19. The Challenges and Future of Advanced Therapies

Selcen Öztürk [1]

[1] *Hacettepe University, Department of Economics, Ankara, Turkey*

19.1 Introduction

Globally, we observe that diagnostic and treatment methods are rapidly changing and evolving, due to epidemiologic and demographic transitions. In this context, personalized medicine is increasingly emerging, because of the recent technological advances in health care service provision. Several definitions have been proposed to define "personalized medicine" (Box 1). A formal definition can be as follows: "Providing the right treatment, to the right patient, at the right time, with the help of new biomarker-based diagnostic tests". Such tests help identify patients at high risk, or patients for whom conventional therapies are less effective, or ineffective – i.e. "stratification" [1].

Patients with the same diagnosis respond differently to the same therapy, due to their different genetic and biological endowments. Personalized medicine evaluates these differences on a molecular basis, and develops advanced therapies which depend on the patient's specific needs. This new field, which is arising from advanced pharmacology and genomics, is defined as pharmacogenomics [2]. Pharmacogenomics focuses on patients for whom pharmaceuticals are ineffective (Box 2). Personalized medicine and advanced therapies are more utilized in genetic and metabolic illnesses, such as cancer or rare genetic diseases. The most recent studies proved the existence of a significant relationship

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Box 1. Different Definitions of Personalized Medicine

- "The use of new methods of molecular analysis to better manage a patient's disease or predisposition to disease" – *Personalized Medicine Coalition*
- "Providing the right treatment to the right patient, at the right dose at the right time" – *European Union*
- "The tailoring of medical treatment to the individual characteristics of each patient" – *President's Council of Advisors on Science and Technology*
- "Health care that is informed by each person's unique clinical, genetic, and environmental information" – *American Medical Association*
- "A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease" *National Cancer Institute, NIH*

Box 2. Percentage of Patients for Whom Pharmaceuticals are Ineffective [2]

- Depression: 38%
- Asthma: 40%
- Cardiac Arrhythmias: 40%
- Diabetes: 43%
- Migraine: 48%
- Arthritis: 50%
- Osteoporosis: 52%
- Alzheimer: 70%
- Cancer: 75%

with certain cancer markers and genes. Therefore, especially for cancer patients with family history of disease, genetic tests help reveal important information about the prognosis, the risk of metastasis, and sometimes even the possible success of the treatment. In this way, genetic tests help prevent unnecessary treatments and their associated costs. Personalized medicine helps identify key molecules in cell proteins. Advanced therapies can be designed to intervene with these key molecules, rather than others, and therefore can be more effective. Thanks to technological advances, the possibility to identify, in the near future, with genetic testing, the metabolic structure of individuals seems plausible; each patient will therefore be treated at the right time and with the right dosage of the right medicine. Advance therapies are expected to develop efficient and successful treatments for many severe, orphan diseases and chronic illnesses, such as cancer. Furthermore, the advances in personalized medicine extend beyond individuals that are already ill, and can offer early risk identification and preventive measures for the entire population [3-5]. For example, many pharmaceuticals used in neurologic and psychiatric treatments are metabolized by an enzyme called cytochrome P450. Cytochrome P450 class includes more than 50 enzymes that are responsible for metabolizing over 90% of pharmaceuticals. The genetic variability of these enzymes creates differences in the patients' responses to several pharmaceuticals. Therefore, gaining information about the genetic structure of the P450 enzymatic class is of great importance in the treatments of several severe and chronic illnesses [6].

