



Value Added Medicines

Rethink, Reinvent & Optimize Medicines,
Improving Patient Health & Access

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Written by :

Prof. Mondher Toumi, MD, PhD, MSc
*Professor in Public Health Department , Research Unit EA 3279
Aix-Marseille University, France*

CEO of Creativ-Ceutical

Cécile Rémuzat, PharmD, MSc
Senior Manager, Creativ-Ceutical



Table of Contents

1.	Introduction.....	3
2.	Pharmaceutical Environment.....	4
3.	Health Care System Inefficiencies related to Medicines.....	6
4.	The Pharmaceutical Business Model is Time Limited	12
5.	What are Value Added Medicines?	15
6.	Value Added Medicines Typology.....	19
7.	Value Added Medicines: What Value Could They Bring to the Society? ...	24
8.	Current Obstacles for Adoption of Value Added Medicines.....	27
9.	Recommendations to Capture the Full Value of Value Added Medicines.	31
10.	Conclusions.....	33
11.	References.....	34

1. Introduction

The current pool of existing molecules potentially re-positioned, re-formulated or combined with new technological platforms and services might offer therapeutic alternatives and opportunities for patients and health care systems. Even if this concept has been known for many years, no common terminology has been agreed for these products and their full potential value is not always recognised and rewarded, creating a disincentive for further development.

In this context, Medicines for Europe^a established one single terminology for these medicines known as value added medicines, defined as *“medicines based on known molecules that address health care needs and deliver relevant improvements for patients, health care professionals and/or payers”*.

This white paper aims to propose a harmonised typology for value added medicines, to describe their potential contribution to health care systems and to present current obstacles to their adoption and value recognition for pricing and reimbursement in Europe. It draws potential recommendations to overcome current barriers to fully capture potential value of value added medicines and incentivise their development for the benefit of the society.

This white paper has been developed by Creativ-Ceutical and funded by Medicines for Europe.

^a <http://www.medicinesforeurope.com/value-added-medicines/>

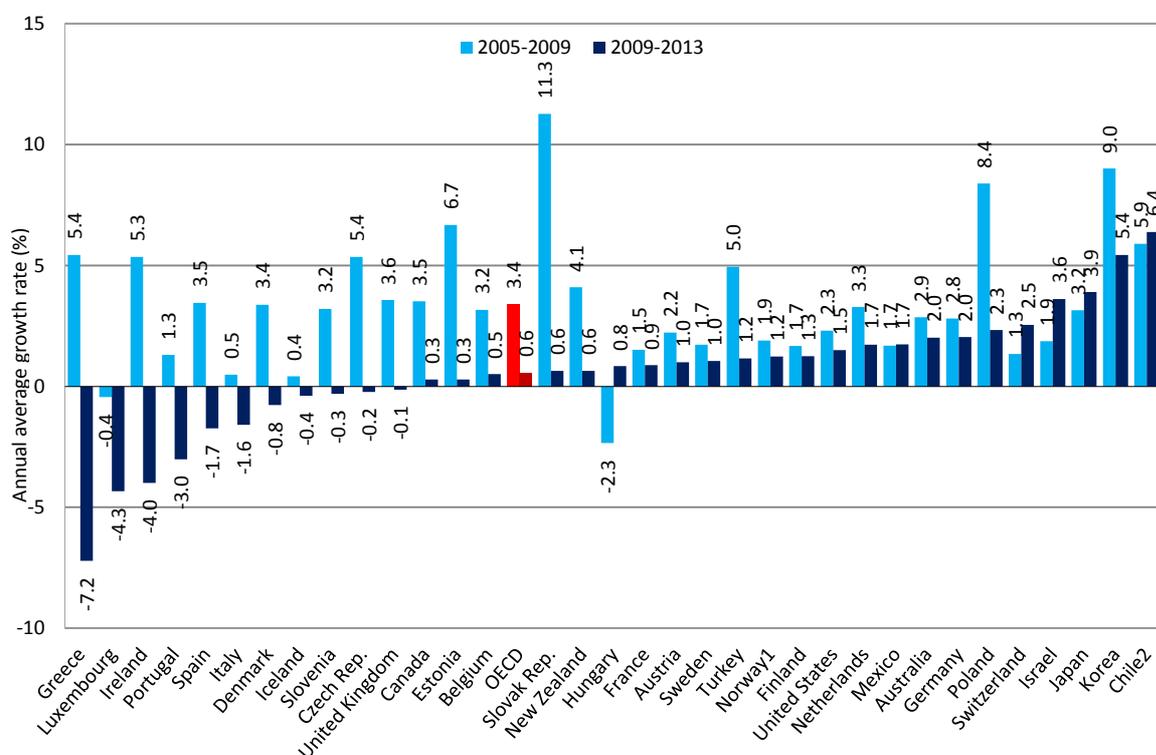
2. Pharmaceutical Environment

Some key factors are expected to increase pharmaceutical budget pressure in Europe:

- Ageing of population: by 2025, more than 20% of Europeans will be aged 65 or over¹.
- Growing prevalence of chronic diseases affecting more than 80% of people over 65 years old in Europe².
 - Some short-term fatal diseases such as cancers are becoming chronic diseases with launch of new effective therapeutic options, leading to long-term expensive patient management.
- Greater use and development of new, innovative and expensive products including therapies targeting new biological pathways such as immunotherapies, personalized medicines^{3,4} and advanced therapy medicinal products (ATMPs) encompassing gene therapies, somatic cell therapies and tissue engineered products⁵.

At the same time, since the economic crisis of 2008, a slowdown or even a fall in health spending growth has been seen in many Organisation for Economic Co-operation and Development (OECD) countries between 2009 and 2013⁶ (Figure 1). Health spending has been reported to rise again since 2012, while growth remains below pre-crisis rates, especially in Europe^{6,7}.

Figure 1. Annual average growth rate in per capita health expenditure, real terms, 2005 to 2013 (or nearest year) (OECD data)⁶



1. Mainland Norway GDP price index used as deflator. 2. Consumer Price Index used as deflator.

Source: OECD Health Statistics 2015, <http://dx.doi.org/10.1787/health-data-en>.

This economic context has led countries to implement various cost-containment measures to contain public medicines expenditure (e.g. mandatory price cuts, cost-savings through increased use of generic and biosimilar medicines, increasing requirements in health technology assessments, and limiting access to some therapies).

This imbalanced situation between increasing demand to deliver better health and budget constraints may challenge the sustainability of health care systems

3. Health Care System Inefficiencies related to Medicines

Health care system efficiency is a key challenge for policy makers when countries have to ensure universal access to and equity in health services to improve health status of the population while ensuring financial sustainability of their health care systems^{8,9}.

It has been suggested that a non-linear relationship exists between health care expenditure and health outcomes, i.e, similar level of health care expenditure does not necessarily translate to similar health outcomes, suggesting some room to improve efficiency in many countries^{8,9,10}.

Literature review^{11,12,13,14,15,16,17,18,19,20,21} and stakeholders' interviews^b reported various health care system inefficiencies related to medicines and associated to:

- Irrational use of medicines
- Non-availability of appropriate treatment options
- Shortage of mature products
- Geographical inequity in drug access
- Health technology assessment and drug coverage
- Drug pricing rules

Health care system inefficiencies related to irrational use of medicines

Irrational use of medicines is considered as wasteful and harmful for both the individual and the population by the World Health Organization²². This can contribute to increase the risk of adverse drug events and lead to morbidity, hospitalisation and mortality. For example, irrational use of antibiotics is a key threat leading to development of antimicrobial resistance (**Box 1**).

^b Interviews conducted with 20 European health care providers and payers in the scope of this project.

Box 1. Irrational use of antibiotics^{23,24,25}

Inappropriate antibiotic use is a large cause of the antibiotic resistance as underlined by the European Centre for Disease Prevention and Control (ECDC)²³ and the World Health Organization (WHO)²⁴, i.e.:

- Overuse of antibiotics, often unnecessarily prescribed for viral infections
- Inappropriate choice of antibiotics, e.g., broad-spectrum antibiotics prescribed when diagnosis not accurately made, or inadequate dosing
- Poor adherence to antibiotic treatments

Antibiotic resistance is a **major public health issue**; **in the European Union, it is estimated that about 25,000 patients die each year** from an infection due to antibiotic-resistant bacteria and multidrug-resistant bacteria infections result in **extra health care costs and productivity losses of at least €1.5 billion each year**²⁵.

