Europeanization and Globalization 5

Nada Bodiroga-Vukobrat
Daniel Rukavina
Krešimir Pavelić
Gerald G. Sander *Editors*

Personalized Medicine in Healthcare Systems

Legal, Medical and Economic Implications

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Nada Bodiroga-Vukobrat • Daniel Rukavina •
Krešimir Pavelić • Gerald G. Sander
Editors

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Editors
Nada Bodiroga-Vukobrat
Faculty of Law
University of Rijeka
Rijeka, Croatia

Daniel Rukavina
Croatian Academy of Sciences and Arts
Rijeka, Croatia

Krešimir Pavelić
Juraj Dobrila University of Pula
Faculty of Medicine
Pula, Croatia

Department of Biotechnology
Centre for High-Throughput Technologies
University of Rijeka
Rijeka, Croatia

Gerald G. Sander
University of Applied Sciences
Ludwigsburg, Germany

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Preface

This book comprehensively presents biomedical, technological and socio-humanistic aspects of personalized medicine. We decided to use the term "personalized medicine" even though today a number of terms are used for this concept including precision medicine, customized drug therapy, genomic medicine or genotype-based therapy, individualized or individual-based medicine, information-based medicine, integrated healthcare, precise medicine or *omics*-based medicine: pharmacogenomics/pharmacogenetics/pharmacoproteomics, predictive medicine, rational drug selection, systems medicine, tailored therapy, translational medicine and stratified medicine. We still think that the term personalized medicine encompasses in the most appropriate way the patient and human complexity as well as other factors of relevance in the medical environment.

The articles published in this book are contributions of invited speakers attending the symposium under the title "Personalized Medicine: Basic and Social Aspects (Challenges for Social Security Systems)". The symposium was held in Rijeka (November 20–21, 2017) in organization of the Department of Biomedical Sciences in Rijeka – Croatian Academy of Sciences and Arts, Jean Monnet Inter-University Center of Excellence in Opatija (Croatia) and University of Rijeka.

The whole concept of the book is thus built on the premise that the individual approach towards the patient might transform the quality of healthcare and effectiveness of medicine in the widest sense. Personalized medicine is gaining momentum and significance as it changes the historical paradigm of "medicine for all" and focuses on the person, on the human being. This shift has been facilitated, among other things, by the use of modern and advanced high-throughput technologies and molecular genetics as well as by system biology approaches that regaining importance daily. Such a change in medicine necessarily requires changes in the healthcare system, health economics and socio-legal aspects with all the implications coming along with that. For example, changes in relationship between a physician and patient are immanent, whereby healthcare professionals will have to make decisions based on complex biological and environmental information as well as on the patient's life style. An equally important aspect of personalized medicine is also in

a proper development of innovative technological solutions for citizens and patients, already recognized as necessary means for advancements in the medical field by European policies. This means that each person will be in charge of own health, a concept that is still in its beginnings. A wide interdisciplinary initiative is required to educate such active participants in decision-making complex issues such as genomics, information and privacy promotion as well as novel technologies. Adequate levels of healthcare literacy should be therefore in the focus of citizen education. Consequently, this book has also been prepared with the intention of encompassing important scientific-medical and socio-humanistic aspects of personalized medicine for a wider professional audience. Expectations from implementation of personalized medicine in the daily healthcare are huge both from the perspectives of the patients and from the doctors. First of all, strengthening and full realization of important principles in the physician–patient relationship are required: the physician is obliged to act in the patient's best interest, patients need to be treated with respect, without discrimination during the whole process, even if the relationship seems to be coming to an end and maximal high-quality healthcare needs to be ensured. The unique relationship depends indeed on the trust between the patient and the physician.

As editors of this book, we believe that policy makers, health authorities and public bodies are encouraged to enter this cross-sectorial debate and enhance public dialogue on this relatively new medical concept and conditions for its success. We would like to thank our dear colleague and friend, one of the main initiators and inspirators of this project, Professor Nada Bodiroga-Vukobrat, who unfortunately passed away recently. With her innovativeness and energy, she has succeeded among a wide audience and scientific community in building the awareness on a comprehensive approach to the problem of personalized medicine in the healthcare system, considering legal, medical and economic implications as inherent aspects of this subject. Thank you, Nada, for the legacy that we now want to share with the readers of the book in a joint forward look towards the future medicine—personalized medicine.

Rijeka, Croatia — Daniel Rukavina
Pula, Croatia — Krešimir Pavelić
Ludwigsburg, Germany — Gerald G. Sander

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Part I
Introduction

Options for Realising and Financing Innovation in the German Healthcare System

Bernd Baron von Maydell and Boris Baron von Maydell

Abstract Personalised healthcare is experiencing the same difficulties as other innovations when it is introduced to the different health systems of countries. However, the high treatment costs and the complicated evaluation of the added value compared to existing methods and procedures represent particularly great challenges for personalised medicine providers and healthcare systems. In the German health care system, a large number of mechanisms have been implemented, on the one hand, to enable the fundamental introduction of innovations and, on the other hand, to permit only those innovations for standard care that bring additional benefits to the respective patients.

The first part of this article discusses the question of the prerequisites and framework conditions that help an innovation to be included in the benefits catalogue of statutory health insurance in Germany. Once this question has been successfully addressed, providers and cost bearers are faced with the difficult task of financially evaluating the new service. This is the subject of the second part.

Ultimately, a new method can only improve care if it is recognised and financed by the health systems. Against the background of increasing costs for new treatment methods, it is the task of the processes described to prevent scaling in new medical procedures.

1 Introduction

The range of medical services offered worldwide continues to grow at an extreme pace. New forms of treatment are extending life expectancy significantly, even for illnesses for which there were no therapy options just a few years ago. Innovations are changing all

Bernd Baron von Maydell was deceased at the time of publication.

B. B. von Maydell (✉)
Department Ambulatory Care, Association of Substitute Health Funds (vdek head office), Berlin, Germany
e-mail: boris.vonmaydell@vdek.com

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areas of medical care to a significant degree, whether it is new methods for examination and treatment, pharmaceuticals, medical products or telematics in the healthcare sector. This rather positive trend is associated worldwide with starkly increasing costs for healthcare systems, with the successful implementation of an innovation in the healthcare sector promising significant returns. There is a large potential for care seen in areas related to Personalised Medicine in particular, which in turn brings with it costs for medicines as well as expenses for the required genetic diagnostics.

In addition to the large potential of some innovations, it is sometimes harder to obtain actual evidence in favour of the manufacturer's promises of a cure once the initial euphoria has dissipated, and not all new forms of treatment actually show better results than already long-established methods. Consequently, the welfare systems of countries around the world are faced with two large issues when implementing innovations:

1. Does the innovation really lead to an objective improvement in care?
2. Are the costs associated with the introduction of the innovation and its incorporation in the healthcare system's benefits catalogue truly justified?

It is probably not in the least possible to answer either question neutrally. Answers can, for example, be dependent on the financial strength of an economy, the affordability of a healthcare system, a society's ethical standards or many other factors. Accordingly, there are different standards for evaluation, and the mechanisms in the world's welfare systems that have been implemented by societies to account for healthcare innovations differ based on those standards. In practical terms, a healthcare system that is barely able to finance conventional radiation therapy for cancer patients would never bother considering whether it is a good idea to add a form of proton therapy to its benefits catalogue. In a healthcare system of this nature, a discussion about rationalisation would take strong precedence over a discussion about implementing innovations.

The healthcare system in Germany, which acts as the focus of this study, is completely different in this respect. In Germany, there is no significant innovation that has not been incorporated into care for cost reasons—in recent years at least. The German healthcare system's mechanisms for responding to the questions, described below, can therefore be transferred to other countries only partially. They have developed from the peculiarities of a self-regulatory, socialised[1] health insurance system and, on top of that, are subject to an ongoing evolution process instigated by numerous healthcare reforms, particularly over the last few years.

What is understood as an 'innovation' is open to a great deal of interpretation. For this article, the phrase 'innovation in the healthcare sector' assumes a broad approach that includes new products and processes along with services and innovations to the system itself. An innovation in the healthcare sector is therefore a

[1]Self-regulation is the overarching organisational principle for Statutory Health Insurance in Germany. It means that providers in the healthcare sector, insured persons and employers handle organisation themselves to direct and help shape the healthcare system (Verband der Ersatzkassen e. V. 2018).

significant change to its structures, products, processes or methods to prevent, treat or relieve health risks or illnesses (Bührlein 2007, p. 6).

This article deals with the point in time at which a healthcare system makes the decision to incorporate new innovations in the market into care and, by extension, the decision to finance these innovations for those insured. Section 2 analyses the various structures for financing innovations in the German healthcare system. Section 3 focuses on the pricing mechanisms developed from those structures. Special attention is also given to pharmaceuticals, as it is in this sector in particular that healthcare system cost increases are dominated by new medicines and expanding Personalised Medicine.

