Regulatory Framework for Innovation Assessment in Advanced Therapies in Europe

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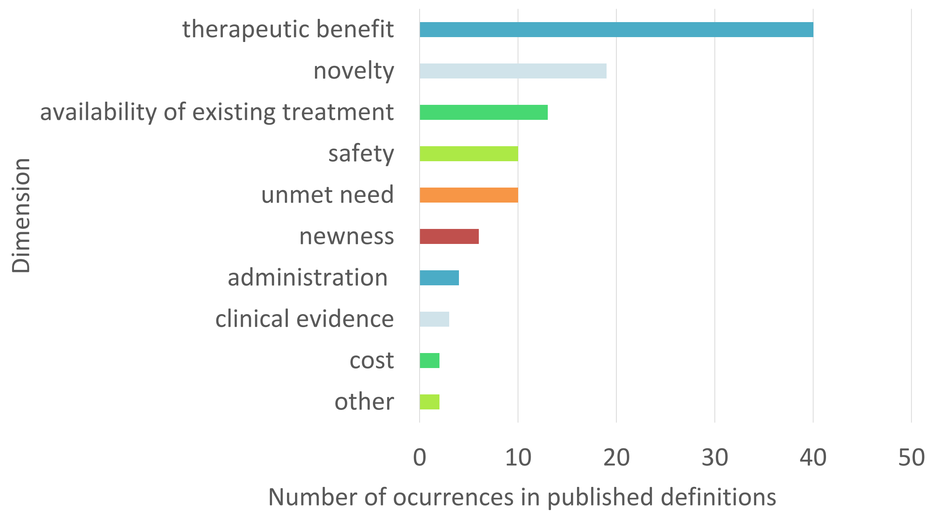
Introduction

Regulation (EC) No 1394/2007 establishes a centralized marketing authorization procedure for Advanced Therapy Medicinal Products (ATMPs) when they are intended to be placed on the market or industrially manufactured. However, the competent authorities of each Member State (Regulatory Medicines Agencies and/or HTA bodies) are responsible for the reimbursement of each ATMP in its territory, meaning that reimbursement models vary from country to country.

In this regard, value-based assessments are increasing their popularity to place on value the social impact of the ATMPs**.** This social value is associated with the expectancy of ATMPs to be a potential cure for unmet medical needs related to genetic diseases, neurodegenerative diseases and tissue malignancies. Although "cure" is a term a little presumptuous, there are no doubts about the improvement in the health and quality of life of patients with usually only one administration of the ATMP, which also implies saving long-term indirect costs (caregivers, hospital fees, concomitant medications, patient follow-ups…) in healthcare systems. In this sense, value-based assessments are becoming useful tools to measure this additional benefits. Some of the factors that are generally take into consideration are: innovation, unmet clinical need, severity of the disease, additional benefit, ethics consideration and costs**.**

Innovation assessment

Due to the peculiarities of the ATMPs, we can categorize them as innovative treatments in the first instance. However, the term "therapeutic innovation" could mean differently for each of the main stakeholders of the pharmaceutical industry. Figure 1. *(de Solà-Morales O et al., 2018)* displays the terms used to describe innovation from definitions identified in the literature.

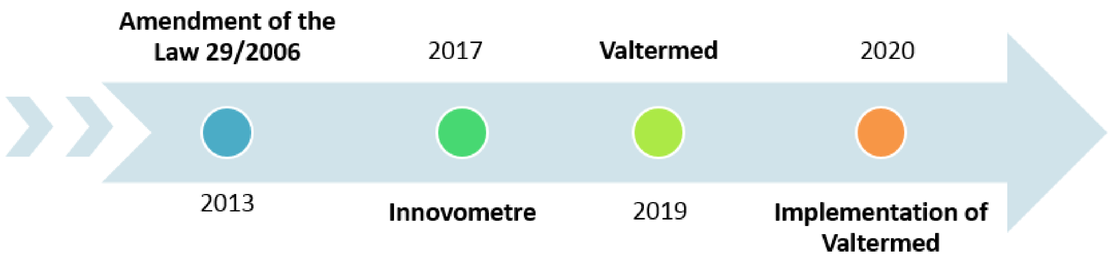


In addition, there is no consensus among Regulatory Medicine Agencies. Currently, there are as many types of innovation assessments as countries. However, we can broadly distinguish two approaches:

- Quality-adjusted life years (QALYs) as value-based assessment. It is used in countries with a greater tradition in economic evaluation such as UK and Canada. They do not measure the innovation level, but they apply a cost-effective approach based on quality-adjusted life years (QALYs) as value-based assessment.
- Categorization of the innovation. Other countries classify the innovation into differentiated categories, either through discrete ordinal scales such as Austria, Germany or Spain, or algorithms such as Italy or Sweden. Some details of some of these value-based assessments are displayed in the table.