Irrational use of medicines can take different forms such as:

- Polypharmacy when the use of multiple drugs is not medically necessary; polypharmacy is reported as a growing problem in elderly patients with a prevalence between 25 and 50% in the population >75 years^{26,27}.
- Lack of treatment coordination (duplication of prescriptions).
- Non-conformance with prescribing guidelines.
- Prescribing inefficiency with the need to develop an algorithm to support efficient prescription by physicians (**Box 2**).

Box 2. Prescribing inefficiency^{28,29,30}

- An observational retrospective study focused on utilisation of proton pump inhibitors and statins showed variation in the utilisation and expenditure of these drugs across Europe, demonstrating further opportunities to improve prescribing efficiency²⁸.
- A study found that there was generally lack of appreciation of the large difference in cost between inexpensive and expensive drugs from physicians, which could lead to prescription of costly medicines despite the availability of lower-cost alternatives²⁹.
- Literature suggests that multiple incentives might positively impact efficient prescriptions, but variety of incentives made difficult formal assessments of these policies³⁰.

- Poor treatment adherence is reported as a major barrier to achieve the potential benefit of available medicines; an overview of adherence to long-term therapies conducted by the World Health Organization in 2003 found around 50% adherence as the average rate in developed

countries³¹. Poor adherence has been estimated to cost about €125 billion annually to European governments and contributing to the premature deaths of nearly 200,000 Europeans annually³².

- Off-label use of medicines in indications with little or no evidence supporting use, and when alternative approved effective therapies do not exist, is frequent and particularly high in some specific therapeutic areas, such as oncology, and in certain patient groups, especially in paediatrics (**Box 3**).

Box 3. Off-label use of medicines^{33,34,35}

- In a position paper of the European Society for Medical Oncology (ESMO), **off-label use of oncology medicines was estimated to reach approximately 50%** (and even more)³³.
- A one-day cross-sectional study conducted on **off-label prescriptions of psychotropic drugs among hospitalized patients in France found about 40% off-label use**, with the highest rates found for anticonvulsants (97%)³⁴.
- Important rates of **off-label use have been also shown in paediatric population and estimated between 33.2% and 46.5% in inpatients and between 3.3% and 13.5% in outpatients** despite European paediatric regulation (2007)³⁵.

- Underuse of generic and biosimilar medicines; generic and biosimilar medicines' uptake varies widely between European countries, which might be explained by insufficient incentives' policies toward these medicines, as well as insufficient information campaigns on generic and biosimilar medicine profiles for physicians, pharmacists and patients (**Box 4**).

Box 4. Various generic and biosimilar medicines' uptake across Europe^{36,37}

- For example, the total volume share of generic medicines in off-patent market is of 7% in Greece and 81% in Germany³⁶, and the volume share of G-CSF biosimilar in off-patent market is of 2% in Belgium, 71% in Germany and 100% in Hungary)³⁷.

- Drug wastage (e.g. vial wastage with inappropriate volume size or tablet wastage with inappropriate pack size).

Health care system inefficiencies related to non-availability of appropriate treatment options

Some therapeutic areas are facing a decline in development of innovative approaches. In the mental health field, a decline of innovation has been reported with decreasing investments in research and development in new treatments for depression, bipolar disorder, schizophrenia, and other psychiatric disorders^{38,39}.

In the field of infectious disease, there is a high demand for new generations of antibiotics in the current context of antibiotic resistance. Only five new classes of antibiotics have been launched since 2000 and high unmet needs remain for new molecules targeting especially gram-negative bacteria^{Error! Bookmark not defined., 40}.

On top of this, current therapies are not well tailored to meet the particular needs of different patient sub-groups, such as vulnerable patients (e.g. pregnant woman, elderly patients, and paediatric population) or patients requiring frequent dosing adjustments, which may lead to inadequate clinical practice to adjust available therapies to patient medical needs including off-label use.

Health care system inefficiencies related to shortage of mature products

Lack of financial attractiveness and ability to competitively supply the market, for example through single lot tenders, or lack of cost coverage to maintain the marketing authorisation and supplying of some older essential medicines may result in stock-outs or market withdrawals by manufacturers. For example, this was the potential reason for withdrawal of extencillin from the French market in 2014, the sole antibiotic for the treatment of syphilis available in the territory and now requiring drug importation from Italy^{41,42}.

Health care system inefficiencies related to geographical inequity in drug access

Disparities in drug access are seen between European countries, i.e., there are obvious discrepancies between countries' access that may not only be driven by affordability although it is a critical driver of poor access. For example, a study assessing access to oncology care in four European countries (France, Germany, Sweden and Poland), based on a review of colorectal, lung and prostate cancer care, found inequalities in access to cancer drugs. Highest and quickest uptakes were seen in France; Germany and Sweden showed similar uptakes for established drugs but Sweden had lower uptakes for new cancer drugs; Poland was far behind these countries with no uptake of some newer cancer drugs⁴³.

Moreover, these disparities in drug access are also found within countries, especially when pharmaceutical budgets are managed at regional levels. For example, in Italy a survey conducted by the Italian Society of Medical Oncology (AIOM) in 2009 showed disparities in oncology drug access between Italian region in terms of inclusion in the regional pharmaceutical formularies and time to patient access⁴⁴.

Health care system inefficiencies related to health technology assessments (HTA) and drug coverage

HTA performed in many European countries has been recognised as an important policy tool to only select the technologies having the best value in relation to their cost for public coverage.

However, some room for improvement remains in terms of HTA methodology:

- Some European countries tend to consider pharmaceutical assessments and reimbursement decisions in a silo, preventing capture of benefits such as transfer of cost-savings outside of the pharmaceutical expenditure budget. For example in Belgium, the reimbursement decision might not consider any savings that may result from a new drug that would decrease the number of hospitalisations.

Within health care budgets, previous work analysing drug reimbursement policies in Europe reported a “drug budget silo” mentality likely to lead to inefficiency when pharmaceutical expenditure is considered separately to overall health care resource budget⁴⁵. On top of this separation between pharmaceutical and other health care resources, a trend has been reported to separate health care budgets from other related budgets such as social care⁴⁶.

- The impacts of treatments beyond health gains are currently poorly assessed. A qualitative study⁴⁶ assessing whether wealth effects of health interventions^c, including productivity gains and savings in other sectors, were considered in resource allocations by HTA agencies and government departments, found that, except in Sweden, the link between health and wealth generally did not influence decision making in terms of budget setting or drug reimbursement decisions. A combination of factors was cited as key hurdles of inclusion of wealth effect into decision making such as system fragmentation, methodological and practical issues, and the economic recession leading government to adopt short-term cost-containment measures.
- HTA of drugs and devices or procedures are performed separately in some European countries, which prevents HTA from fully capturing the benefit of using the drug and device or procedure combined and can lead to patient access delays or even inconsistent decisions when processes are not coordinated. For example, pharmaceutical drugs and the associated companion diagnostics are evaluated separately in France, Germany, Italy and Spain, while in England, companion diagnostic evaluation is integrated into the National Institute for Health and Care Excellence (NICE) technology appraisal of the associated medicine⁴⁷.
- Some European countries implemented different HTA and drug coverage procedures between drug classes which might lead to inefficient allocation of resources as illustrated below.
 - Orphan drugs or end of life drugs can enjoy privileged assessments. For example, in 2009, the NICE introduced end of life criteria to improve access to end of life treatments which could potentially be recommended at a higher cost-effectiveness threshold than “standard” medicines. In 2014, the Scottish Medicines Consortium (SMC) introduced a new process for assessing medicines treating end of life and very rare conditions (orphan and ultra-orphan medicines) setting up a Patient and Clinician Engagement (PACE) group to give patient groups and clinicians a stronger voice in SMC decision making.

