



HTA

Health Technology Assessment and Plasma Protein Therapies: A Troubled Match

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PLASMA PROTEIN THERAPIES: A SPECIAL TYPE OF PHARMACEUTICALS

Plasma-derived medicinal products comprise a special type of biologics. Since the introduction of the first large-scale method for separating therapeutic proteins from blood plasma with cold ethanol fractionation during World War II, the plasma protein therapeutics sector has experienced continuous growth.¹ In the past 70 years, the implemented business strategies resulted in developing new fractionation techniques, inventing alternative manufacturing methods—such as recombinant DNA technology, testing efficacy in new patient populations, and improving product safety and manufacturing efficiency. Today, plasma protein therapies (PPTs) are included in the World Health Organization’s (WHO) “Essential Medicines List,” which recognizes priority medicines based on the evidence of clinical efficacy and safety, with the purpose to ensure global health equity and meet the care needs of populations.²

PPTs are used for treating many chronic rare diseases, such as primary immunodeficiency (PID), hemophilia, chronic inflammatory demyelinating polyneuropathy, and

alpha-1 antitrypsin deficiency—and in some, there are no treatment alternatives. The global clinical need for PPTs for evidence-based indications is still largely unmet.³ Particularly in countries with low gross domestic product, patient access is often limited. However, developed economies—driven by budgetary constraints—have also been introducing cost containment measures, such as compulsory rebates and clawbacks, ignoring PPTs’ manufacturing complexity and value for patients.

HEALTH TECHNOLOGY ASSESSMENT TO DETERMINE THE VALUE OF PLASMA PROTEIN THERAPIES

Approaches to the “value assessment” of health care interventions has been extensively debated by scientists and policymakers in past decades, without leading to a consensus. Health Technology Assessment (HTA)—used to determine the value of pharmaceutical products and to support national reimbursement decisions in Europe since the 90s—show inconsistencies in methods and conclusions. HTAs may be aimed at assessment of the level of therapeutic benefit (e.g., in Germany and France) or the level of cost-effectiveness

as applied in most European countries.⁴ Incremental cost-effectiveness ratio (ICER)—the outcome of such analysis—is typically calculated as a ratio between the additional cost imposed by the new therapy and the respective health gain expressed in quality-adjusted life years (QALYs), as compared to the best available treatment alternative. The application of a single ICER threshold in national reimbursement decisions is not common.⁵ The WHO recommends considering health technologies with an ICER below the value of the gross domestic product (GDP) per capita as very cost-effective, between one and three times GDP value as cost-effective, and not cost-effective if exceeding 3x GDP per capita.⁶ HTAs have also been increasingly used for the evaluation of PPTs, even though stakeholders caution that such analysis in many cases is inappropriate.⁷⁻⁸

The deficiencies of current HTA methods for assessing the value of PPTs are numerous.

EFFICACY AND COST-EFFECTIVENESS ASSESSMENT

First, in some conditions such as PID, absence of a treatment alternative can make HTAs an unethical evaluation method.⁹ The inability to conduct randomized trials and the evidentiary uncertainty caused by a limited number of observations, individual treatment responses and non-linear pharmacokinetic behavior of PPTs complicate bivariate judgement (effective versus not effective) based on short-term observations. The need for a methodological shift to adaptive trial designs, which allow for iterative evidence generation and a timely recognition of a drug's efficacy or lack thereof in certain subgroups, has been recognized.¹⁰ Conditional market entry schemes with post-launch evidence generation may offer a solution.

Second, measuring value through a mathematic calculation of cost per QALY has several limitations. Uncertainties in the clinical effect in small patient groups and subgroups, as well as high manufacturing costs result in high ICERs or infeasibility to calculate an ICER.¹¹ Moreover, the assumed neutrality of the QALYs (i.e., no matter who gains them) does not seem to be supported by societal preferences regarding health care resource allocation.¹²