2 Options for Financing the Introduction of Innovations in the German Healthcare System

Innovations may enter the German healthcare system through highly varied means. Firstly, these means are dependent on the dual insurance system in Germany, where 72.4 million people (as of October 2017) have Statutory Health Insurance and 8.8 million people (as of May 2017) are covered by a Private Health Insurance fund. The two systems handle innovations differently and have come to differing regulations on how innovations are financed. Secondly, there are also regulations within the Statutory Health Insurance system that are mandatory for all funds as well as regulations that each fund is free to make a decision on with policyholders. This freedom of contract represents a significant aspect of the competition between Statutory Health Insurance funds in Germany. Also, within the Private Health Insurance system, there are different providers that each offer different insurance policies, with each being a result of the competition between the funds and thereby more or less also allowing policyholders to utilise innovations. Figure 1 illustrates the various options through which innovations can penetrate the German healthcare sector. A discussion of the processes developed specifically for the Statutory Health Insurance system then follows, as almost 90% of the German population are insured under this system and therefore can use only it to take advantage of innovations.

2.1 Benefit Assessment by the Federal Joint Committee[2] Upon Integration Into the Standard Care Offered by Statutory Health Insurance (Block I in Fig. 1)

The German healthcare system is characterised by a stark distinction between Out-of-Hospital and In-Hospital Care. This distinction is also reflected in the way

[2]The Federal Joint Committee (G-BA, *Gemeinsamer Bundesausschuss*) is the highest-level decision-making committee run by German doctors, dentists, psychotherapists, hospitals and health

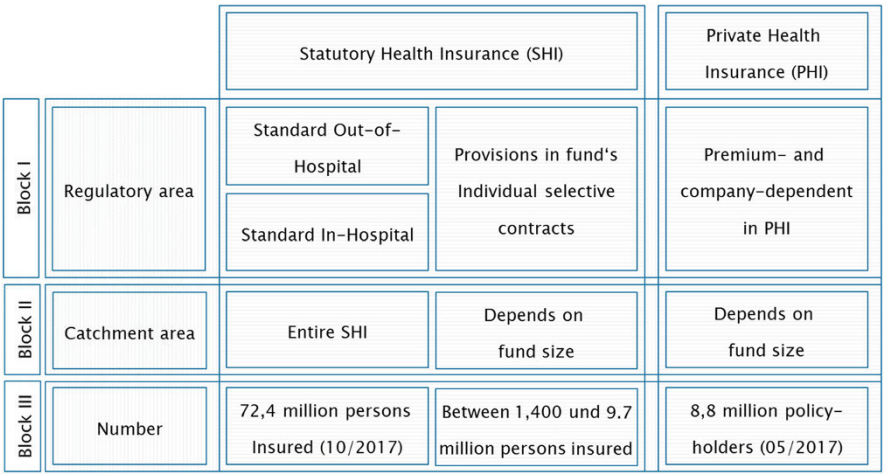

Fig. 1 Options for financing innovations in the German healthcare system (own illustration)

innovations are treated in the respective areas. Based on SGB V (*Sozialgesetzbuch*, Social Security Statute Book 5) Section 135(1), Out-of-Hospital Care is subject to general '*prohibition before authorisation*'. This means that new methods of examination and treatment may only be provided if the Federal Joint Committee have explicitly approved of their therapeutic benefit, medical necessity and economic viability. For In-Hospital Care, on the other hand, SGB V Section 137c provides for general '*authorisation before prohibition*'. This means that a hospital may provide a new examination or treatment method as long as the Federal Joint Committee has not explicitly ruled out its use. Accordingly, there are no limits to the utilisation of innovations in In-Hospital Care resulting from the influence of legislators. However, it cannot be assumed that the use of innovations in hospitals is completely unregulated. Rather, the regulation for financing hospital treatment via DRG payments acts in itself as a natural limit to costly innovations. If innovations are not factored into the calculation of DRGs, hospital trusts are only able to finance their usage to a limited degree.

The Joint Federal Committee therefore acts as a hub for the approval of innovations when seeking authorisation in the Out-of-Hospital Care sector or when prohibition is sought in the In-Hospital Care sector. The committee is the highest-level decision-making committee run by doctors, dentists, psychotherapists, hospitals and health insurance funds working jointly. They regulate large parts of the healthcare system by issuing directives per SGB V Section 91 et seq. Examples of innovations

insurance funds working jointly. By issuing directives, they set the catalogue of benefits offered by the Statutory Health Insurance funds for more than 70 million insured persons and, in doing so, determine what benefits are eligible for payouts under the medical care offered by the Statutory Health Insurance system. Furthermore, the G-BA decides on actions for quality assurance in hospital and non-hospital areas of the healthcare sector (Federal Joint Commitee 2018b).

that are relevant in this respect are new methods of examination and treatment per SGB V Section 468 or the early benefit assessment of pharmaceuticals under SGB V Section 35a. The G-BA contract the Institute for Quality and Efficiency in Health Care (IQWiG) to prepare for their decisions. IQWiG conducts research and analyses academic material (studies) to formulate a recommendation that, after a plausibility review by the G-BA, leads to corresponding directives and, finally, a decision that is binding for health insurance funds (Federal Joint Committee 2018a).

2.2 Establishment of Innovations by Means of Regulations in Selective Contracts with Statutory Health Insurance Funds (Block II in Fig. 1)

Statutory Health Insurance funds are permitted to enter into 'selective', i.e. optional, contracts for any benefits that have not yet been rejected by the Federal Joint Committee. Consequently, individual funds can, by themselves or in cooperation with others, integrate additional innovations into their standard care that would otherwise not or not yet be included. SGB V offers an array of legal foundations that funds can use to substitute or add on to benefits included with standard care. Examples of these are:

- selective contracts per SGB V Section 140a (Special Care)
- pilot projects run by health funds per SGB V Section 63
- benefits described in a health fund's charter per SGB V Section 11(6)
- general practitioner contracts per SGB V Section 73a (Primary Care Practitioners)

To encourage the use of selective contracts, an innovation fund was established at the G-BA in 2015 through the Statutory Health Insurance Care Improvement Act. An annual budget of €300 million was provided to promote projects that improve care across sectors and have the potential to be incorporated into care on a permanent basis. For example, these could include telemedicine, care projects in structurally weak areas, pilot projects with delegation and substitution of benefits; and pilot projects focussing on safety in pharmaceuticals. An innovation committee at the G-BA defines concrete criteria for funding and decides on applications for funding (Leonhardt 2015, p. 33) (Fig. 2).

The innovation fund was introduced so as to fix deficits resulting from the parallel existence of collective and selective contracts. The original goal when implementing this fund-specific freedom through selective contracts was to try out innovations on a small scale before incorporating the agreed benefit into the standard catalogue offered by the Statutory Health Insurance system in the instance of its success. Because of a lack of evaluation of existing selective contracts, there are few past examples of such a transition of benefits from selective to collective contract being successful. The health funds responsible for the selective contracts only had a limited individual interest in financing a cost-intensive evaluation on top of the usually

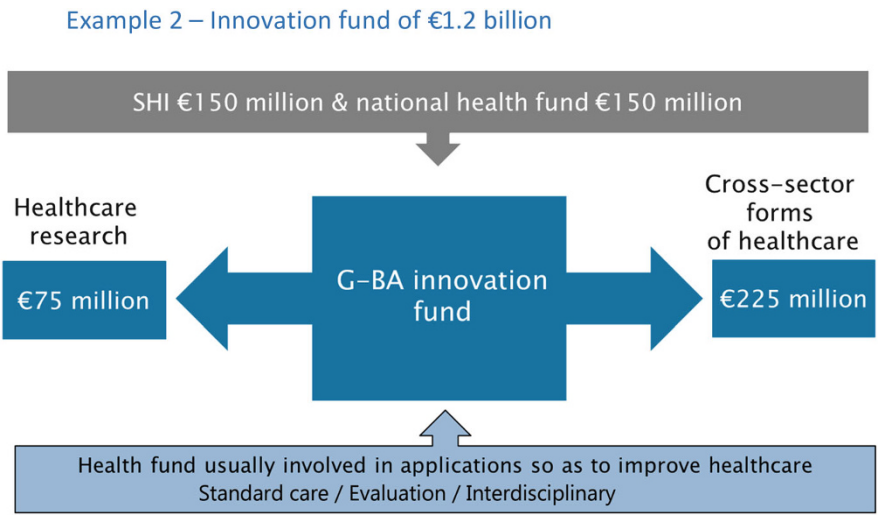

Fig. 2 Financing of the innovation fund in the Statutory Health Insurance system (own illustration)

already expensive benefits in the selective contract. The innovation fund addresses this deficit by making evaluation a requirement for funding and financing the innovative benefit in parallel.