^c Semi-structured interviews with decision makers and academic experts conducted in eight countries Australia, France, Germany, Italy, Poland, South Korea, Sweden, and the United Kingdom

- Conditional reimbursement can be restricted to specific categories of medicines; for example for expensive hospital-only medicines in the Netherlands⁴⁸.
- Re-assessment of drug reimbursement can differ between categories of medicines. For example, in France, the actual benefit (AB or SMR- *Service Médical Rendu*) of drugs included on the list of medicines refundable by National Health Insurance should be re-assessed every 5 years, while this re-assessment is not systematically required for medicines included on the list of medicines approved for hospital use. In the Netherlands, drugs reimbursed in out-patient settings are not re-assessed unless there are serious safety issue; even if more effective and/or cost-effective new drugs are approved, the old drugs will not be delisted.
- In some European countries, there is no HTA for hospital-only medicines. For example, in Germany, hospital-only medicines are exempted from early benefit assessment procedure. In Sweden, hospital medicines were usually not assessed by the Swedish Dental and Pharmaceutical Benefits Agency (TLV); however between 2011 and 2014, the TLV has been commissioned by the Swedish Government to run a pilot scheme to conduct health economic assessments of selected hospital drugs. TLV assessment of selected hospital medicines is still currently in process.

Health care system inefficiencies related to drug pricing rules

Many medicines are currently approved for multiple indications with potential different value across indications. European countries generally apply a single price across all indications, which may either restrict access to the most cost-effective indications if the price is based on the indications with the highest value, or disincentive companies from launching the drug in indications with the lowest value, thus depriving society of the treatment needed to address an unmet need.

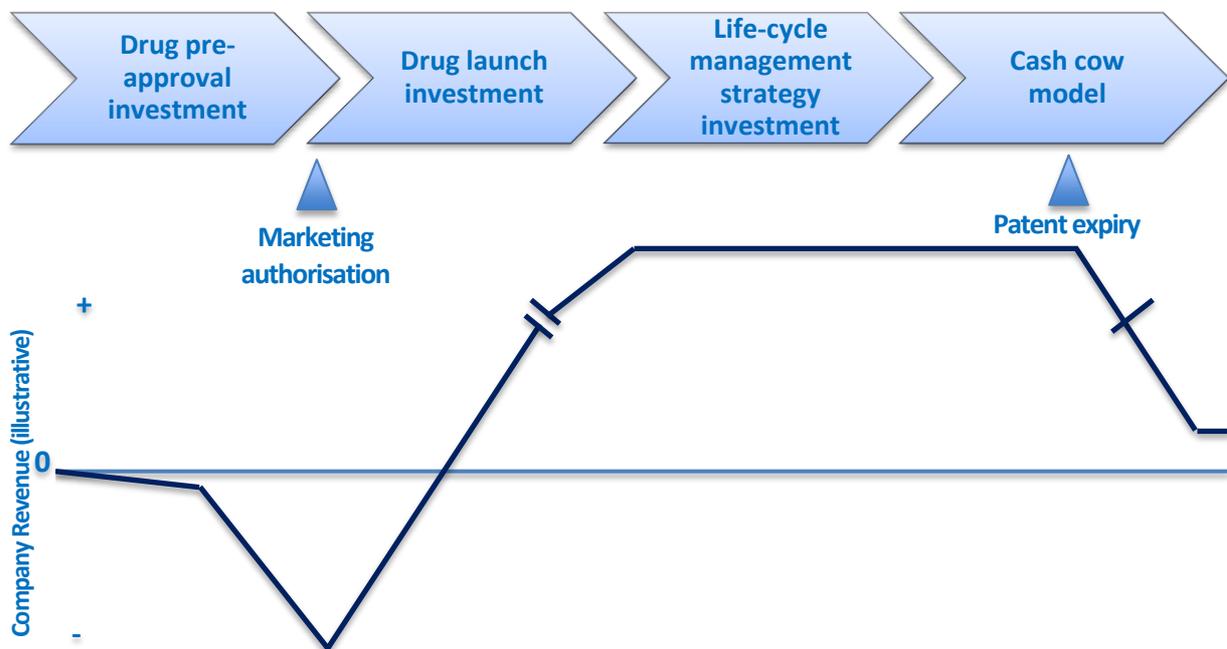
In some countries, even if there is a uniform price irrespective of clinical indications, indication-specific pricing has been achieved through different mechanisms. For example in France, HTA is conducted per indication and the price is based (among other criteria) on a weighted average of the value of all the indications. In Italy, different payback schemes for the same drug are agreed per indication between the Italian Medicines Agency (AIFA) and the drug manufacturer at time of reimbursement decisions.

- *All these health care system inefficiencies deserve attention and should be addressed whenever possible*
- *Value added medicines might contribute to address some of these inefficiencies related to irrational use of medicines, non-availability of appropriate treatment options, shortage of mature products and geographical inequity in drug access*
- *Inefficiencies related to HTA, drug coverage and drug pricing rules might be an hurdle for value recognition of value added medicines*

4. The Pharmaceutical Business Model is Time Limited

The branded originator pharmaceutical business model assumes an investment to develop and launch a medicine, and potentially further investment to prolong its life cycle. When the peak sale is reached, investment is halted and the product generates continuous revenue until patent expiry (high revenue, low cost), at which point a generic version enters the market at a competitive price. Experience shows that branded originator medicines continue to generate small but persistent revenue with no investment after the generic medicines entry (Figure 2).

Figure 2. Pharmaceutical business model



This model implies that product investment is suspended as products reach patent expiry, when important knowledge has been gathered on the drug through the clinical development program and post-launch studies in terms of efficacy/effectiveness, safety and tolerability in the whole population and in potential segmented population for better benefit-risk ratio. At this time, any product room for optimisation is well mastered and additional efficacy data in different populations and/or new indications might have been identified as potential added product value.

As such, the current pharmaceutical business model prevents the capture of any potential additional value of medicines once drugs are near or in the post-exclusivity/patent protection phase due to the lack of reward of investments, leading to substantial loss of opportunities for the society and patients.

“Repurposing of established medicines” is currently in discussion at the European Commission through the Commission Expert Group on Safe and Timely Access to Medicines for Patients (“STAMP”) recognizing the importance to fully investigate different opportunities that a molecule could bring for patients, with faster development times, at reduced costs and risk for pharmaceutical companies⁴⁹. The background note prepared by the UK Medicines and Healthcare products Regulatory Agency (MHRA) to provide a basis for STAMP's consideration of the issue cites current European regulatory incentives for drug repurposing which include⁴⁹:

- Non-cumulative period of one year of data exclusivity granted for a new therapeutic indication for a well-established substance provided that significant pre-clinical or clinical studies were carried out in relation to the new indication (Paragraph 5 of Article 10 of Directive 2001/83/EC).
- Period of data and market protection of 8+2 years covering indication(s) and appropriate formulation(s) for already authorised products developed for paediatric populations (Paediatric-use marketing authorisations (PUMA), Article 30 of Regulation (EC) No 1901/2006).
- Market exclusivity of 10 years for repurposed medicines granted an orphan drug designation.

In addition, as authorities are conscious of the dis-incentive for manufacturers to repurpose mature products and to invest in this field, they have launched a number of initiatives to enhance such practice to secure opportunities to identify and capture their whole benefit. For example, new partnerships have been established between public funders, the pharmaceutical industries and academic investigators in drug repurposing (**Box 5**). These programs aim to identify potential value in products that were either shelved or already on the market for more or less long period and that may or not be covered by a patent.

Box 5. Examples of partnerships have been established between public funders, the pharmaceutical industries and academic investigators in the field of drug repurposing^{50,51}

- The Medical Research Council in the United Kingdom did a partnership with AstraZeneca in 2011 to give access to clinical and preclinical compounds to academic researchers for potential repurposing⁵⁰.
- In France, the National Cancer Institute (INCa), in agreement with the French National Agency for Medicines and Health Products Safety (ANSM), launched in 2013 the AcSé program which is a program for secure access to innovative targeted therapies that offers cancer patients, for whom validated therapies have failed, access to targeted therapies, based on a molecular abnormality of their tumour; the AcSé crizotinib project was the first clinical trial of the AcSé program⁵¹.