19.2 Recent Developments in Advanced Therapies

In 2014, after a 14-year discovery process, the European Commission authorized the first gene therapy, Glybera® (alipogene tiparvovec), for the treatment of lipoprotein lipase deficiency (LPLD, type 1 hyperlipidemia). LPLD is a very rare disease, found in 1-2 individuals in 10 million [7]. The initial application process for the gene therapy for such ultra-rare disease started in December 2009, and the European Authorities rejected the
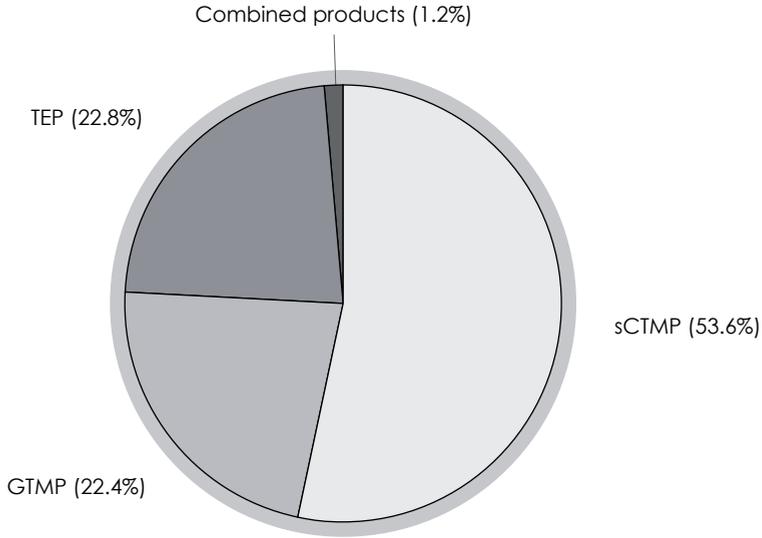
Figure 1. Advanced therapy drugs classification. Modified from [8]
GTMP = Gene Therapy Medicinal Products; sCTMP = somatic Cell Therapy Medicinal Products;
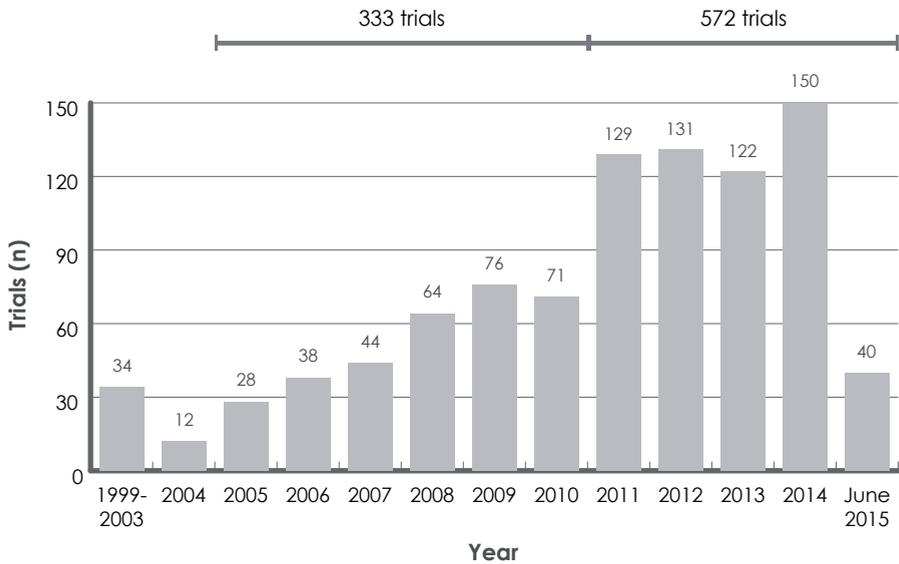TEP = Tissue Engineered Products

Figure 2. Number of registered trials from 1999 to 2015. Modified from [8]

application twice, due to the lack of wide-ranged efficacy tests. After a final re-examination in 2012, alipogene tiparvovec was approved and authorized for the marketing in the EU. However, five years after the approval, Glybera® was withdrawn from the market, not because of effectiveness or safety issues, but because of its high costs and limited use. In August 2017, the FDA announced the approval of Kymriah® (tisagenlecleucel) for children and young adults suffering from acute lymphoblastic leukemia (ALL), thus introducing the first gene therapy into the US market.