PATIENT PERSPECTIVE AND OVERALL IMPACT ASSESSMENT

Third, current HTAs insufficiently involve the patient perspective. When evidence is scarce or uncertain and diseases are rare and complex, effective partnerships seem essential to determine the true added value of therapies and ensure that they are provided at the fairest possible price.¹³ Participation of patients should be considered in all phases of the project; in recent years, there has been greater recognition of the value of patient reported outcomes (PROs). Structural use of generic and disease-specific PROs in HTA is recommended but not consistently integrated in policy decisions.¹⁴ While clinicians admit to having limited expertise in handling patient perspectives,¹⁵ information from qualitative research, such as

patient interviews or focus groups, can provide policymakers with invaluable contextual information in order to understand the burden of a rare disease and how the treatment under assessment affects the patient.¹⁶

Fourth, next to the clinical and cost-effectiveness assessment, evaluation of the ethical, organizational, and societal impact of health technologies are recommended by the EUnetHTA's "HTA Core Model."¹⁷ However such methodologies are still in the early stages and barely applied in practice limiting the scope of information provided to decision-makers.

MANUFACTURING COMPLEXITY

Finally, the manufacturing complexity and specific dynamics of the plasma protein therapeutic sector are not considered in reimbursement decisions, particularly when reimbursement reductions are being applied. The manufacturing of plasma protein therapeutics is a highly-sophisticated process that takes about seven to twelve months from plasma donation to completion of the finished product. The process includes robust safety standards at each step, such as: donor screening, testing of each donation, plasma pooling and testing, protein purification, virus inactivation, and prion removal, etc. Because plasma is a biological product, rigorous testing and quality assurance occur throughout the manufacturing process.¹⁸ The cost structure of a plasma product is therefore completely different than that of small-molecule pharmaceuticals. The cost of collecting raw material (i.e., human plasma) can typically contribute to more than 60 percent of the overall cost of manufacture. In small molecule pharmaceuticals, introduction of a generic version of a drug has been shown to reduce price by up to 90 percent relative to the brand version. The manufacturer of a subsequent version of a PPT will have to devote time and invest in clinical trials, manufacturing, and post-approval safety monitoring similar to first-in-class PPT.¹⁹

An additional complexity that impacts the economics of plasma fractionation is that with each liter of plasma, a maximum protein output has to be achieved; while diversification of the product portfolio is essential for the business sustainability.²⁰ According to some analytics, if a fractionator would extract only one type of protein, their business would be uneconomic and at least a three-product portfolio is considered as necessary for a viable operation.²¹ Regional differences and variations in demand may affect the economic sustainability of the sector.

Further, the supply of plasma derived therapies is entirely dependent on the availability of healthy donors. Currently, free competition in the sector is disturbed by the "not-for-profit" fractionators that usually enjoy monopolistic protection by national authorities. This is based on the concept of self-sufficiency of plasma supply through voluntary unpaid donations.²² Low plasma supply in Europe remains a challenge when considering the growing global demand for PPTs.

In the past 10 years, many conceptual frameworks for the assessment of rare disease therapies have been developed²³ to overcome the limitations of contemporary HTA methods.

NEED FOR A NEW APPROACH TO VALUE ASSESSMENT OF RARE DISEASE THERAPIES

In the past 10 years, many conceptual frameworks for the assessment of rare disease therapies have been developed²³ to overcome the limitations of contemporary HTA methods. Most of the frameworks are a multi-criteria decision analysis (MCDA) and include a broader range of assessment elements than traditional HTAs, e.g., rarity and burden of disease, availability of treatment alternatives, level of health impact and uncertainty of effectiveness, vulnerability of patient population, manufacturing complexity, etc. However, application of these frameworks in reimbursement decisions remains limited.

In conclusion, timely diagnosis and treatment with PPTs has been shown to significantly prolong the life expectancy of people with rare diseases (e.g., PID and severe hemophilia) allowing those affected by these conditions to live normal and productive lives.²⁴⁻²⁵ However, current HTA methods are limited. This prevents information on the value of PPTs for patients and the complexity of their manufacturing and economics from being systematically captured. The result is inadequate information to policymakers. Patient associations caution that HTA's, which follow established rigid methodologies—may be used as a means to mitigate costs rather than a way to improve the quality of care in rare diseases.²⁶ Nowadays, some payers treat PPTs as if they were an easy-to-produce commodity. Alternative paradigms to assess “value for money” for interventions in rare diseases should be developed with high priority.²⁷ ●

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