Finally, some national initiatives regulate off-label use of marketed medicines use such as Temporary Recommendation for Use (RTUs) in France⁵².

These recent initiatives demonstrate the importance of drug repurposing from a public health perspective and the willingness of regulatory stakeholders and public health authorities to encourage their development.

The current pharmaceutical business model is time limited and under-resourced/dis-incentivised to invest in drug repurposing; while regulatory incentives and initiatives have been put in place, demonstrating the public health need for drug repurposing, current obstacles to their adoption and value recognition from HTA and pricing perspective in Europe continue to exist

5. What are Value Added Medicines?

Various nomenclatures have been used to describe the concept of value added medicines in the literature with different definitions; some are broad while others are more restricted; some are based on outcomes, while others are based on processes or a mix of both (Table 1).

Some illustrative examples of definitions for this category of medicines are provided in Table 2.

This heterogeneous concept is driven by value enhancement of existing medicine through a broad range of processes. Contrary to products like generic medicines, biosimilar medicines and hybrids, there is no regulatory definition. The recent STAMP initiative described above raises this issue and will consider the opportunity to provide a definition.

Definition adopted by Medicines for Europe is the following: **“Value added medicines are medicines based on known molecules that address health care needs and deliver relevant improvements for patients, health care professionals and/or payers.”**

Box 6 provides more details on what is considered as relevant improvements, their impacts and the drug repurposing model of value added medicines.

Box 6. Value added medicines concept (Medicine for Europe)

- **Value added medicines will deliver relevant improvements that include:**
 - Better efficacy, safety and/or tolerability profile
 - Better way of administration and/or ease of use
 - New therapeutic uses (indication/population)
- **Those improvements contribute to:**
 - Better adherence, health outcomes or quality of life
 - Improved safety and efficiency of health care professional resources
 - Increased treatment options and preventing therapeutic escalation
 - Improved cost-effectiveness and ultimately access to health care
- **The added value of these medicines may be achieved through:**
 - Drug repositioning
 - Drug reformulation
 - Drug combination (drug/drug or drug/device or drug/service)

In this absence of a common terminology for value added medicines, it is important to develop a specific typology to allow assessment of the potential value of these medicines and to understand the origin of their value

Table 1. Various nomenclatures and definitions related to value added medicines

Nomenclature	Definition (s)
Super generics	<p>“Improved version of an original drug which has lost product patent protection”⁵³ <i>Also referred to as added value generics, generic plus, innovative generics</i></p> <ul style="list-style-type: none"> ➤ It is reported a shift in this terminology for “non-generic identity” (hybrid terminology most commonly used)⁵⁴
Premium generics	<p>Nomenclature defined by Daiichi Sankyo Espha (<i>Daiichi Sankyo generics subsidiary</i>) with launch of “high value-added generic drugs” including “innovations in formulation and labelling to make drugs easier to ingest and harder for patients to mistakenly or incorrectly take”⁵⁵</p>
Specialty generics	<p>Generic drugs which “benefit from more sophisticated technologies (such as controlled or immediate release) or from special pharmaceutical ingredients (self-molecules or biological active substances)”⁵⁶</p>
Re-innovative generics	<p>“Products built upon a re-innovation framework between incremental and radical innovation. They improve the next generation with revised and refined features”⁵³</p>
New therapeutic entities (NTEs)	<p>Nomenclature defined by TEVA as “new specialty medicines based on known and approved chemical molecules. These molecules are reformulated, repurposed or re-engineered to be delivered in a new way to address specific, unmet patient needs”⁵⁷</p>
Enhanced therapeutics	<p>“Drug products derived from existing generic drugs that provide additional benefits to the patients and the health care system”⁵⁸</p>
Improved therapeutic entities	<p>“Products that offer a therapeutic advantage or differ from the me-too generic product in the sense of a patient centric drug delivery or product design or simply a more efficient product design and manufacturing process”⁵⁹</p>
Incremental innovation	<p>“Closely related molecules with different attributes that may offer significant value in treating particular disease variants or patient segments”⁶⁰ “Process of exploring and improving radical products” “Improvements in therapeutic quality, safety, and efficacy over existing medicines”⁶¹ “Creating minor improvements or simple adjustments in a product’s current state”⁵³ “Either new approved drugs created from an already existing molecule or approved modifications to existing drugs.” “There are 5 types of incremental innovation”⁶²:</p> <ul style="list-style-type: none"> ➤ New dosage form which affects the dosage form and the does amount ➤ New formulation which affects combination of chemicals in the drug ➤ New combination – the creation of combination drugs from existing molecules ➤ New indication – using an existing drug to treat a different condition ➤ New active ingredient - drugs that contain the same active moiety but include a different enantiomer, racemate, salt, ester, complex, chelate, or clathrate.” <p><i>Also referred to as adaptive innovation⁶¹ or marginal innovation^{63,64}</i></p>
Re-innovation	<p>“Process of innovation and product development that occurs after a new product is launched, building upon early success but improving the next generation with revised and refined features”⁵³</p>
Hybrid products	<p>“In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where</p>

	the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided (as per Art. 10(3) of Directive 2001/83/EC) ^{65,66}
Bio-superior products	<p>“Intended to have attributes that are better than the first-generation product (...)</p> <p>A bio-superior utilises cutting-edge technologies such as protein engineering, and novel drug formulation and delivery approaches to enable its superiority over a first-generation product, possibly improving its efficacy or safety profile or improving administration route or reducing dosing frequency”⁶⁷</p>
'Third Sector' drugs	<p>“Compared to a NCE (New Chemical Entity), a Third Sector brand uses a proven molecule, lowering time and costs in development and, depending on the innovation, reducing regulatory risk.</p> <p>Compared to a generic, a Third Sector brand has a certain level of differentiation by addressing a specific payer, health care provider or patient unmet need and can aim for a higher price and/or market share.</p> <p>Some Third Sector brands may also have exclusivity and patent protection of some element of the offering, for example, a unique delivery system which generics cannot copy.”⁶⁸</p>
Drug repurposing	“Includes all the re-development strategies based on the same chemical structure of the therapeutically active ingredient as in the original product” ⁶⁹
Drug reformulation	“Reformulation is, by the simple definition of the term, making a particular change in the formulation of the original drug. This can be achieved by exploiting advances in formulation technology to change the release of the active substance, pharmaceutical forms, and/or route of administration but it can also concern some excipients with no impact on the pharmacokinetic parameters. No change should be incurred in the structure of the active pharmaceutical ingredient except when it is a chiral switch. (...). Cases where the development of a new product does not include a change in the original formulation (i.e., change of dose, package size, etc.) should also be excluded” ⁶⁹
Drug repositioning	“Process of finding a new indication for a drug or compound. (...) New indication is distinct from the already approved/intended indication of the original product, where ‘distinct’ implies an anatomical and/or therapeutically distinct indication referring to the 10 th version of the International Classification of Diseases (ICD-10). The situation where the new indication involves a different pharmacological target (off-target repositioning) is the only exception where a new use in a similar indication will be covered by the actual definition” ⁶⁹
Drug re-profiling/ Drug reusing/ Drug rediscovery	“The usage of known drugs for new diseases. The main objective of drug re-profiling is to discover methods for using approved drugs or discarded clinical candidates in the treatment of new diseases” ⁷⁰

Table 2. Illustrative examples of value added medicines

Case	Description
Case 1	Fixed-dose combination of 2 products already available on the market and used as free dose combination in arterial hypertension to reduce pill burden and avoid intake errors in a highly medicated patient population
Case 2	Self-injected subcutaneous formulation of a product already available on the market as intravenous formulation administered only at hospital under medical monitoring in a severe inflammatory disease
Case 3	A new formulation of a well-known chemotherapy product helping to reduce serious side effects of the original product used in many chemotherapy regimens
Case 4	Re-positioning of a well-known product in a rare pediatric indication as an alternative to reference treatments not specifically approved in this indication
Case 5	New inhaled device to administer genericised products in COPD indication with evidence of reducing inhaler errors versus current device used with these active substances
Case 6	Extended-release formulation of a product already available on the market reducing administration regimen from once-weekly injection to 3-monthly injection in a neurocognitive disease indication
Case 7	Therapeutic drug monitoring device developed in association with a known cancer therapy exhibiting a narrow therapeutic window to potentialise drug efficacy while minimizing toxicity
Case 8	Injectable drug to be kept refrigerated that will be provided to the patients with cool bags and sharp containers (not provided with the reference product) aiming to facilitate daily usage by the patients

6. Value Added Medicines Typology

Value added medicine is a broad concept that could come in several forms; therefore it is useful to standardise the concept through a relevant typology. Three different dimensions were taken into account for the development of a typology for value added medicines:

- Categories of value added medicines with regards to the recognition of benefit
- Disease environment
- Patient segmentation to identify populations with the highest opportunities of benefit

Two different algorithms were built allowing for assessment of the value of value added medicines.