Advanced therapy drugs – that have been developed and are currently being tested – mainly target specific, severe and rare diseases, such as cancer and cardiovascular, musculoskeletal, immunological, neurological and hematological conditions. These drugs can be mainly classified as Gene Therapy Medicinal Products (GTMP), somatic Cell Therapy Medicinal Products (sCTMP), Tissue Engineered Products (TEP) and combined products. As shown in Figure 1, the majority of pharmaceuticals are somatic Cell Therapy Products.

The growing attention to personalized medicine can be seen in the significant increase in the number of trials that have been conducted with advanced therapy drugs from 1999 to 2015 (Figure 2).

Even with these high numbers of trials, today (2017) there are only 8 advanced therapy pharmaceuticals available in the EU market, and 15 in the US (Table 1). Therefore, it is possible to argue that the development of advanced therapy pharmaceuticals and personalized medicine are slower than expected. The reasons for this slow progress are three-fold: scientific – the development processes of advanced therapy pharmaceuticals are complex and R&D is intensive; regulatory – there are significant imperfections in the regulation of advanced therapy pharmaceuticals; and economic – there are issues regarding cost-effectiveness analyses, pricing and reimbursement [1]. In addition, it's possible to argue that, due to these imperfections, the incentives for personalized medicine and the innovation of advanced therapy drugs are not aligned [5].

Even considering the clear cost benefits and the social needs, Authorities may be reluctant to pay large, one-time sums for advanced therapies, for several reasons. Firstly, the effectiveness of the therapy might be in question. Since the approval of advanced therapies encounter problems with available data, the one-time payment must concern a "projected" duration of efficacy rather than an "actual" duration. Secondly, with the recent efforts to decrease pharmaceutical spending, such amounts can create arguments and criticism. In addition, especially for rare diseases, patients might not use advanced therapies. Therefore, even considering their proved effectiveness and cost benefits, the reimbursement of advanced therapies might encounter the reluctance on the part of third party payers. The governments' role should also be clarified in the pricing and reimbursement decisions regarding advanced therapies. A thoughtful structuring of the reimbursement system will also help the pharmaceutical companies to increase the level of investment in advanced therapies, which in return will yield higher benefits for society [9]. Advanced therapies pose a dilemma to health policy Authorities in terms of serious health improvements and challenges due to imperfections in cost-effectiveness analyses, market access, and the decisions on pricing and reimbursement.

Name	Classification	Marketing authorization holder	License date
KYMRIAH	Gene Therapy	Novartis Pharmaceuticals	30.08.2017
ZALMOXIS	Somatic cell therapy	MolMed	18.08.2016
NOVOCART INJECT	Tissue Engineered Products	TETEC	27.06.2016
STRIMVELIS	Gene therapy	GlaxoSmithKline	26.05.2016
IMLYGIC	Gene therapy	Amgen Europe	16.12.2015
HOLOCLAR	Tissue Engineered Products	Chiesi Farmaceutici	17.02.2015
NOVOCART 3D	Tissue Engineered Products	TETEC	29.08.2014
ZYTOKIN	Tumor Vaccine	Deutsches Rotes Kreuz Blutspendedienst	13.06.2014
BIOSEED-C	Tissue Engineered Products	BioTissue Technologics	4.06.2014
T2C001	Tissue Engineered Products	t2cure	31.03.2014
DCVAX-L	Tumor Vaccine	Northwest Biotherapeutics	21.02.2014
MUKOCELL	Tissue Engineered Products	UroTiss Europe	23.12.2013
CHONDROSPHERE	Tissue Engineered Products	co.don	12.12.2013
MACI	Tissue Engineered Products	Genzyme Europe	27.06.2013
GLYBERA	Gene therapy	uniQure	25.10.2012
PROVENGE	Gene Therapy	Dendreon	29.04.2010