Regulatory Agency	Country	Criteria	Innovation assessment	Ref
Italian Medicines Agency	Italy	✓ Unmet therapeutic need ✓ Added therapeutic value ✓ Quality of evidences	▪ Non innovative ▪ Conditionally innovative ▪ Innovative	*Motola D. et al, 2006*
Swedish Medical Products Agency	Sweeden	✓ Unmet therapeutic need ✓ Safety & efficacy ✓ Administration ✓ Mode of action	▪ A1– New therapy ▪ A2– New therapy ▪ B1 – Improved effect ▪ B2 – Improved safety ▪ C1 – Simpler adminstration ▪ C2– Simpler dosage ▪ D– New mode of action ▪ E– Me-too drugs	*Ahlqvist-Rastad et al., 2004*
Agence nationale de securité du médicament et des produits de santé	France	✓ Quality of effect ✓ Clinical significance ✓ Evidence	▪ ASMR I – Major ▪ ASMR II – Important ▪ ASMR III – Moderate ▪ ASMR IV – Minor ▪ ASMR V – Non clinical improvement	*Haute Autorité de Santé. 2014.*
Federal Institute for Drugs and Medical Devices	Germany	✓ Added therapeutic value	▪ Major ▪ Considerable ▪ Minor	*AMNOG law, 2011*

Spanish situation



- Spanish policy makers took the first steps in 2013 with the Amendment of the Law 29/2006 of 26 of July. This regulation states that the innovative value of novel drugs would be taken into consideration for Price & Reimbursement (P&R) decisions.
- In 2017, a quantitative method – "innovometre [innovometro]"- was developed by the University of Alcalá de Henares in collaboration with the former Spanish Ministry of Health, Social Policy and Equality to assess the therapeutic innovation level of new drugs *(Zaragozá et al., 2017).* The aim of this methodology was to quantify the innovation level considering four parameters: the incremental therapeutic value, the safety profile, the burden of the disease and the healthcare associated costs. However, it was never officially implemented.
- Currently, the Spanish Government together with the Spanish Healthcare System Services are working on the "VALTERMED" method. This system aims to assess the therapeutic value of disruptive therapies in order to collect relevant information for P&R decision making. The first technical proof of concept has already been tested with CAR-T therapies, and it is expected to be oficially implemented by December, 2020.

The paradox of Zalmoxis

In September 2017, the Italian Medicines Agency using their innovation assessment – the Motola system- catalogued Zalmoxis as "non innovative medicine" because of its moderate clinical benefits, its moderate added therapeutic value and low quality of evidence data.

Zalmoxis is a somatic cell therapy containing allogeneic T cells genetically modified for the treatment of adult patients with leukemia and other high-risk haematological malignancies in association with haplo-identical hematopoietic stem cell transplantation developed by the biotech company Molmed.

Zalmoxis was given 'conditional approval' by the European Medicine Agency in 2016. This means that there is more evidence to come about the medicine, which the company is required to provide.

Recently, the Company Molmed has decided not to renew the comercial authorization approved by EMA, taking into account the overall results of the interim analysis voluntarily carried out by the Company as part of the review of the product development plan, as well as the interactions with EMA in the latest months.

Take-home messages

- Value-based assessments are increasing their importance for policy makers to assess novel disruptive treatments with high social impact, such as advanced therapies medicinal products.
- There is a lack of consensus about which criteria should be included in these value-based asssessments and how to take into consideration the innovativeness of a novel treatment because of the multidimensional nature of the term "innovation".
- Several European Regulatory Agencies have already developed methods to assess the innovation potential of novel drugs and are implementing them into their mechanisms for decision making.
- Spain is working on the implementation of a new value-based assessment – Valtermed- specially designed to assess the therapeutic value of disruptive therapies (such as CART- cells).
- The Zalmoxis case points out that the innovation level could be a track to predict the success of commercialized ATMPs.