- One algorithm related to the value added medicines typology itself including 6 dimensions^d (Figure 3):

- **Repurposing model (which might be combined)**

- **Drug repositioning model** which aims to extend drug indication and can be classified as minor or major^e

e.g. Revatio® (sildenafil); sildenafil has been originally developed as an antihypertensive drug, firstly repositioned in erectile dysfunction and lastly repositioned in pulmonary arterial hypertension with an orphan drug designation status.

- **Drug reformulation model** which aims to make a particular change in the formulation of the original medicine including and can be classified as minor or major^e, including:

- Changes in pharmaceutical formulation (including excipients)

e.g. Pheburane® (sodium phenylbutyrate) is a repurposed formulation of Ammonaps® developed as a coated granule formulation reduces/removes the bitter taste associated with the active substance (different excipient used to mask the unpleasant taste of the active substance).

- Changes in strengths

e.g. Siklos® (hydroxycarbamide): specific pediatric formulation developed (100 mg tablets) in addition to the adult formulation (1000 mg); primary repurposing was in new indication : Sickle cell syndrome for which the product was granted with an orphan drug designation status.

^d This algorithm is based on a previous work conducted by Susana Murteira and Creativ-Ceutical as part of thesis research (Murteira S, Ghezaiel Z, Karray S, Lamure M. Drug reformulations and repositioning in pharmaceutical industry and its impact on market access: reassessment of nomenclature. *Journal of Market Access & Health Policy* 2013, 1: 21131.)

^e In terms of risk for the company to develop such new indication/reformulation (return on investment)

- Changes in routes of administration (e.g. oral route versus intravenous route)

e.g. Herceptin® (trastuzumab) was originally developed as intravenous formulation and then as subcutaneous formulation.

- Changes in the active substance such as enantiomers, salts, esters, crystals, and prodrugs

e.g. Proton pump inhibitors: Nexium® (esomeprazole) which is (S)-enantiomer of Mopral® (omeprazole).

- Changes in pharmacokinetic parameters in terms of release of active substance

e.g. Risperdal Consta® (risperidone) was the first long-acting injection formulation of an atypical antipsychotic to reach the market.

- Changes in the drug delivery system (e.g. new medical device or new drug delivery technology)

e.g. DuoResp Spiromax® (budesonide/formoterol); Spiromax inhaler was a new inhaler designed to improve ease of use and consistent dose delivery and confirming dose intake to patients through a taste of lactose and a dose indicator.

Another typical example of new drug delivery technology was the first liposomal formulation of doxorubicin, Doxil® approved in 1995, and reducing toxic effects of doxorubicin.

- Innovation in labelling/packaging (e.g. specific packaging with temperature sensors)

- **Drug combination** which aims to combined 2 or more on-patent and/or off-patent products

e.g. Lots of examples of drug combinations are available, especially antihypertensive medicines (e.g. Twynsta® (amlodipine/telmisartan), Sevikar® (amlodipine/olmesartan)) and anti-HIV medicines (e.g. Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), Triumeq® (dolutegravir/abacavir/lamivudine)).

▪ **Regulatory status**

Repurposed products may have been authorised or not for their originally developed targets and might be on-patent or off-patent at time of launch.

Original products may have never been marketed, but still may be repurposed in different circumstances:

- Cases where original product is marketed in one country (e.g. Germany) and repurposed in another country where the original product is not authorised (e.g. Europe or United States).
- Cases of original products initially approved but withdrawn from the market (e.g. thalidomide).
- Cases of discontinuation in the development of original products (e.g. sildenafil developed in angina and repositioned in erectile dysfunction).

▪ Targeted indication

- Repurposed products may act via the same mechanism of action as the original product, i.e., same target (on target), or may act via a new mechanism of action, i.e., new target (off target).
- The targeted indication might be expected if this is a known clinical target for the repurposed product (e.g. it is well known that antiepileptic drugs might be effective in bipolar disorders and pain), or unexpected if this is an unknown clinical target for the repurposed product (e.g. antiepileptic drugs which would be effective in Parkinson disease).

▪ Combined device/service

Innovative or similar device/service might be combined to an original product.

Medical device examples: new inhaler, nasal spray device or pre-filled syringe

Service examples: cool bags for refrigerated products, pill reminder systems, smartphone adherence applications to support patients in organizing and taking their medications

▪ Benefit

Patient benefits have been classified in 7 categories as high, moderate or low:

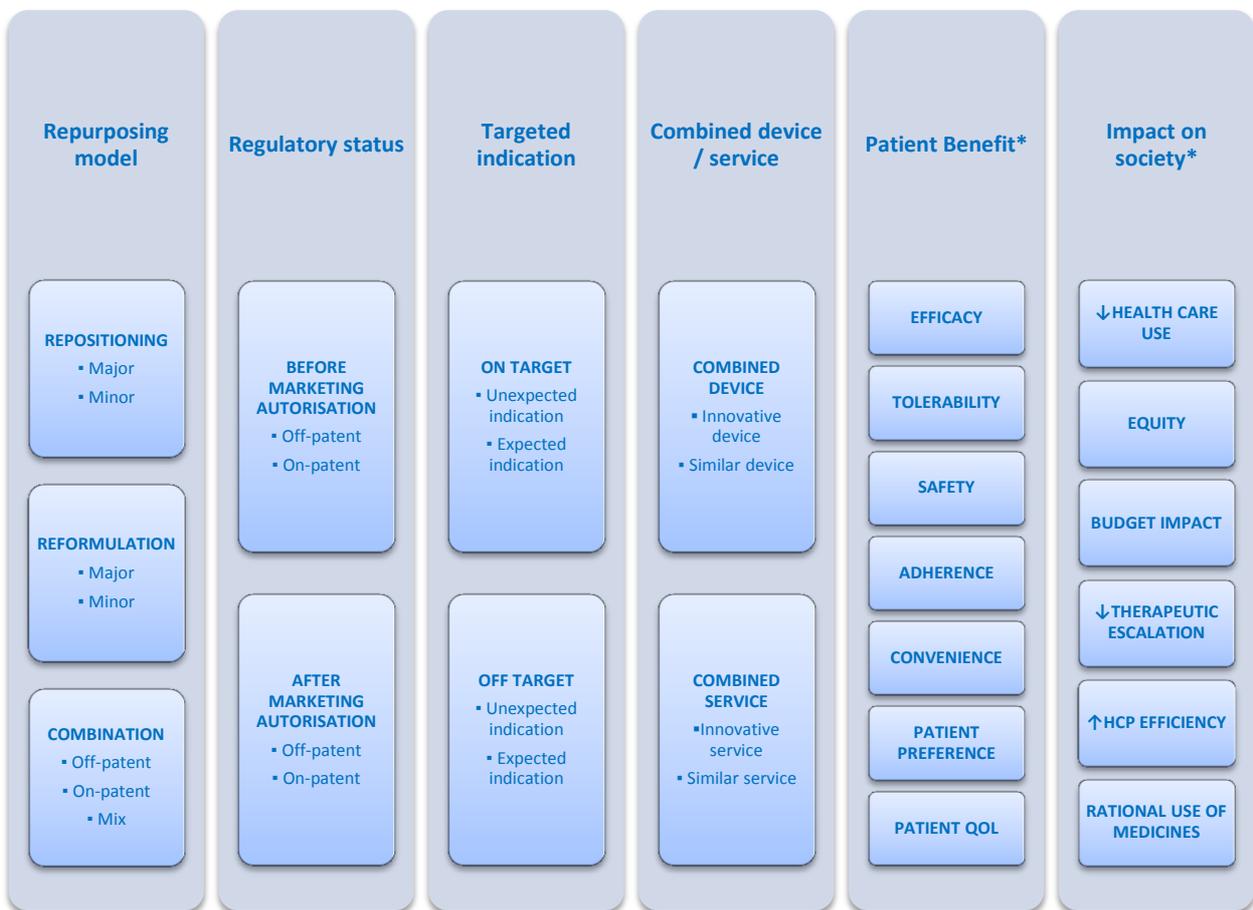
- Efficacy
- Tolerability
- Safety
- Adherence
- Convenience
- Patient preference
- Patient quality of life