Table 1. Advanced therapy medicinal products currently on the market

19.3 Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is a widely used tool in health economics and policy. In short, CEA aims to measure the potential success of any intervention comparing the relative costs of different actions aimed to achieve the same outcomes or effects [10]. In order to compare the costs and effectiveness of a course of action, monetary measures of both the outcome and cost must be provided. In terms of health policy, the outcome is usually measured by evaluating the changes in life expectancy or improvements in quality of life. However, measuring these aspects with money is challenging. The first challenge
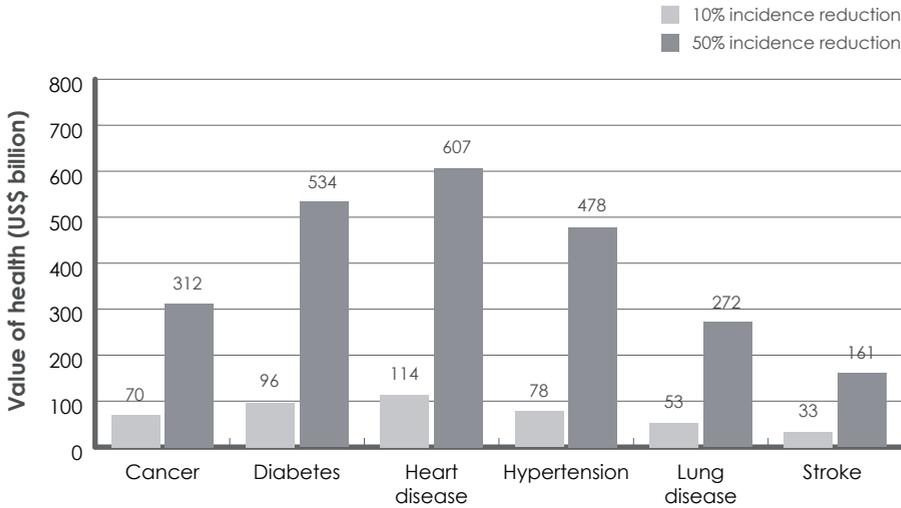
Figure 3. Potential benefits from personalized medicine calculated as cumulative value of additional QALY generated (2012-60, valued at US$ 100,000 each). Modified from [5]

derives from the basic question of microeconomics: "for whose benefit?". We can find different values for the same outcome by considering the perspective of the individual, the society, the payer or the pharmaceutical company. In addition, as reported by Porter (2010) [11], determining the relative outcomes is a complex process in health economics. Porter [11] proposed a "three-tier hierarchy" for outcome evaluation: the first tier includes "survival", or "the degree of health recovery", the second tier contains "time to recovery" and "disutility due to the treatment process", and the third tier embraces "the sustainability of recovery" and "long term consequences of the therapy". In health economics, unfortunately, only the first tier is usually used, and the other two are ignored in terms of outcome evaluation.

Even with only the first tier analysis using survival or the degree of health recovery, the possible individual and social benefits of advanced therapies are undeniable. Dzau et al. [5] use a simulation model to estimate the potential benefits of personalized medicine in early risk detection (Figure 3). With the help of personalized medicine, the individual risk levels for diseases such as cancer, diabetes, heart disease, hypertension, lung disease and stroke can be calculated. With efficient interventions on high-risk individuals, the benefits are reported as a 50-year increase in life expectancy, and $ 100,000/QALY are reported.

Measuring costs can be challenging, due to the uncertainties of the market, difficulties in measuring opportunity cost and external effects [10]. Even considering these major challenges, CEA is widely used in both investment and reimbursement decisions in health economics and policy. The nature of advanced therapies makes it even more difficult to

perform a CEA, because it's also important to recognize the risks involved with genetic tests. Furthermore, genetic tests are very expensive, therefore – even though they might provide important information, especially in the early stages of the disease – due to their high costs they are only adopted at a later stage, after the failure of several treatments.

