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Orphan drugs: lower hurdles for market access, pricing, and reimbursement?

REIMBURSEMENT CRITERIA AND PROCESSES OF ORPHAN MEDICINAL PRODUCTS IN FRANCE, GERMANY, AND ENGLAND.

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INTRODUCTION

An increasing amount of new treatments obtain orphan designation from the European Medicines Agency (EMA 2019). Since 2000, the number of applications for orphan medicinal product designation reached 3,443 with 2,247 of these achieving positive opinions and 169 orphan marketing authorizations. Orphan drugs are usually highly priced but there is more uncertainty around their data (i.e., short-term trials, placebo controlled, small numbers of patients, etc.) which causes a challenge from a reimbursement and health technology assessment (HTA) perspective. Orphan drugs are generally assessed by national bodies through HTA with the corresponding requirements varying by country. The purpose of HTA is to demonstrate the value of a new technology, against currently available alternatives. Different HTA bodies will use HTA to negotiate price reductions and save money. Therefore, understanding how the appraisal requirements and processes vary between countries is paramount for a successful orphan product launch.

WHAT ARE THE ELIGIBILITY CRITERIA AND HTA PROCESSES FOR ORPHAN DRUGS IN THE EU3?

Despite their status, orphan drugs are mostly subject to the classic route of assessment. However, there are some nuances linked to specific treatment criteria (see Table 1).

FRANCE

In France, despite following the classic assessment route, an orphan drug benefits from an accelerated procedure by the Transparency Commission (reduced from 90 to 30 days after dossier depot). The Haute Autorité de Santé (HAS) still assesses the medical benefit (SMR) and added medical benefit (ASMR). However, regardless of the ASMR, orphan indications are covered by the long-term illness provision (ADL31), which grants full reimbursement of treatment (Service Public 2019). Despite the orphan status, for products receiving an ASMR of I, II, or III or in case of an expected budget impact exceeding €20 million in year 2, an in-depth economic analysis (including a cost-effectiveness analysis) is likely to be required (HAS 2019). In all cases, price negotiations still take place for orphan drugs in France.

GERMANY

In Germany, an orphan drug with expected sales under €50 million per year, is assessed by the Gemeinsamer Bundesausschuss (G-BA) without a relevant comparative therapy, as the orphan status grants them an assumed added benefit. The dossier that is submitted still focuses on the benefit of the product and trial results must be reported. However, no comparative assessment takes place. As a result, the extent of the assumed additional benefit can only be rated as 'major', 'considerable', 'minor', or 'non-quantifiable ('no additional benefit' or 'less benefit' do not apply). In contrast, when the medicinal product's sales exceed a threshold of €50 million, a full benefit assessment against an 'appropriate' comparator (e.g., best supportive care) will be conducted without the orphan status advantage of an assumed benefit (G-BA 2011). Last year, the German parliament decided that the €50 million threshold will not only include retail sales but also hospital sales, which may result in G-BA reassessing several orphan medicines (Deutscher Bundestag 2019). After benefit assessment, the product will undergo the rigorous process of price negotiations. In the case of 'old' substances (active ingredients available before the AMNOG process started in 2011 and which are usually exempt from assessment), a HTA assessment may still be required by the G-BA for new indications with regulatory data protection, independently of any potential orphan drug status or any sales thresholds.

ENGLAND

In England, standard National Institute for Health and Care Excellence (NICE) appraisal and criteria are applied to orphan drugs. However, for ultra-orphan products, defined by specific criteria (see Table 1), NICE have a highly specialized technology assessment (HST) route, in which case the treatment benefits of a higher cost-effectiveness threshold compared to normal HTA; £300,000 *vs.* £20,000 to £30,000 (House of Commons 2019). The HST evaluation process is similar to the classic HTA process, with additional relevant criteria to fulfill and specific data considerations (see Table 1, NICE 2017). For HSTs, the cost-effectiveness assessment includes costs to the NHS and personal social services. Decision making is based on the total budget for specialized services, its allocation, and the level of expenditure in comparable health areas. NICE has recently initiated a review of its methods for both technology appraisals and highly specialized technologies (HSTs), including a review of the process of guidance production for HST (NICE 2019).