▪ **Impact on society**

Impact on society has been classified in 7 categories as high, moderate or low:

- Reduction in health care use
- Equity (e.g. expanded access to a medicine to a wider part of the population)
- Budget impact
- Reduction in the therapeutic escalation (e.g. new intermediate effective dosage, or new alternative therapy reducing switch to last resort therapies)
- Improvement of health care provider efficiency
- Rational use of medicines

Figure 3. Value added medicines Typology



ROA – route of administration

QOL – quality of life

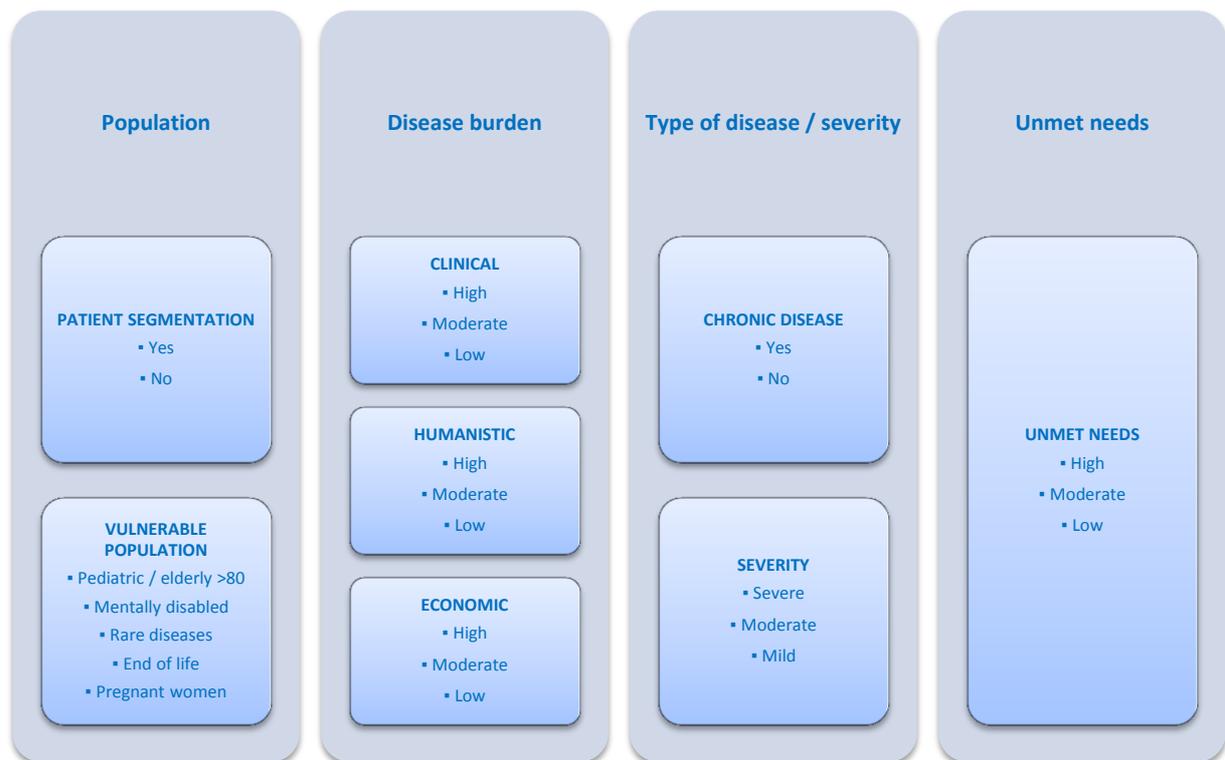
HCP-health care professionals

* Each benefit and impact on society category is rated as high or medium or low

- One algorithm related to disease environment as the general context of the disease and the target population cannot be disconnected from the typology when assessing the whole value of the product. This algorithm includes 4 dimensions (**Figure 4**):

- **Population (patient subgroups and vulnerable populations)**
- **Disease burden (clinical/humanistic/economic)**
- **Type of disease (acute or chronic)/severity**
- **Unmet needs**

Figure 4. Disease environment



7. Value Added Medicines: What Value Could They Bring to the Society?

Value added medicines provide an important value to society by addressing health care inefficiencies, improving efficient use of available resources and favourably impacting health care budgets.

Value added medicines may represent an opportunity to address health care system inefficiencies related to:

- Irrational use of medicines
 - Through new drug formulations or drug combinations, value added medicines could contribute to improve adherence issues of already available therapies (**Box 7**).

Box 7. Value added medicines and adherence: key example of antimicrobials²⁴

The World Health Organization (WHO) recognises the importance of value added medicines to improve patient's adherence and to contribute to fight against resistance to antimicrobials: *"Innovations in drug formulation can improve patients' adherence to treatment or enhance the effectiveness of antimicrobials. For example, in patients with both tuberculosis and HIV infection, the use of fixed-dose formulations of multiple antimicrobial components facilitates compliance with the full course of treatment. Innovations to encourage patients' compliance with treatment and optimizing treatment regimens can help to limit the risk of resistance."*²⁴

- Through drug repositioning and drug reformulations for specific patient groups (e.g. paediatric population), value added medicines could contribute to limit off-label use of medicines.
- Through new and appropriate drug packaging and vial conditioning, value added medicines could contribute to limit drug wastage.
- Inappropriate treatment options
 - Value added medicines represent an opportunity to tailor and expand access of well-known therapies to particular patient subgroups' needs such as vulnerable patients or patients requiring frequent dosing adjustments.
 - Value added medicines could contribute to the faster development of new therapeutic options in areas of unmet medical needs benefiting from the knowledge gained from the previous drug development and life cycle. It may also happen through the evolution of scientific knowledge, for example when a new mode of action is discovered for an existing product or a new effect is discovered for a well-established mode of action.
- Shortage of mature products

Value added medicines provide opportunity to create new market attractiveness of mature products which avoid product shortage in some countries.

- Geographical inequity in drug access

Disparities in drug access between and within countries are often linked to the prices of medicines and the lack of infrastructures for the delivery of health care. Value added medicines might contribute to address geographical inequities:

- Either by the opportunity they represent to create an intermediate step before switching to costly products (see below), thus improving the affordability and limiting geographical access inequity,
- Or by the opportunity they represent to provide new drug formulations for hospital-only medicines which could be used in out-patient settings, thus improving access in remote rural areas for example.

Value added medicines may represent an opportunity to better address health care provision and organisation and could contribute to reduction and re-allocation in health care use.

For example, chemotherapy reconstitution process is not related to health care system inefficiency; however a ready to use chemotherapy which might improve drug handling and save time for health care providers would represent an important benefit in terms of use of available health care resources.