19.4 **Market Access**

In 1906, the federal US government introduced the Food and Drug Act. In 1962, the amendments to this Act gave the FDA the task to test and approve new pharmaceuticals. The FDA review process – which is lengthy and complicated – has three phases. Including the research and development (R&D) process, a new drug is estimated to take an average of 14 years to be fully developed [10]. Apart from the entry barriers, the intense R&D process and the regulations regarding safety and health technology assessments (HTAs) can limit or delay the market access of new pharmaceuticals. Limited and delayed access is more pronounced with advanced therapies, since they are individual-specific and cannot count on controlled trials with large number of patients.

After the mid-1970s, the FDA introduced new policies to speed up the approval process for "important" pharmaceuticals. According to Philipson et al. [12], the decrease in approval times following the new FDA policies led to significant improvements for patients, due to a faster access to pharmaceuticals. On the other hand, as noted by Olson et al. [13], this rapid access carries risks related to an increase in adverse reactions.

During the last decade, advanced therapies originated a significant debate, because of the rapid technological improvements and the media attention on the subject: therefore, the FDA and the EMA closely monitored and addressed this issue. Within the 21st Century Cures Act, the FDA defined the pharmaceuticals eligible for Regenerative Medicine Advanced Therapy (RMAT). According to section 3033 of the 21st Century Cures Act, a drug is considered RMAT if it involves "cell therapy, therapeutic tissue engineering product, human cell and tissue product or any combination using such therapies or products". Similarly, the EMA defines advanced therapy medicinal products (ATMPs) as "medicines for human use that are based on genes or cells". A Committee for Advanced Therapies (CAT) monitors the safety and efficacy of such pharmaceuticals.

It is important to acknowledge the need for advanced therapies and their potential benefits for the individual's life expectancy and well-being. While R&D efforts continue to increase in this area, it's important to find and suggest solutions to bring advanced therapy pharmaceuticals to the market as soon as possible. In addition, the need for a regulation of such pharmaceuticals in terms of safety, effectiveness and reimbursement is especially important, to get a wider access to these drugs [14]. Finally, in order to avoid delays in market access, regulatory approval processes should be harmonized.

An early market access is important for both pharmaceutical companies and patients; however, the risks associated with an early access should not be ignored. Due to the lack of several efficacy data, such as those from randomized controlled trials, the risks associ-

ated with advanced therapies are greater than those of traditional drugs. When it comes to rare, life-threatening diseases, policy-makers should be willing to take higher risks. Acknowledging such need in health policy, both the EMA and the FDA offer a "fast track" option in the case of advanced therapies, stating however that the increased level of risk acceptability is – and must be – temporary. The main problem is that pharmaceutical companies are taking advantage of this earlier access, while regulatory agents are taking the risks. This situation can be considered an example of a principal-agent problem: in health economics it occurs when companies (agents) are acting to maximize their profits, while increasing the risk for patients, especially when regulatory institutions, such as the FDA and the EMA, bear this risk [15,16].

19.5 Pricing and Reimbursement Policies

The increasing importance of advanced therapies also brings to our attention the discussion of the pricing and reimbursement of such therapies. In order to foster investments in advanced therapies, it is estimated that a spending of over $1 million is necessary. However, the potential economic advantages of advanced therapies should also be considered. Brennan and Wilson [9] cite in vivo gene therapy for hemophilia B as an example. The cost of the standard therapy for hemophilia B – which is a rare, severe disease affecting 1 in 20,000 males – is equal to $ 200-300,000 per year, for a total of $ 4-6 million (lifetime treatment), while in vivo gene therapy, which costs just over $ 1 million and requires a one-time treatment, is less expensive.