2.3 Fast Entry Options for Innovations Via Private Insurance or Direct Financing (Block III in Fig. 1)

Approximately 10% of the German population are covered by Private Health Insurance. The principle of prohibition before explicit authorisation, as described above, does not normally apply when medical benefits are provided under a Private Health Insurance policy (depending on the policy). As a consequence, a doctor or dentist, for example, has the option of billing using the Fee Schedule for Doctors/Dentists (GOÄ/GOZ) for services that are not included in the Statutory Health Insurance benefits catalogue. Professor Jürgen Wasem describes the parallel existence of Private and Statutory Health Insurance in relation to the implementation of innovations as follows: *'The competition between the two systems definitely has its positive sides. The minor barriers to market entry and the relatively flexible system for remuneration in the Private Health Insurance system promote the rapid introduction of innovations. That being said, emphasis is put on efficiency and evidence in the Statutory Health Insurance system and this leads to the necessary proof of quality and also process innovations. All patients benefit from this gain in quality.'* (Wasem 2017).

The early integration of innovations can lead to the advantages described above, yet, on the other hand, can also result in medical problems resulting from still

insufficient evidence. The conflict between early implementation of an innovation and less than clear evidence can be illustrated using two practical examples:

Private Health Insurance covered the costs of antibody-coated, drug-eluting stents for coronary heart disease from an early stage. However, the final report by the IQWiG, dated 29 September 2015, concluded that there was no noticeable benefit provided by such stents over time. There was not one patient-relevant endpoint for which there was an indication of benefit or harm associated with treatment by implanting an antibody-coated, drug-eluting stent when compared with the control group, and in either case these were patients for whom a stent implant was indicated because of coronary heart disease (IQWiG 2015a, p. 12).

The second example concerns biomarker testing for breast cancer. In this respect too the IQWiG has concluded that there is no indication of benefit or harm for any of the currently offered biomarkers when it comes to a biomarker-based strategy for deciding for or against adjuvant chemotherapy in cases of primary mammary carcinoma (IQWiG 2015b). This example is all the more significant as patients have opted to forgo chemotherapy because of biomarker testing, although chemotherapy would have been beneficial at later stages of the disease.

Both examples show that early integration of innovations is not always in the patient's interests and, by extension, early financing of innovations does not generally lead to better care.

3 Pricing When Implementing Innovations in Care

Even if innovations improve the efficiency of a healthcare system over the short term and even increase efficiency reserves over the long term, they can sometimes cause considerable cost pressures at the time of implementation. On one hand, this can be attributed to the development of the innovation often incurring great costs and industry seeking to recoup the cost of these investments as soon as possible. On the other hand, an innovation may create an alternative treatment that in some circumstances may also for the first time enable a chance of recovery for patients with a specific and/or life-threatening illness. To deny such patients this new treatment method for financial reasons cannot be ethically justified in these individual cases. Healthcare systems must therefore respond to cases such as these, while at the same time the financing options described in Sect. 2 have utterly different mechanisms for enabling or denying provision of the service.

Examples of exceedingly expensive innovations in the healthcare system have grown in number over recent years. This in turn means that publicly financed healthcare systems in particular are faced with serious problems. If a decision is made in favour of rationalisation, insured persons will be excluded from a medical advance that is potentially relevant to their care. If a decision is made to cover such innovations, mechanisms must be found that influence the pricing or use of the innovation such that inclusion of the new benefits is enabled without affecting other sectors of the healthcare system. Universal healthcare systems are characterised by

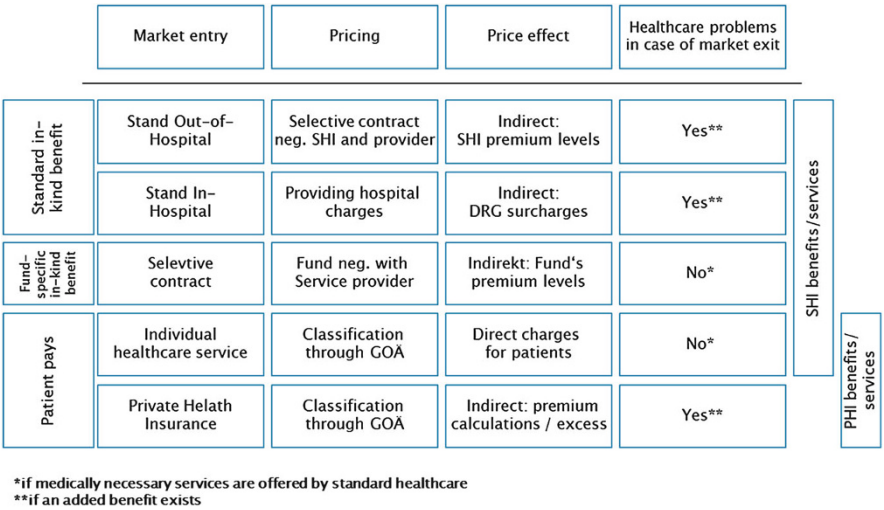

Fig. 3 Pricing, price effects and healthcare problems in case of market exit depending on market entry (own illustration)

scarce financial resources which, in Germany for example, have led to the efficiency dictate specified in SGB V Section 12, which has had a decisive influence on case law in all aspects of that statute book.

Pricing in healthcare depends on the way in which a new service has entered the system. Impacts and the potential occurrence of healthcare issues because of a foreseeable exit of the service provider depend on the market entry. Figure 3 illustrates schematically the pricing, price effects and potential healthcare problems depending on the method of market entry.

3.1 Pricing Based on the Benefit-in-Kind Principle of Statutory Health Insurance

Different pricing mechanisms have emerged in the Out-of-Hospital and In-Hospital sectors because of the aforementioned difference between the principles of '*prohibition before authorisation*' and '*authorisation before prohibition*'. The basis for remuneration of standard In-Hospital care in Germany are the diagnosis-related groups (DRGs). They allow every hospital to make its own decisions based on the principle of authorisation before prohibition on what medical intervention is medically necessary for a patient and, by consequence, what intervention will be used during In-Hospital treatment. This free decision enables the use of medical innovations. However, there is a need to balance budgets resulting from the size of any given DRG, which of course limits the willingness of a hospital to subsidise the use

of expensive investments over the longer term. SGB V provides for mechanisms to offset this financing problem via adjustments, supplements and deductions.

Pricing in standard Out-of-Hospital healthcare is based on a benefit assessment conducted by the Federal Joint Committee. If the assessment finds a positive benefit, prices are set in a manner that varies depending on the type of innovation. If it relates to services performed by doctors, for example, the Valuation Committee,[3] a joint committee made up by the National Association of Statutory Health Insurance Physicians[4] and National Confederation of Regional Statutory Health Insurance Associations,[5] determines an appropriate fee for the new service. If the innovation relates to new pharmaceutical products, negotiations are held directly between the manufacturer and the National Confederation of Regional Statutory Health Insurance Associations. SGB V provides escalation mechanisms for all pricing processes by way of arbitration offices or arbitrators. Because the pharmaceuticals sector in particular has been affected by costly innovations in the last few years, further analysis specific to the sector is provided later in this article, using the example of the Sofosbuvir drug for hepatitis C.

Statutory Health Insurance funds in Germany spent €202.05 billion in 2015. Of that, €34.84 billion went to pharmaceuticals (Federal Ministry of Health 2017). In 2015, the rates of increase in the pharmaceuticals sector were especially dominated by new treatment methods for patients with chronic hepatitis C. €1.265 billion alone was spent on medicines for treating hepatitis C, with expenditure for Sofosbuvir and Ledipasvir running up to €725.3 million (Schwabe and Paffrath 2016, pp. 9–10). Considering that the number of patients with an HCV antibody prevalence needing treatment is approximately 0.3% of the overall German population (Robert Koch Institute 2017, p. 280) and that total expenditure in the Statutory Health Insurance system was €202 billion for 71 million people, the extent of the financial burden on the healthcare system is noticeable.

On 17 July 2014, the Joint Federal Committee attested a substantial added benefit for the treatment of patients with chronic hepatitis C viral infection (HCV) for the

[3]The Valuation Committee is a committee of doctors and health funds acting jointly for organisational purposes. For this reason, it is also known as the Doctors' Valuation Committee. It is made up of six members, with three appointed by the National Association of Statutory Health Insurance Physicians and three by the National Confederation of Regional Statutory Health Insurance Associations. The Institute for the Valuation Committee manages the Valuation Committee (Institute for the Valuation Committee 2018).