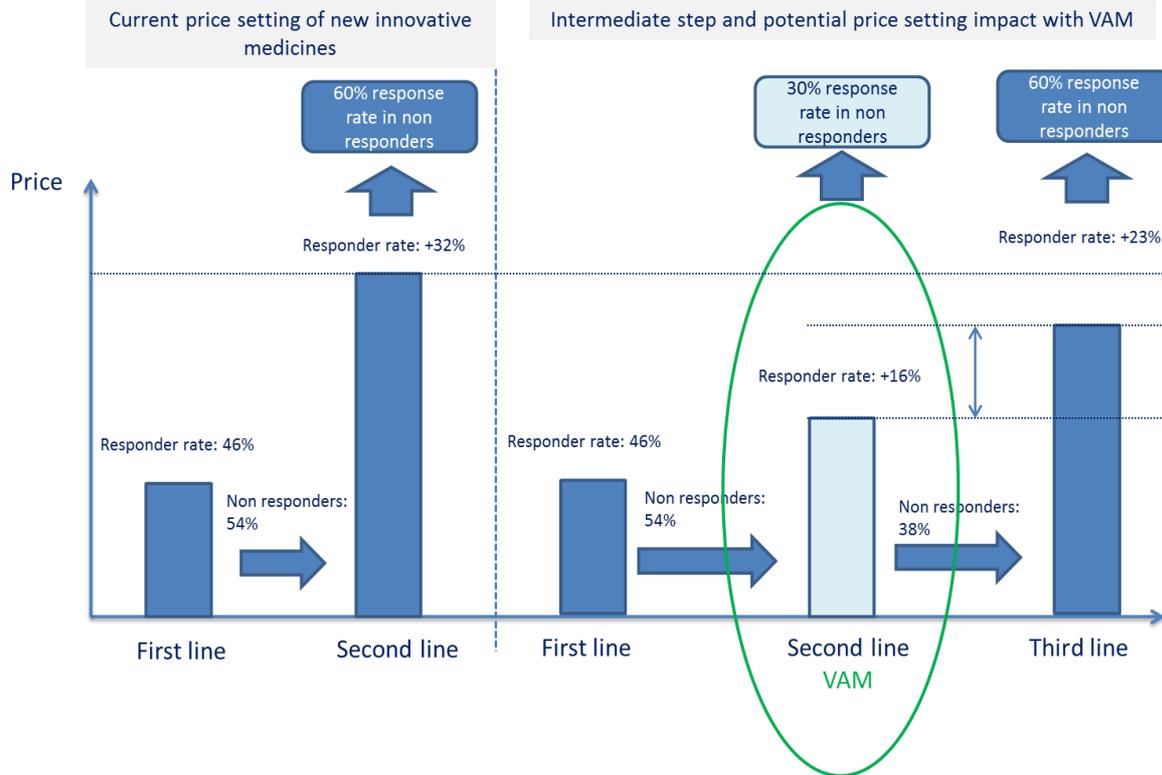
Value added medicines could contribute to improve patient convenience of use and satisfaction with health care through improvement of their usual therapies.

This might further participate to enhance patient compliance/adherence, especially for patients treated for chronic diseases.

In the current cost-constraint environment, value added medicines may represent an opportunity to create an intermediate step before switching to costly products and reduce budget impact.

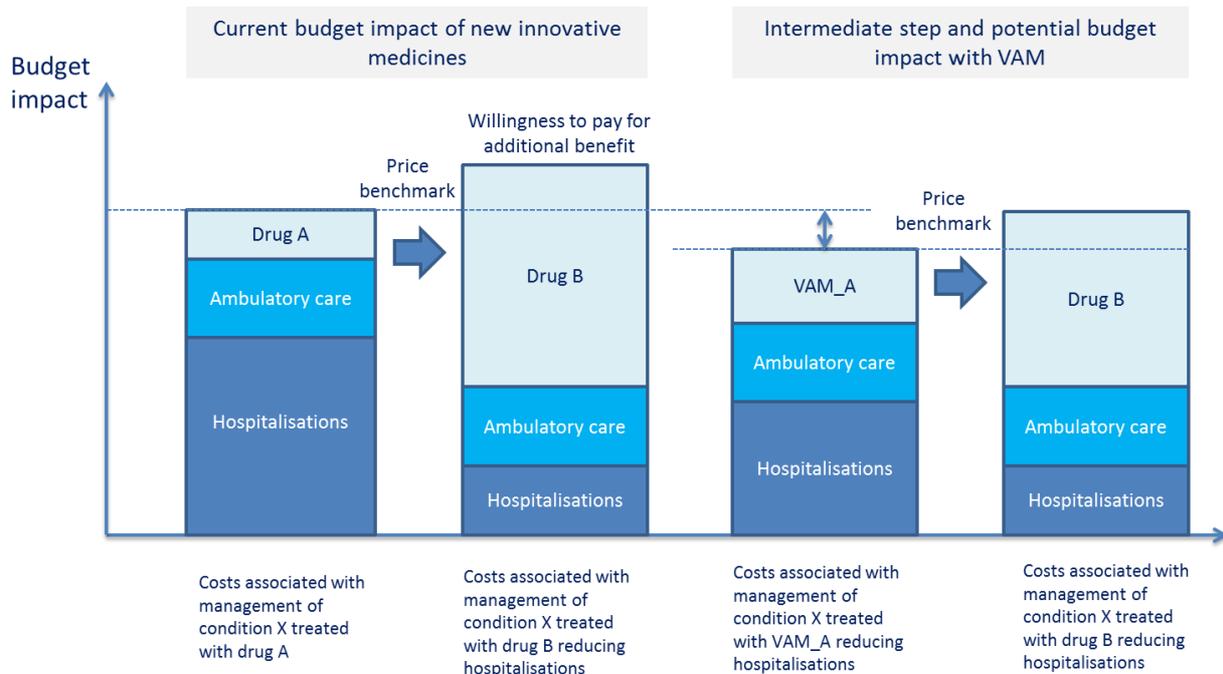
Figure 5 and **Figure 6** illustrate the potential impact on price setting and budget impact, respectively, that value added medicines may have if expensive innovative medicine (with improved efficacy profile versus value added medicines) is expected to be launched in the same indication. Value added medicines might be pushed as a second-line option versus the originator, while most innovative therapy might be niched as third-line option, which could have positive budget impact.

Figure 5. Illustrative representation of intermediate step created by value added medicines and potential price



VAM: Value added medicines

Figure 6. Illustrative representation of intermediate step created by value added medicines and potential budget impact



VAM: Value added medicines

8. Current Obstacles for Adoption of Value Added Medicines

Various obstacles have been identified that prevent optimal utilisation of value added medicines and achievement of related societal benefits. Some of the health care inefficiencies related to HTA, drug coverage and drug pricing rules identified in section 3 may constitute further hurdles for adoption of value added medicines.

HTA obstacles

- Existing stigma:
 - Value added medicines might be alternatively perceived by HTA bodies like generic medicines unworthy of independent HTA, or as an anti-generic medicines strategy preventing capture of savings from drug genericisation.
 - HTA bodies might consider value added medicines as “non-risky strategy” which might negatively impact assessment of these products.
- Value added medicines benefits may not be fully captured by HTA bodies due to:
 - Budget silo; e.g., cost-savings achieved across a hospital health care organisation.
 - Separate assessment of drugs and devices/procedures in some countries.
- In the current cost-constrained environment, there is an increasing demand for robust evidence to demonstrate the additional benefit of a new drug versus the therapeutic strategy, with a growing request for real-world data. Added value of value added medicines might be sometimes complex to demonstrate (e.g. better adherence, non-acceptance of surrogate endpoints) and the level of requested evidence disconnected from relevant reward from HTA bodies and ultimately payers.
- Depending on countries and product category, value added medicines might enjoy a more or less lenient assessment. For example, conditional reimbursement might apply only for expensive products.
- The absence of benefit acknowledgement by HTA bodies might discourage health care providers from using value added medicines.

Pricing obstacles

By pushing price down, some pricing policies might negatively impact value added medicines access such as:

- Systematic positioning as generic medicine and inclusion of value added medicines in internal reference pricing groups based on active substance.
- Tenders/procurement policies with award criteria based exclusively on economic criteria for active substance (lowest price).

- External reference pricing, especially when value added medicines are considered differently from a pricing and reimbursement perspective (e.g. internal reference pricing, tendering, etc.).