Most countries experienced a rapid increase in the healthcare expenditures over the last 50 years. Moreover, there is concern that most countries will not be able to finance their healthcare expenditure in the future [17]. Pharmaceutical expenditure consists of approximately 10-15% of health spending. In other words, pharmaceutical expenditure is

Countries	2000	2005	2010	2013	2014	2015
Australia	7.6	8.0	8.5	8.8	9.1	9.4
France	9.5	10.2	10.7	10.9	11.1	11.1
Germany	9.8	10.3	11.0	11.0	11.1	11.2
Japan	7.2	7.8	9.2	10.8	10.8	10.9
Norway	7.7	8.3	8.9	8.9	9.3	10.0
Turkey	4.6	4.9	5.1	4.4	4.3	4.1
United Kingdom	6.0	7.2	8.5	9.9	9.8	9.9
United States	12.5	14.5	16.4	16.3	16.5	16.9

Table 2. Proportion of total health expenditure in GDP for selected OECD countries [OECD Statistics]

Countries	2000	2005	2010	2013	2014	2015
Denmark	9.07	8.58	7.70	6.90	6.76	6.76
Norway	10.21	9.66	7.65	7.59	7.49	7.66
Netherlands	12.29	11.14	9.82	7.76	7.64	7.87
United States	11.37	12.47	11.94	11.38	11.97	12.23
Germany	14.08	15.39	14.97	13.99	14.36	14.31
France	16.90	17.57	16.36	14.99	15.01	14.74
Czech Republic	24.66	25.70	20.42	17.93	17.11	17.32
Australia	15.70	15.22	15.63	14.99	14.39	14.23
Mexico	19.94	35.60	31.50	27.35	27.01	27.20

Table 3. Proportion of pharmaceutical expenditures compared to total health spending for selected OECD countries [OECD Statistics]

a significant driver of the increase in healthcare costs in most countries. Table 2 shows the proportion of total health expenditure in gross domestic product (GDP) for selected OECD countries. It is clear that, for all countries, there is an upward trend, which implies a considerable burden on the budgets. However, it is also important to mention that pharmaceutical expenditures have been found to have significantly positive effects on the patients' life expectancy [18].

Table 3 shows the proportion of pharmaceutical expenditures compared to total health spending for selected OECD countries. In spite of the introduction of new technological pharmaceuticals into the market, there is a surprisingly decreasing trend in the share of drug expenditure with respect to total health spending. This declining trend can be attributed to series of pricing policy interventions and the penetration of generics in most countries.

Despite the cost-reduction trend which occurred in recent decades, pharmaceutical companies experienced rapid growth rates in terms of size and profits. These growth rates attracted the attention of media, society, policy makers and insurance companies and introduced several challenges in terms of expenditure and reimbursement [10].

The delicacy of the issue and the structure of the pharmaceutical market make regulation very important. In a context characterized by monopolistic competition, with a small number of companies, differentiated products, active barriers to entry and high levels of profit, the pharmaceutical companies possess market power, hence they have the ability to increase prices beyond marginal costs and to discriminate prices. As is well known in microeconomics, these issues lead to a decrease in efficiency [19].

Barriers to entry in pharmaceutical industry are of great importance. A barrier to entry is defined as any factor that will restrict the entry of new companies into an existing market [20]. Patents, which are highly utilized in pharmaceutical industry, are the best example of entry barriers [21]. With active barriers to entry, certain companies can have the monopoly power on a specific product and enjoy high levels of profit for a certain period, therefore the social surplus decreases. In pharmaceutical industry, companies ac-

tively use patents (with many variations of the product) to impede entry [10]. Because of this, it is possible to argue that the pharmaceutical industry is the most heavily regulated industry worldwide in terms of safety, market access and reimbursement.

Prices in the pharmaceutical industry have long been discussed, due to the high levels of profit for the industry. Pricing strategies depend on the monopoly power of the companies and the monopsony power of the legal Authorities over the pharmaceutical industry, as well as R&D spending, risks involved, price discriminations, regulations and competition levels. In addition to the similar attributes in terms of safety and efficacy issues, pricing and reimbursement strategies differ among countries and health systems. Pricing and reimbursement decisions are key concepts for the market access of drugs. When advanced therapies are considered, pricing and reimbursement are even more controversial, due to the high costs associated with such therapies. On the other hand, early market access is important for advanced therapy pharmaceuticals, since they mostly target severe and chronic illnesses.