[4]The National Association of Statutory Health Insurance Physicians is the umbrella association for the 17 regional Associations of Statutory Health Insurance Physicians. It organises extensive, locally-provided Out-of-Hospital healthcare and represents at national level the interests of doctors and psychotherapists working in the Statutory Health Insurance system (National Association of Statutory Health Insurance Physicians 2018).

[5]The National Confederation of Regional Statutory Health Insurance Associations (*GKV-Spitzenverband*) is the main representative of Statutory Health and Nursing Insurance funds in Germany and at European and international levels. It is responsible for the overall conditions necessary for healthy competition in quality and efficiency in healthcare and nursing care (National Confederation of Regional Statutory Health Insurance Associations 2018).

drug Sofosbuvir in their benefit assessment of pharmaceuticals with new agents (Federal Joint Committee 2014). The process for including new medicines in the benefits catalogue is regulated by the Act on the Reform of the Market for Medicinal Products and came into effect on 1 January 2011. The purpose of the legislation is to stem the strongly increasing expenses incurred by Statutory Health Insurance funds on medicine in recent years. The process for assessing benefit and calculating the amount coverable is depicted in Fig. 4.

After the decision of the Federal Joint Committee on the added benefit of Sofosbuvir, the provider Gilead's pharmacy retail price (including manufacturer discount) was set at €18,860.00 for a packet of 28 tablets (i.e. around €700 per tablet). In the subsequent negotiations between the manufacturer and the National Confederation of Regional Statutory Health Insurance Associations (see Fig. 5), the manufacturer's selling price and therefore also the pharmacy retail price was reduced to €16,840.00 (Arznei Telegramm 2015). Nobody can objectively evaluate whether the above pricing is appropriate for an incidence rate of 300,000 patients in Germany alone. What is obvious, however, is that only few healthcare systems worldwide can finance such pricing given the incidence rate described above. As illustrated in Fig. 5, prices are set through negotiations between the provider and the National Confederation of Regional Statutory Health Insurance Associations when the product's market entry is through standard Out-of-Hospital care. Because of the financial volume, the Sofosbuvir example truly has a direct impact on the premiums charged for Statutory Health Insurance. Many innovations do not result in this level of direct impact because of smaller financial volume, however the cumulative effect of various innovations can be similar. If an agreement had not been reached when setting the price of Sofosbuvir and an arbitration office not found an appropriate price for both parties either, the manufacturer would most probably have taken its product off the market. This would have had considerable consequences on the options for treating hepatitis C patients in Germany. In hindsight, the purpose of this exercise was not to question whether Sofosbuvir needed to be incorporated into standard care, but whether its negotiated price was justified.

3.1.1 Pharmaceuticals Focus 1: What Price Is Appropriate for a Medicinal Product in Germany?

It is difficult to find neutral factors that can be used to calculate a suitable price for a medicinal product. An initial benchmark would be the economic strength of the country in which a medicinal product is offered. The OECD compared average per-capita expenditure on medicinal products in 31 industrial nations for the year 2015. At US$766, Germany comes in at fourth place behind the US, Switzerland and Japan. Average per-capita expenses were US$553 per year (OECD 2017). Germany therefore ranks in the upper quartile of OECD nations. That may be appropriate given the country's economic strength, although, when compared to the average, the question arises as to why this difference exists.

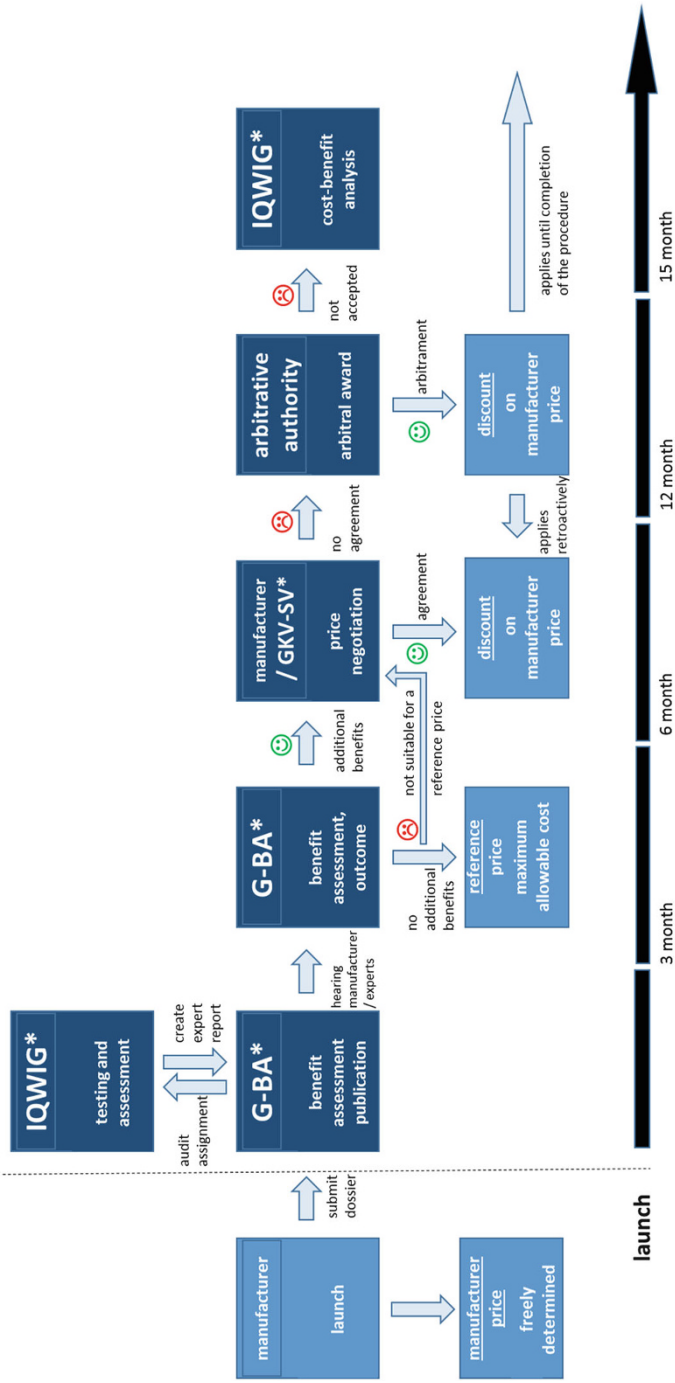

Fig. 4 Infographics on the Act on the Reform of the Market for Medicinal Products (own illustration based on Federal Ministry of Health 2010, p. 18)

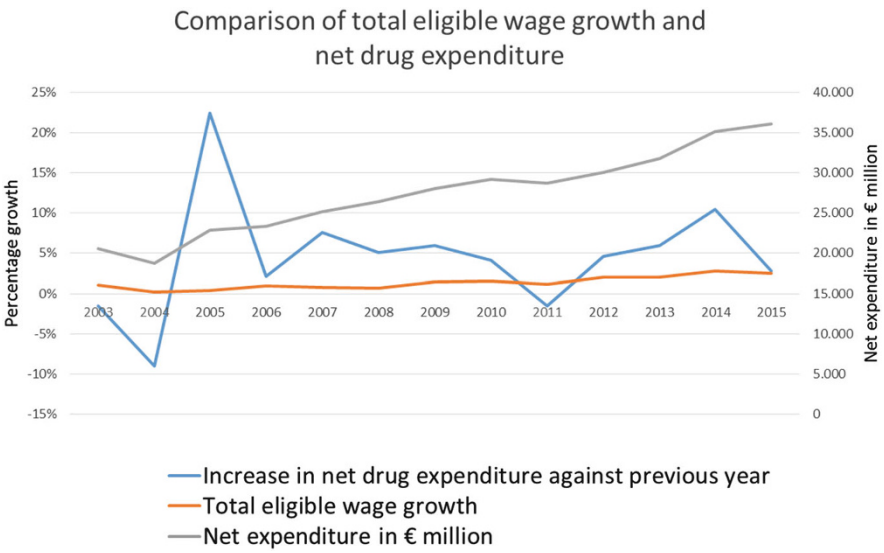

Fig. 5 Rate of increase in pharmaceutical expenditure relative to eligible wage growth (own illustration based on von Maydell and Carstensen 2016, p. 197)

A look at the increase of pharmaceuticals in Germany over the last few years (see Fig. 5) explains the high figure produced by the international comparison. In Germany, pharmaceutical expenses in the last 10 years continually increased more than the sum of basic wages did, i.e. the sum of wages and salaries from which health insurance premiums are drawn.

Generic drugs are not relevant for this rate of increase, as the Statutory Health Insurance funds' tenders for discount contracts result in below-average prices in international terms, with the result that patented drugs are instead causing it.

