starting from product discovery until market access being the optimal times to apply right before First in Human Ready, after human PoC and before market authorization.
Expert tips	A description of the European HTAs can be found here: https://health.ec.europa.eu/health-technology-assessment_en

	• The Sponsor of a given clinical development identifies the need for a national scientific advice with HTA, ideally by the end of phase II, before beginning of phase III. • The number of HTAs and the selection of which HTA to approach is a strategic decision of the sponsor, that may vary depending on the degree of uncertainty on the country procedures, clinical differences in the standards of care for the indication sought for the new treatment, and strategic considerations of the company, amongst other factors. • The name of the procedure may be different in each country (HTA Scientific Advice, pre-submission meeting, Technical consultation, amongst others). • The Sponsor contacts with the selected National HTA to request advice, and which are the requirements for the procedure and fees of the HTA, where applicable. • A product briefing document is produced that is shared with the HTA ahead of discussions. The document includes a summary of product data and a list of questions with background support and proposed sponsor positioning regarding the potential response. • The HTA reviews the briefing document and prepares answers to the Sponsor's questions. The answers include whether the sponsor positioning is endorsed or not acceptable, and if an alternative positioning is hold by the HTA. Answers may be issued in writing or verbally during a face to face meeting with the sponsor; the number of meetings may vary between HTA depending on their internal procedures. • Also depending on the HTA, a final report with recommendation may be issued, or company minutes of the face to face meeting are circulated. PROs: Generally national scientific advice with HTA is a more direct, shorter and agile procedure than a full parallel consultation process through EUnetHTA. Also, national scientific advice may be a first approach to obtain initial opinions to prepare a future parallel consultation procedure through EMA/EUnetHTA, including a preliminary selection of preferred participating/leading HTAs in the multistate procedure. When issues on lack of predictability are limited to one singular country, the direct consultation with the concerned HTA may be agile and may allow the sponsor and the HTA to define mutually agreed solutions to be implemented only at the national level, with no involvement of other territories where a more standard approach can be done. Also, if higher exigencies or more strict policies are expected, these can be handled in isolation, avoiding generalization of the worst scenario to HTAs in other countries if a

	parallel consultation with regulators and health technology assessment bodies was done involving the concerned HTA. CONs: Asking for individual advice to all concerned HTAs is time and resource consuming and inefficient. Also, risks of individual advice with no multistate coordination include divergent advice from several national HTA for a single product. Inconsistencies between recommendations may pose a difficult scenario to Sponsors, who will have to deviate from part of the advice received. Asking for advice is not binding, but any deviation from previously received recommendations will require justification and may become problematic at the time of application. Because of that, generally a parallel consultation procedure is more sensible than several national procedures. Waiting for advice before closing the designs of phase III trials may represent a delay. Outcomes of the advice may require changing key features of the clinical plan, leading to strategic discussions on clinical positioning, objectives and goals of the clinical development plan. This can be difficult to manage within the sponsor team.