According to Lu and Comanor [22], the prices of new pharmaceuticals with significant therapeutic contribution, determined by FDA ratings, are higher at the time of introduction, with premiums ranging from 51 to 79%. The prices of high-ranking pharmaceuticals decline at a slower rate over time, compared to low-ranking pharmaceuticals. A high level of competition from branded rivals negatively affects introductory prices, whereas generic competition has a positive impact. Therefore, Lu and Comanor [22] conclude that the main strategy when introducing a new innovation is the "skimming strategy" – where highest introductory prices are lowered over time – and if the drug is an imitative (generic) product, the pricing strategy is classified as "penetration strategy" – where a lower price is offered for a new product, to lure customers, proving Dean's [23] hypothesis.

Prices in the pharmaceutical industry are also closely related to the associated risk levels. Risks can arise from the chemical property of the drug, as well as the regulations. The perception of high prices and profits – whether justified or not – and increased health expenditures in the pharmaceutical industry leads to heavy regulations and price controls. The main aim of these price controls is to decrease public spending on pharmaceuticals, while increasing social benefits. There are different types of price control used by the Authorities, such as; reference pricing, item-by item negotiation, formula pricing, profit regulation and budgetary controls (line item and global budget) [24].

In the reference pricing system, pharmaceuticals are grouped and compared within their reference groups, and the lowest price is paid within the group [25]. Reference groups can be based on active ingredients – as in the US – or on disease – as in Germany. However, since advanced therapy pharmaceuticals are heavily personalized, a reference group pricing system is not plausible. Many countries, such as Italy and Canada, also use the prices of similar pharmaceuticals in other countries as reference. This drives down the price of drugs of multinational companies, through an increasing international competition. Once again, such strategy is also not possible in the case of advanced therapy pharmaceuticals. Formula pricing is used in Japan, where pharmaceuticals are priced through their formularies. The UK uses the profit regulation system, where companies negotiate with the Authority, are allowed a certain percentage of profit, and set the price accord-

ingly. This leaves big companies with high R&D costs with higher levels of return, since the profits are calculated after R&D and other costs are deducted. Such policy is plausible for advanced therapy pharmaceuticals; however, Authorities will have to face even higher levels of pharmaceutical expenses and increasing level of company profits.

Pricing policies and regulations differ for each country worldwide. Even within the EU, where the drug approval systems are homogeneous, local governments make decisions about pricing and reimbursement

19.6 Discussion and Perspectives

Given the recent developments in technology in the pharmaceutical industry, advanced therapies will be on our agenda in the coming years. Initiatives regarding the legislation, regulation and pricing strategies for advanced therapies must be taken early in the process, for increased social benefits. Unfortunately, the current level of regulations regarding pricing and reimbursement is not promising. Several questions need to be answered, such as: Will governments and/or health insurance companies reimburse advanced therapy pharmaceuticals? How will the reimbursement/insurance policy work in advanced therapy pharmaceuticals? Authorities should commit to eliminate the grey areas in terms of advanced therapy pricing and reimbursement. Apart from the reimbursement decisions, a harmonization of the approval processes of advanced therapy pharmaceuticals seems necessary in order to ensure early market access.

European and US legislations and regulations regarding the testing, manufacturing, marketing and use of advanced therapy products should be harmonized, in order to produce effective results within personalized medicine. Advanced therapy reimbursement options and strategies are very important in personalized medicine, and should urgently be addressed by all countries. Data collection at an early stage is also of great importance for reimbursement decisions. Ideally, pricing and reimbursement issues should be addressed during the phase of discovery of advanced therapy medicinal products. In addition, the costs associated with advanced therapies should be assessed, and decision-makers should consider the possible effects of increased health expenditures [26]. In order to create successful policies, all stakeholders – such as scientists, universities, hospitals, pharmaceutical companies and governments – should be involved in the decision-making process [27].

19.7 Acknowledgements

19.8 **References**

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