A comparison of EU prices by the AOK Research Institute shows that Germany remains frontrunner amongst the 250 most frequently sold patented drugs. In all countries studied, prices are between 18% (UK) and 35% (Sweden) lower than the public German catalogue prices after being adjusted for GDP. Even when considering all known discounts, the prices in the comparison countries are still 4% (UK) and 24% (Sweden) lower than the reduced German catalogue prices (Busse et al. 2017, p. 201f). One reason for this significant difference could be the rapid entry of pharmaceuticals into the German market. Germany generally has the largest share of medicinal products entering the market for the first time. The time between approval and sales launch is also shorter than in all other European countries. In 2015, the average time between approval and the date of first sale in Germany was 3.1 months. In the United Kingdom, for example, it was 4.5 months, in the Netherlands 13 months and in Greece even 25 months (QuintilesIMS 2017, p. 12).

Summarised briefly, there is a sophisticated benefit assessment performed when introducing innovations in Germany. A negotiation process regulated in detail by relevant legislation then follows this and includes predetermined escalation

mechanisms. All steps in this process lead to a quick implementation of innovations for positive healthcare, although not to a price that is suitable for the process, that is at least on average when compared internationally or that in any way considers the enormous potential sales for manufacturers in the German healthcare market. So what must be changed to, firstly, achieve pricing that is average when compared internationally and, secondly, prevent an increasing burden on the social security system because of a rate of increase that exceeds eligible wage growth?

3.1.2 Pharmaceuticals Focus 2: Lack of Pricing Regulation for Pharmaceutical Innovations in Germany

One important reason for the relatively low price reduction for Sofosbuvir was the disparity at the negotiating table between the pharmaceutical industry and the National Confederation of Regional Statutory Health Insurance Associations. The disparity is primarily the result of the manufacturer's monopoly position when it owns a drug with added benefits. This monopoly situation means that payers face a classic dilemma, because the potential threat of a manufacturer not to offer the corresponding medicine on the German market could result in deficient care. According to von Maydell and Carstensen (2016), manufacturers and payers currently apply the criteria described in Fig. 6 during negotiations on drug prices.

To shift the disparity in negotiations between the manufacturer and the payer in favour of the latter and add more weight to the argument for lower pricing, there are currently various additions being discussed in Germany. These include expansion of the benefit assessment used by the Federal Joint Committee for medicines into a cost-benefit analysis as normally used by the NHS in the United Kingdom. Furthermore, manufacturer research and development costs should only be factored in if they are the result of the manufacturer's own research (and not of research that is already government-funded) and divided proportionate to the share of the global market held. It is incomprehensible why research and development costs consistently receive new funding from every country in which a drug is approved. A third line of reasoning currently being discussed is the limited ability to prescribe innovations for subpopulations for which the benefit assessment has said there is a

Manufacturer criteria	Payer criteria
• Extent and probability of added benefit relative to appropriate, comparable treatment • Proportion of patients enjoying added benefit relative to the overall population for which the drug is approved • Comparable drugs • Comparable European prices	• potential savings on future illness costs • investment, research and development costs (depending on need and relevance) • threat potential of a market withdrawal

Fig. 6 Criteria when negotiating drug prices

tangible added benefit and, based on that, offer different pricing for such subpopulations (von Maydell and Carstensen 2016, p. 209ff).

3.2 *Price Setting by Health Insurance Funds and Service Providers Through Selective Contracts*

The selective contracts entered into by health funds vary dramatically in terms of content. Insured persons participate in the model of care offered by the selective contract and utilise the associated new benefits on a voluntary basis. Figure 4 shows that significant care issues should not arise when a selective contract is terminated because otherwise the selective contract's content would have to be transferred to standard insurance coverage. As the benefit assessment requires a long period of time in the Joint Federal Committee, selective contracts are ideal for temporarily covering new services with added benefit for patients.

In addition to content, the costs incurred by the benefits offered in a selective contract vary considerably. The Organisation of Professional Paediatricians, for example, offers a selective contract in telemedicine that has already been taken up by several funds. PädExpert networks paediatricians working in a general physician capacity with paediatricians who are qualified as or work as specialists. The aim of the network is to treat children and youths with chronic or rare diseases. Using PädExpert, the 'general practitioner' for the child or youth can consult a highly qualified paediatrician online and ask for support—from diagnosis through to potential options for treatment (Association of Professional Paediatricians (BVKJ) 2018). The model on offer improves care when compared to consultation with a single paediatrician, and at relatively low cost too. An evaluation would be needed to confirm whether it is also of benefit when compared to personal contact with a specialist paediatrician or whether there are increased benefits for overall care by consulting specialist paediatricians more frequently. Such an evaluation would be required before the model could be incorporated into standard healthcare, with the current selective contract acting as a useful complement to the system.

A model of care in another league entirely is proton therapy, which previously has only been covered in Germany through selective contracts. In Essen, for example, an ion beam therapy centre opened in 2015 for radiotherapy of cancer cells. Launching the centre cost approximately €140 million. The higher accuracy of this form of particle therapy seems to enable better treatment results than with traditional forms of radiation for certain types of cancer, e.g. hepatocellular, lung, pancreatic and oesophageal carcinomas and head and throat tumours. The cost of treatment is triple that for conventional cancer therapy and comes in at round €18,000.

Although both of the aforementioned selective contracts are completely different and cover entirely different areas of medicine, pricing is based solely on negotiations between the service provider and the fund offering the benefit. Standard insurance coverage offers alternatives for both forms of treatment that are sufficient, suitable

and efficient for the efficiency dictate for Statutory Health Insurance funds per SGB V Section 12. The differing level of severity amongst the patients who need treatment and have access to one of the two selective contracts then, however, leads to a difference in the benefits offered if a fund has not entered into these selective contracts. Where proton therapy is indicated, the mechanisms for cost reimbursement described in Sect. 3.2 will probably come into effect, whereas such mechanisms will not be available for patients who wish to make use of the telemedicine services offered by PädExpert.

3.3 Pricing Based on the Reimbursement Principle of Private Health Insurance and for Services Paid Directly

Individual doctors may offer services that exceed the scope of the Statutory Health Insurance benefits catalogue. As these services are not covered under the benefit-in-kind principle, patients must themselves pay the doctor directly for these services. In the German healthcare system, these services have come to be known as 'individual healthcare services', with the services on offer being many and diverse. For any individual healthcare service to have gained such status, either the Federal Joint Committee must have not (yet) found added benefit at the current point in time—as these services would otherwise be incorporated into standard coverage—or the service must have received a negative assessment. Individual healthcare services are offered by doctors on a private basis and may be billed using the Fee Schedule for Doctors (GOÄ) if the specific service is listed on it. As the rate used by the doctor to multiply the fee listed on the schedule varies based on time and effort for the service, so too does the price paid by the patient, which means that supply and demand determine the cost for a patient when they go to the doctor's practice. Should the service in question not be listed on the schedule, the doctor has the option of billing for a service of similar value in terms of nature, expense and time required. This mechanism strengthens the options a doctor has to set individual prices. Treating individual healthcare services and innovations in the same manner is difficult because a service rejected by the Joint Federal Committee can surely no longer be seen as an innovation. The same service delivery and pricing conditions apply to individual healthcare services as with other innovations that are covered by Private Health Insurance. Setting prices based on the services of comparable value results in there only being hurdles when introducing services that are extremely expensive or contain something highly unusual. Market entry is therefore easier than under the Statutory Health Insurance system.

While individual healthcare services mean that persons with Statutory Health Insurance have a direct financial burden, innovations have a more indirect effect on Private Health Insurance policyholders via premium and excess adjustments.

Services rendered outside of the standard insurance system gain particular importance if a patient is suffering from a life-threatening illness, all approved treatment

methods have been tried and there is still a method for which the Federal Joint Committee has not yet issued a final statement. As scientific evidence of the added benefit of an innovation may sometimes take years to collect, situations such as the preceding one may also arise in the interim period when the medical benefit of an innovation is still being scientifically evaluated. In the German Out-of-Hospital Care sector prior to 2006, there was a problem whereby patients with serious illnesses wanted to utilise services for which the Federal Joint Committee had not yet taken a decision or for which there were not yet any sufficient studies that could be used as a basis for a final decision. The Federal Constitutional Court issued the so-called 'Santa Claus judgement' on 6 December 2005 (case no.: 1 BvR 347/98) for this situation. Under this judgement, persons with Statutory Health Insurance and a life-threatening illness for which the standard system does not offer a method of treatment can apply for non-standard services that offer a not-entirely-remote prospect of recovery or improvement in the disease's progression. This judgement by the Federal Constitutional Court was a milestone in the German healthcare system's handling of medical innovations. It is now the responsibility of Statutory Health Insurance funds to assess the described situation in each individual case and cover the costs for the insured person if a positive decision is made. On 1 January 2012, the Federal Government's *Act on the Improvement of Healthcare Structures in the Statutory Health Insurance System* integrated the contents of the 'Santa Claus judgement' into the new Section 2(1a) of SGB V and, in doing so, filled a difficult hole in healthcare coverage with new methods of treatment. Thanks to the balanced wording of Section 2(1a), legislators have succeeded in, firstly, maintaining the important limitations on market entry provided by evidence-based benefit assessments by the Federal Joint Committee and, secondly, addressing the individual interests in treatment alternatives for patients with life-threatening illnesses.