Due to these pricing rules, pharmaceutical companies might decide not to invest in value added medicines, not to launch or to withdraw value added medicines from some less favourable countries leading to inequities in value added medicines patient access across countries.

Moreover, a single pricing rule across all indications might disincentive companies from developing value added medicines in indications with the “lowest value” from a pricing perspective, despite this indication addressing an unmet need.

Lack of reward for manufacturers

There is uncertainty about return on investment related to value added medicines development cost. As described previously, the pharmaceutical business model is time limited and prevents originators from capturing any potential additional value of medicines once drugs are near or in the post-exclusivity/patent protection phase due to the lack of reward for these late-stage investments. Therefore, when a product is close to losing intellectual property or data protection, the marketing authorisation holder usually stops any investment and any additional potential opportunities may be lost for the patients and the society. While some recent initiatives from the regulatory side show the willingness of regulators to enhance the development of value added medicines, pricing and reimbursement of value added medicines remains a key hurdle for manufacturers to invest in the development of such medicines.

First, there is an uncertainty about reward of investment to bring evidence requested by HTA bodies, as well as high hurdle to obtain benefit acknowledgement because of generic stigma. In some cases, the benefit of value added medicines may be complex to evidence when it relies on improvement of patient’s preference, compliance, convenience of use, etc. Such benefits are poorly or not captured by Quality-Adjusted Life Year (QALY) which is the reference measure of medicine value in several countries, and require substantial investments to be proven through study designs acceptable by HTA agencies. Even if studies are performed, there is a high uncertainty that the results will be endorsed by HTA bodies even if the studies were requested by the authorities **(Box 8)**.

Box 8. Key French example of uncertainty about reward of investment to bring evidence requested by HTA bodies^{71,72}

In France, as part of coverage with evidence development, Risperdal Consta® (long-acting injectable formulation of oral risperidone) was requested in 2005 by the Ministry of Health to conduct a one-year observational study to compare hospitalisation rates among patients suffering from schizophrenia treated with different antipsychotic drugs.

The design was validated by the French National Authority for Health (HAS) and the Directorate-General for Health. A total of 2,092 patients were included in the study, of whom 550 were being treated with Risperdal Consta® and 1,659 were monitored for up to 12 months. The use of Risperdal Consta® versus other antipsychotic treatments was associated with a reduction in the risk of hospitalisation (relative risk of hospitalisation 0.66 [0.46; 0.96]), supporting the high value of this depot reformulation.

Despite the fact that study design had been validated by the HAS, they considered that, by essence, an observational study carried multiple confounding factors making the interpretation of the study very difficult; therefore, in 2010 following a re-assessment of the drug by the HAS, the study did not change the improvement in actual benefit (IAB) scoring and it was maintained as minor. The French pricing committee granted an escrow agreement associated to a coverage with evidence development (managed entry agreement) to this drug assuming that while the drug would be granted a premium list price, the company would receive payment based on the price of cheaper comparators and the difference would be deposited as public funds in “Caisse des Dépôts et Consignations” until study results were available, either for potential transfer of money to the company should the results evidence reduction in hospitalisation rate or to the social security services (public health insurance) in case of negative results.

This example illustrates that a very complex, long, expensive and uncertain and high commercial risk study imposed and controlled by HTA bodies led ultimately to the lack of any additional benefit recognition compared to the initial assessment while the results were outstanding.

Price of value added medicines can be set by criteria other than added value. Payers may change the rules for value added medicines and integrate, for example, the investment risk in their decision with a preconceived opinion that the investment risk in originator product is higher so the value should be weighted by the risk to set the price. There is a clear feeling from payers that a repurposed product is an obvious low risk investment. Therefore, their willingness to pay may be lower for the same added value as a new therapeutic class product. This breaks the rule of value based pricing established in most countries. This is seen in France for example where the Pricing Committee (CEPS) takes into account the level of risk taken by the company when setting prices⁷³. Moreover, taking the example of France, some specific pricing rules might be pre-established for

some value added medicines called “follow-on” by the CEPS and defined as medicines being “*usually a variation on its predecessor: an enantiomeric form, new pharmaceutical form, prodrug, etc.*” for which prices should be aligned to the price of generic versions of the original product or if the original product is not off-patent, the price of the “follow-on” might be aligned to the price of the originator with specific contractual conditions following generic entry of the originator to have price reduced to the generic price of the originator⁷³.

9. Recommendations to Capture the Full Value of Value Added Medicines

Previous sections described a real need to enhance the recognition of value added medicines by all stakeholders as medicines offering societal value distinct from originator and generic products based on the same active substance.

Policy recommendations

- Pricing and Reimbursement (P&R) Pathways:
 - P&R assessment should offer the possibility for HTA pathways taking into account special characteristics of value added medicines:
 - Value added medicines should be eligible for multi-HTA early dialogue and parallel scientific advice (EMA-Multi-HTA early dialogue).
 - There should not be legislative barriers preventing companies from pursuing HTA for selected value added medicines in order to demonstrate relevant improvements for patients, health care professionals and/or payers.
 - HTA decision making framework should take into account the special characteristics of value added medicines not currently captured:
 - To enlarge scope of benefit considered in decision-making such as patients' and health care providers' preferences, more weight on quality of life and health economic benefit.
 - To accommodate for different time points at which evidence can be assessed, for example the use of modelling techniques to predict the outcome, as well as coverage with evidence development to capture real world benefits.
 - Pricing policies should reward value added medicines development:
 - Value added medicines specificities should be acknowledged in tenders/procurement policies to allow differentiation from pure generic medicines.
 - Early entry agreement should be made available for value added medicines to allow bringing evidence along commercialization.
 - External reference pricing should not apply systematically for value added medicines.
 - Value added medicines should not be integrated systematically in internal reference pricing.

- Value added medicines should not be assimilated systematically to generic medicines because of the lack of new chemical entity status.
- Reward incremental innovation and make HTA requirements proportionate to potential reward (i.e. if requirement is to invest a lot of money, this should be rewarded). For example, if the a potential value added medicines benefit will be rated as modest by HTA bodies regardless of outcome, a very complex, heavy, long and expensive study should not be required to be performed; ultimately the possible expected economic reward should be proportionate to the level of requirements from HTA bodies.
- Allow indication-specific pricing for drugs having multiple indications with potential different value across indications.

Industry proactive approach

- Validate surrogate endpoints, e.g. for one specific technology such as a specific new inhaler developed for administration of drugs to treat asthma; one study might be conducted to validate that reduction of error with inhaler X is correlated with a better efficacy in terms of reduction in asthma exacerbation; for all products developed with inhaler X, the evidence in the reduction of errors with inhaler X might be considered as valuable to acknowledge on the benefit in terms of efficacy.
- Invest in patient registries and post-authorisation studies to collect real world data.
- Raise acceptance of value added medicines through communication campaigns to differentiate value added medicines from generic medicines and decrease stigma as counter-acting generic medicine perception and the negative role of such therapies that prevent capturing savings from generic use.
- Engage patient's groups and health care providers to identify their needs and ensure developed value added medicines address established and well-documented unmet needs.
- Engage in early dialogues with HTA bodies/payers to best fit their expectations for value added medicines development and obtain recognition of additional value.

10. Conclusions

Value added medicines represent an opportunity for society to address a number of drug related health care inefficiencies related to irrational use of medicines, non-availability of appropriate treatment options, shortage of mature products, geographical inequity in drug access and also present an opportunity to deliver better health to patients, to enhance health care system efficiency and contribute to the sustainability of the health care systems.

There is currently a gap between increasing regulatory authority interest in capturing value added medicines benefits and the resistance of HTA bodies/ payers, who tend to ignore this important segment of the pharmaceutical field. Current HTA framework, generic stigma, and pricing rules such as internal reference pricing or tendering processes in place in some countries prevent the full recognition of value added medicines benefits, discouraging manufacturers from bringing such products to the market.

This situation calls for policy changes to foster appropriate incentives to enhance value recognition of value added medicines from HTA and pricing perspective and deliver the expected benefit to the society.

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Creativ-Ceutical

215, rue du Faubourg Saint-Honoré

75008 PARIS, France

<http://www.creativ-ceutical.com/>