Table 1: HTA eligibility criteria and assessment types in the EU3

Country	HTA eligibility criteria	HTA assessment type
France (HAS)	› Marketing authorization with orphan drug designation › Extra definition of "rare cancer" if the cancer occurs in <6 in 100,000 patients per year OR requires specialized treatment due to untypical tumor location or complex disease characteristics	› Normal assessment
Germany (G-BA)	› Marketing authorization with orphan drug designation	› Partial assessment (assumed added benefit)
	› Marketing authorization with orphan drug designation with sales revenues > €50 million per year	› Full benefit assessment
England (NICE)	› Orphan drug: 5 in 10,000 patients	› Normal assessment
	› Ultra-orphan drug (all need to apply): ○ 1 in 50,000 patients ○ The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centers in the NHS; ○ The target patient group is distinct for clinical reasons; ○ The condition is chronic and severely disabling; ○ The technology is expected to be used exclusively in the context of a highly specialized service; ○ The technology is likely to have a very high acquisition cost; ○ The technology has the potential for lifelong use; ○ The need for national commissioning of the technology is significant.	› Highly specialized technology assessment

ARE THERE NON-HTA ACCESS ROUTES FOR ORPHAN DRUGS?

FRANCE

Independently of the European regulations, orphan drugs in France can be accessed by patients and fully reimbursed before marketing authorization via a Temporary Authorization of Use (ATUs) - at a non-negotiated price. The manufacturer must submit the registration dossier within six months of the start of the ATU. Another procedure worth highlighting is the Recommendation for Temporary Use (RTUs) which allows patients to benefit from a treatment that is used off-label, either outside of marketing authorization or already registered but for which a new indication is under assessment (ANSM 2017). The eligibility criteria for this process are twofold; there must be a medical need and the risk/benefit ratio of the product needs to be favorable. In any case, after marketing authorization, the HTA process will be triggered.

GERMANY

Outside of the leniencies stated above for orphan drugs, namely being granted an assumed benefit and permittance to submit a condensed HTA dossier, orphan drugs are not provided additional exemptions from the HTA process in Germany. New active ingredients can however opt out of, or be exempt from, the benefit assessment and dossier obligation entirely, when the anticipated re-occurring revenues in the outpatient sector do not exceed €1 million (G-BA 2020). This exemption, however, is not specific to orphan drugs, neither does it provide much semblance of great benefit to orphan or ultra-orphan drugs due to the high prices which orphan and ultra-orphan drugs typically apply. Furthermore, a request for exemption must be made in this instance to the G-BA, and the success of such an opt-out request should not be automatically assumed.

ENGLAND

When orphan or ultra-orphan drugs are not selected to be appraised by NICE HTA they fall under the remit of the commissioning process at NHS England (House of Commons 2017). This process is recurring on an annual basis and new treatments and technologies are ranked according to their clinical and cost effectiveness. Treatments are routinely commissioned based on this ranking and the remaining specialized commissioning budget for the year. Treatments that are not selected to be routinely commissioned can still be commissioned on an individual patient basis and will be re-assessed the following year (House of Commons 2017).

HOW CAN YOU PREPARE FOR SUCCESSFUL MARKET ACCESS HTA SUBMISSION AND ACCESS FOR ORPHAN DRUGS?

First, a full understanding of the rules and requirements of appraisal systems in different countries at an early stage of development is necessary in order to prepare a market access road map that allows sufficient time to implement all the relevant market access activities. Secondly, the necessary clinical evidence, economic evidence, and comparator justification need to be prepared and assessed in their relation to payer relevance and impact on pricing. Finally, the clinical and economic data should be combined with a strong justification of burden of disease and unmet need in a value story that resonates with payers.

These activities are essential in order to develop a solid reimbursement submission, achieve optimal pricing, and enable timely patient access to new products.

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