4 Final Observation

Medical progress in the form of innovations must be provided to all insured persons even if the system of health insurance is publicly financed. At the same time, innovations should not be allowed to destabilise a public health insurance system because of high costs. If it is assumed that innovations at least make treatments more expensive over the short term, then the design of a healthcare system will inevitably involve a conflict between the promotion of medical progress and the necessity of having a realistic model for funding it.

Benefit exclusions are not available as instruments for rationalisation in the German healthcare system, which means that the question arises of whether the described instruments are enough to allow innovations without endangering the system's financial viability. The arguments concerning the introduction and financing of innovations that have been presented in this article can be summarised with the following theses:

- The German healthcare system offers various options for introducing innovations.
- There is a successful system for assessing the benefit of innovations presided over by the Federal Joint Committee.
- The demand for evidence-based medicine means that time is required for evaluation. Selective contracts and one-off, situation-dependent decisions on reimbursement can be used to provide innovations in the mean time while innovations are evaluated.
- Pharmaceutical innovations in particular are integrated into care very rapidly.
- The payer (i.e. health fund) and the service provider frequently negotiate prices for innovations based on their added benefit.
- The German healthcare system pays very highly for innovations in comparison to other countries.

The German social security system received sufficient funding in 2017 thanks to a high employment rate. Consequently, the high prices for implemented innovations have not yet led a discussion on rationalisation. Changes to the age pyramid in Germany and an associated reduction in the number of employees paying into the social security system will mean that the finances of the Statutory Health Insurance system will take a noticeable turn for the worse over the coming years. For this reason, the disparity between payers and manufacturers during price negotiations should be counteracted in the future and the payer's position in price negotiations bolstered by means of legislation. This process can be supported even further by more strongly establishing cost-benefit analyses during the evaluation of innovations.

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Clinical Evaluation of Medical Devices in Europe

Hans P. Zenner and Mijo Božić

Abstract The new EU Regulation (EU) 2017/745 on medical devices, which took effect on May 26, 2017, is crucially important for medical device manufacturers and CE certification, as well as the recertification of their products. On clinical evaluation, the present contribution discusses the main differences between EU Directive 93/42/EEC and EU Regulation 2017/745 in the following six areas: (i) Stronger requirements for clinical safety and evidence of clinical efficacy, (ii) Classification, (iii) Clinical evaluation, possibly including clinical trials, (iv) Post-market clinical surveillance, (v) Clinical documentation and reporting, and (vi) Introduction of the European Commission's scrutiny procedure.

1 Introduction

The new EU Medical Device Regulation (MDR)[1] is of crucial importance for manufacturers of medical devices when it comes to certification and recertification of their products, with the exception of in vitro diagnostic medical devices. In addition to comprehensive extensions, the MDR combines provisions of the Directive 93/42/EEC concerning medical devices (MDD) and Active Implantable Medical Devices Directive 90/385/EEC (AIMDD), which it supplemented. The older MDD and AIMDD remaining in force until 2020 contain provisions for putting a medical device into service based on clinical evaluation.

[1]For the main reasons behind the adoption of the new Regulation on medical devices see for example Gemke (2017) p. 15 or Handorn (2018) p. 95.

H. P. Zenner (✉)
HP Zenner Clinical Evaluation, Tübingen, Germany

The University of Tübingen, Tübingen, Germany
e-mail: office@hpzenner.de

M. Božić
The University of Tübingen, Tübingen, Germany
e-mail: Mijo.Bozic@med.uni-tuebingen.de

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Unlike the directives, the new EU regulation is directly applicable in all EU states. An additional adaptation of national laws on medical devices like the Mediziniproduktgesetz (MPG) in Germany remains possible.

A separate EU regulation applies to in vitro diagnostics—the Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) from April 5, 2017, replacing the hitherto valid Directive 98/79/EC on in vitro diagnostic medical devices.

The new MDR and certification procedure resulting from this are much more complex than the procedures previously applied under MDD/AIMDD/MPG. Compared to the MDD, the MDR contains a hundred additional provisions. The number of annexes has increased, and there is a series of further legal documents, the preparation of which is still ongoing.

However, there are no significant differences in many areas. Despite more detailed wording, no entirely new requirements are foreseen.

2 Results and Discussion

2.1 Regulatory Sphere

The MDR will apply from May 26, 2020. The manufacturers will have to follow the MDR when placing medical devices on the market for the first time. Products already approved on the market must be adapted to MDR no later than 5 years after the date of application of MDR. For products approved under MDD/AIMDD/MPG from the second quarter of 2020, this period will be shortened to 4 years. If there is no new EU declaration of conformity because, for example, the clinical evaluation in the technical documentation is incomplete, the EU certificate may be refused.

Each medical device is assigned to a particular class. This classification system is based on the potential hazard, type of application, and approval requirements. Classification was previously performed under rules set out in MDD/AIMDD.

In the case of a first-time CE certification under the MDR, the medical device (if applicable, also some products intended for non-medical use) is assigned to a class according to 22 classification criteria set out in Annex VIII “Classification rules”. Annex VIII to EU MDR also provides for a different classification. In the course of MDR, the previous assignment of some medical devices to a particular class will be changed compared to the procedure applied under MDD/AIMDD, which is expiring in 2020.

Two new MDR classification rules for active medical devices are particularly notable. Under Rule 11, stand-alone software is hardly assigned to class I any longer, as most software falls at least in class IIa or higher, especially if the software can cause death or persistent adverse health effects. From class IIa on a notified body involvement is required. Under Rule 22, a number of systems (e.g., closed-loop feed-back systems: invasive control systems, such as active therapeutic devices with

integrated or embedded diagnostic function) and implants (e.g., orthopedic joint and spinal implants) previously assigned to class IIb are now supposed to meet the more stringent requirements of class III. All products that contain or consist of non-material are also affected (Rule 19). The same holds for invasive devices with respect to body orifices, which are intended to administer medicinal products by inhalation (except surgically invasive devices; Rule 20), as well as devices composed of substances or combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body (Rule 21). Devices manufactured utilizing animal or human tissue or drugs (e.g., insulin) are subject to more stringent requirements.

Under the MDR, manufacturers of products that have been put into service under MDD/AIMDD must timely review the new classification rules and update their technical documentation, including clinical evaluation and possibly including a clinical trial. Class IIa, IIb, and III medical devices may require a systematic clinical reassessment. In doing so, they must consider the new provision on the equivalence of the products, as well as the options under which a clinical trial can legitimately be dispensed. If such a review is omitted, the CE certificate may be invalid.

Under the new EU MDR, this evidence of the clinical efficacy of a medical device and patient safety is generally provided by a clinical evaluator who is a specialist in the relevant medical specialty possessing personal clinical experiences in the application of the specific or similar medical devices and/or in the diagnosis and management of the conditions intended to be diagnosed or managed by the device.[2]

More often than before, a clinical trial will be required. The MDR sets out in detail how clinical evaluations and clinical trials should be performed. Clinical evaluation of medical devices is part of the technical documentation relating to a medical device. At the same time, the manufacturer must submit a clinical development plan, including a plan for post-market clinical follow-up.

An explicit rule relating to non-critical products, which would allow a waiver of clinical evaluation, does not exist. A waiver of clinical data for a clinical evaluation, however, is basically permitted for absolutely non-critical products, such as screws, wedges, plates, and instruments.

In addition to the EU MDR, there are other regulations and standards that require a clinical evaluation of medical devices. These include the established MEDDEV guidelines[3] to ensure compliance with the old guidelines.

[2]MEDDEV 2.7/1 rev 4, p. 15: "With respect to the particular device under evaluation, the evaluator should in addition have knowledge of: - the device technology and its application; - diagnosis and management of the conditions intended to be diagnosed or managed by the device, knowledge of medical alternatives, treatment standards and technology (e.g. specialist clinical expertise in the relevant medical specialty)".

[3]European Commission's guidance documents to assist stakeholders in implementing directives related to medical devices. List of Guidance MEDDEVs available on: https://ec.europa.eu/growth/sectors/medical-devices/guidance_en, accessed on July 28th 2018.

Furthermore, not only the manufacturers, but also the suppliers, importers, distributors, and sales organizations (economic operators) can be affected. Exceptions in this regard are economic operators of component parts, such as screws, wedges, plates, and instruments.

If comparable devices are used for clinical evaluation, then these reference products must be technically, biologically, and clinically equivalent to investigated products being subject to evaluation. As with the MEDDEV 2.7/1 rev 4 there should be no clinically relevant differences. Manufacturers must demonstrate an equivalence by providing the data for the reference product. Class III and implantable devices can only refer to data of comparable validity if the manufacturer has the reference devices in its possession and able to generate the necessary data. As a rule, they (manufacturers) need contractually regulated access to all data and test results relating to the reference product.

In addition to the new MDR clinical trials of medical products must be planned and performed under EN ISO 14155[4] "Clinical investigations of medical devices for human subjects - Good clinical practice" and other relevant regulations.[5]

The reporting system includes the results of the clinical evaluation, possibly including (if applicable) the clinical trial protocol documents, investigator's brochure, patient information, and informed consent, as well as additional reports and plans, such as the Clinical Development Plan and the Summary of Safety and Clinical Performance. The MEDDEV 2.7/1 rev. 4 also sets out requirements to be met. The clinical evaluation combined with risk management can be tested as well.[6] Furthermore, documents on clinical post-market surveillance are required.

Post-market Surveillance is a continuous process that updates the clinical evaluation (Annex XIV Part B). This applies in particular to class III medical products and implantable devices that are subject to more stringent clinical requirements as set out in EU MDR. Clinical post-market surveillance includes:

- Post-market Clinical Follow-up (PMCF)
- Other studies
- Vigilance system/reporting of incidents to responsible national authorities—in Germany, the Federal institute for Drugs and Medical Devices
- Customer contacts
- Screening of scientific literature and other sources of clinical data
- Identifying possible systematic misuse or off-label use of the device
- Continuous review and update of clinical evaluation.

[4]ISO 14155 is now a single standard that consolidates the previous 14155-1 and ISO 14155-2. ISO 14155 does not apply to in vitro diagnostic medical devices.

[5]These include national regulations, such as the German Regulation on Clinical Trials with Medical Devices and the German Medical Devices Safety Plan Regulation. On the other hand, the following provisions will no longer apply: Medical Devices Act sec. 20 ff., and the Ordinance on Clinical Trials with Medical Devices.

[6]Such a test is meant to show if the results of clinical evaluation are consistent with the statements in the risk management file.

Additional reports and plans under the MDR include the Post-market Surveillance Report, Periodic Safety Update Report (PSUR), and Summary of Safety and Clinical Performance. As part of the PMCF for class III and implantable devices, the safety/clinical evaluation/performance summary reports must be updated at least once annually.

An important issue in this context is the reporting of serious incidents.[7] They should be reported without delay within the framework of the vigilance procedure. 'Incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error because of ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side effect (MDR Art. 2 no. 64).

'Serious incident' within the meaning of MDR Art. 2 no. 65 means any incident that directly or indirectly led, might have led, or might lead to any of the following:

(a) The death of a patient, user, or other person
(b) The temporary or permanent serious deterioration of a patient's, user's, or other person's state of health
(c) A serious public health threat.

Responsible national authorities (in Germany, the Federal institute for Drugs and Medical Devices, BfArM) evaluate the risk resulting from the incident. At the same time, the manufacturer undertakes corrective measures in cooperation with the national authorities to eliminate existing risk.

Manufacturers are also required to report any significant increase in the frequency or severity of incidents that are not serious or are expected to have undesirable side effects that could have a significant impact on the benefit-risk analysis (Art. 88 (1) MDR). Furthermore, serious adverse events (SAEs) must be reported in the course of a clinical trial or performance evaluation (Medical Devices Safety Plan Ordinance, sec. 3 (5)).

2.2 Classification of a Medical Device

Classification has a significant impact on the necessity and extent of a potentially required clinical evaluation, including clinical trials and clinical post-market surveillance.

The MDD contains 18 rules, which are divided into rules relating to non-invasive, invasive, and active products, as well as special rules. Each MDD/AIMDD medical device is assigned to one of four classes based on the hazard potential, type of application, and licensing requirements.

In the case of a first time CE certification and recertification according to MDR the classification of a medical device—and some products not intended for medical

[7] See more on these issues in Lippert (2018), pp. 299–303.

use[8]—will be conducted according to 22 classification criteria set out in Annex VIII "Classification criteria".

In the case of CE certification (2020 at the latest) or recertification according to MDR (no later than 2024), the assignment of some medical devices to a particular class will change compared to the currently applicable MDD/AIMDD expiring in 2020. Two new classification rules relating to active medical devices should be mentioned.

Software intended to provide information that is used to make diagnostic or therapeutic decisions—especially if such decisions have an effect that may cause death or an irreversible deterioration of a person's state of health—is classified as class IIa and higher.

A number of systems (e.g., closed-loop feedback systems: invasive control systems, such as active therapeutic devices with integrated or embedded diagnostic function) and implants (e.g., orthopedic joint and spinal implants[9]) previously assigned to class IIb, are now expected to meet the more stringent requirements of class III. Active therapeutic devices with an integrated or incorporated diagnostic function, which significantly determines patient management by the device, such as closed loop systems or automated external defibrillators, are classified as class III.

All devices incorporating or consisting of nanomaterial (Rule 19); all invasive devices with respect to body orifices, with the exception for invasive devices, which are intended to administer medicinal products by inhalation (Rule 20); and devices that are composed of substances or of combinations of substances that are intended to be introduced into the human body via a body orifice or applied to the skin and that are absorbed by or locally dispersed in the human body (Rule 21), are affected as well.

All devices manufactured utilizing tissues or cells of human or animal origin, or their derivatives (e.g., insulin) will have to meet more stringent requirements.

Not only the manufacturers, but also suppliers, importers, distributors, and sales organizations (economic operators) included in a supply chain, can be affected.

[8]Under the MDR, a total of six product groups can be optionally marked with "CE". They are listed in Annex XVI "Products without an intended medical purpose". A prerequisite is that they meet requirements relating to medical devices provided for in the EU MDR.

[9]Prostheses for all joints and many, if not all, joint prostheses in the body are currently assumed to fall in future into the class III. It is not clear if this (rebuttable) presumption applies to all joints equally. The MDR significantly expands the range of joint implants that were already classified higher by Directive 2005/50/EC. Under Rule 8, partial joint replacements and other joint implants also fall into class III. For manufacturers, it may be helpful to think in advance of whether their products affect joints as defined by the MDR, e.g., the hand or tarsal bones or temporomandibular/jaw joint. Spinal disc replacement implants and implantable devices that come into contact with the spinal column are assigned to class III. However, the phrase "implantable devices that come into contact with the spinal column" raises questions. Strictly speaking, it could also include bone cements for vertebral body erection. An exception applies to (ancillary) components, such as screws, wedges, plates, and instruments. It is not yet clear how a rod or screw system should be classified and what is meant by a wedge in spinal column surgery. Therefore, further publications are needed to make the content, meaning, and scope of this rule more precise.

Their activities can be subjected to auditing by notified bodies and, thus, be part of a clinical evaluation. The exception in this regard applies to manufacturers' economic operators dealing with minor components, such as screws, wedges, plates, and instruments.

The MDR is a novelty, as it provides for manufacturers to submit a clinical development plan, including a plan for clinical follow-up. Consequently, in addition to the normative and technical requirements relating to a new product, the specification will have to include evidence of clinical safety, minimal possible stress, and effective benefits.

The planning and execution of an essential part of preclinical tests relating to a new medical device will of course be influenced by the subsequent clinical use of the product in question. Therefore, in the course of examining the technical documentation, the notified body will also consider the clinical interpretation of the preclinical tests relating to medical devices.

2.3 Clinical Evaluation of the Medical Device

The new EU regulation significantly increases the requirements regarding the burden of proof for safety and efficacy by means of a clinical evaluation and, if applicable, the manufacturer's own clinical examination. Under the MDR, this proof of the clinical efficacy of a medical device and patient safety is generally performed by a clinical evaluator by means of a specialist clinical evaluation of medical devices. The clinical evaluation of medical devices is a substantial part of the technical documentation for each medical device. For some medical devices, clinical evaluation will also require a complex clinical trial. Clinical trials will tend to be the exception rather than the rule. In a large number of cases in the future, clinical evaluation will also be performed without clinical trials.

The evaluation includes evidence of the clinical function being claimed, including the effect size and related efficacy in patients. Notified bodies may also consider further claims of the manufacturer in their examination, which may then also be clinically proven. Further, risk-benefit analysis will be required.

Further clinical aspects may include, for example hygiene requirements up to the sterilizability, biocompatibility, impermeability, stability, or measuring the accuracy of a product. Issues such as compatibility with other products, including third-party products, safety, and operating instructions, and training programs for healthcare professionals may be tested as well.

The evaluation is completed by assessment of the acceptability of the benefit/risk ratio. In this final consideration of risk, burden, and benefit, the benefits must clearly outweigh the risks.

Procedure Without Clinical Trial A benefit-risk analysis and the related assessment are based on the collection and review of the data and literature. The clinical

evaluation is based mostly on clinical data,[10] which must already exist. Necessary data and literature selection are determined by whether the medical device is novel or comparable to an already existing technology. For existing data, clinical evaluation will be based primarily on data from literature databases recognized by the US Federal Drugs Agency (FDA) and/or BfArM notifications, or data from competing companies.

As required by MEDDEV 2.7/1 rev. 4, the reference product must be technically, biologically, and clinically equivalent to a product in question to such an extent that there are no clinically relevant differences. Moreover, the manufacturers must demonstrate an equivalence by providing the data for the reference product. In the case of class III and implantable devices, the manufacturer can only refer to data of comparable validity if it has the reference devices in its possession and is able to generate the necessary data. As a rule, they need contractually regulated access to all data and test results relating to the reference product. Otherwise, the company will have to submit its own clinical results.

In contrast to the integrated software of a medical device, which is clinically evaluated together with the medical device, stand-alone software[11] is characterized by having only two essential interfaces:

1. Graphical user-product interface (GUI)
2. Product (data) interface.[12]

Unlike pharmaceutical law, medical device law protects not only the patient, but also users and third parties. The scope of protection is broader, which usually requires more effort related to the clinical risk assessment of medical devices.

The results of the clinical evaluation significantly influence risk management. Only the clinical evaluation can support the assumptions of benefit and, thus, the acceptance of the benefit-risk ratio as presented in the risk management file. The clinical evaluation must also support the assumptions in the risk management file related to risk. The results of the post-market clinical follow-up should also be considered in clinical evaluation and risk management.

A clinical evaluation without clinical data may apply to some non-critical products only. The exception shall be justified by a clinical evaluation demonstrating compliance with the essential requirements by means of a technical performance assessment, product testing, and preclinical assessment, considering the features of the body-product interaction, the intended clinical performance, and the manufacturer's information.

[10]Regarding the clinical evaluation requirements for medical devices, the MDR is a novelty as it provides that manufacturers must produce a clinical development plan, including a post-market clinical follow-up plan.

[11]See more on medical device software in Lücker (2018), p. 282 ff.

[12]See more on clinical evaluation of stand-alone software in Terhechte (2018), p. 324 ff.

Clinical Trials of Medical Products If sufficient clinical evidence is not available to demonstrate the required clinical safety and performance of a product, clinical trials must be performed. Novel products, implantable medical devices, and class III devices must always undergo a clinical trial. In particular cases, this can be waived if existing clinical data are sufficient. A clinical trial is to be performed without exception on:

- New indication
- New anatomical region of the human body
- Modifications to a product being placed on the market/put into service when these might have a significant effect on safety or efficacy
- Significant extension of application time
- Insufficient literature on effectiveness/efficacy and risks.

Clinical trials on medical products must be planned and performed under EN ISO 14155 "Clinical investigations of medical devices for human subjects - Good clinical practice" and other relevant regulations.[13]

The requirements of EN ISO 14155 are comparable to those of the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use—Guideline for Good Clinical Practice (ICH-GCP) for clinical trials with medicinal products. Further provisions to be followed can be found in the German Regulation on Clinical Trials with Medical Devices ("Verordnung über klinische Prüfung von Medizinprodukten", MPKPV) and in the German Medical Devices Safety Plan Regulation ("Medizinproduktesicherheitsplanverordnung", MPSV).

The conduct of clinical trials with medical products and IVD requires approval by the responsible national authorities. Thus, In Germany this requires under MPG sec. 20 (1), approval by the responsible higher federal authorities, such as the Federal Institute for Drugs and Medical Devices (BfArM), or the Federal Institute for Vaccines and Biomedicines (PEI, Paul Ehrlich Institute), and a favorable opinion by a legally approved ethics committee, such as of a public law Chamber of Medicine (Landesärztekammer) or of a university hospital (Universitätsklinikum). Applications must be submitted via the German Institute of Medical Documentation and Information (DIMDI).

2.4 Documentation and Scrutiny Procedures

In addition to the medical or clinical quality of the clinical evaluation, documentation and traceability form part of the complex and demanding reports and plans.

The reporting system includes the results of the clinical evaluation, including any applicable clinical trial protocol documents, investigator's brochure, patient

[13] See footnote number 6.

information, and informed consent, as well as additional reports and plans, such as the Clinical Development Plan and the Summary of Safety and Clinical Performance. The MEDDEV 2.7/1 rev. 4 also sets out requirements to be met. By the notified body accordance of the risk management with the clinical evaluation may be checked as well.[14] Furthermore, documents on clinical post-market surveillance are required.

As far as notified bodies are concerned, the supervision of their activities by the competent authorities will be intensified, which may result in increased documentation burden and the growing pressure of self-justification on their side.

This includes the new scrutiny procedure, which focuses on reviewing the submitted clinical evaluation. To meet this task, the notified body will create a CEAR for implantable class III products and active class IIb products intended to administer drugs/medicinal products in the human body based on the clinical evaluation, with exceptions for cases in which recertification or mere modification is being carried out. The CEAR will be submitted to the Medical Device Coordination Group (MDCG), an expert committee of the European Commission, which must decide within 21 days whether it will present a scientific opinion on the CEAR.

If applicable, the panel must provide the scientific opinion on the CEAR within 60 days. The notified body must consider the scientific opinion by making its decision and, if necessary, grant the certificate with restrictions or conditions. If the opinion is not completed by the deadline, the notified body may proceed with the certification with no amendment.

2.5 Post-Market Clinical Follow-Up (PMCF)

Following the placement of a medical device on the market, the EU MDR requires a manufacturer to carry out PMCF continuously to assess the benefits and risks related to the device. The main purpose of PMCF is to identify potential long-term risks that could not be detected within the pre-market clinical evaluation. The results of the follow-up should be considered within the continuous update of the clinical evaluation and risk management. Clinical evaluation is therefore an ongoing process that must be repeatedly documented through regularly reviewed plans and reports by the notified body.

To assess potential safety risks, manufacturers need to gather clinical data continuously. The manufacturer is supposed to create a structured system of long-term follow-up including clinical trial results, registers, controls, or spot checks.

The documentation should comprise essential updates, including but not restricted to additional reports and plans such as a post-market surveillance report, PMCF report, Periodic Safety Update Report (PSUR), and Summary of Safety and Clinical Performance. For specific product groups, manufacturers must submit

[14]See footnote number 7.

safety/clinical evaluation/performance summary reports relating to the safety and performance of their products on an annual basis. This applies in particular to class III medical devices and implantable products, which are subject to more stringent clinical requirements for PMCF.

Certain incidents during post-market surveillance and during clinical trials are to be reported to the National Authorities i.e. in Germany the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI) via the electronic system for vigilance and post-market surveillance (currently DIMDI). 'Incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error because of ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side effect (MDR Art. 2 no. 64).

The EU MDR extends the notified body's powers regarding post-market clinical surveillance. Unannounced audits, spot checks, and product tests strengthen the role of the EU in implementing procedures and help reduce risks resulting from unsafe medical devices.

2.6 Recertification

After first-time certification, the notified body carries out annual reaudits. Moreover, medical devices must be recertified by notified bodies no later than 5 years after the CE mark is awarded. Upon successful completion of the (re)audit, a product is awarded with a renewed Certificate of Conformity. Exceptions are currently being negotiated.

Under the still applicable MDD/AIMDD rules, recertifications by the notified bodies are only possible until the end of the transitional period ending on May 26, 2020. From that date forward, manufacturers must be able to produce an EC certificate under the new MDR for the recertification of medical devices. Thus, manufacturers have the option to apply for an extension of their existing certificates immediately prior to May 26, 2020. These would be valid then until the middle of 2024 at the latest.

Under the MDR, proof of the clinical effectiveness of a medical device and its safety in the course of recertification should be provided by means of a specialist clinical evaluation only in exceptional cases. A waiver of clinical data for clinical evaluation is basically permitted only for non-critical products, such as screws, wedges, plates, and instruments.

The evaluation is completed by assessing the reasonableness of the benefit/risk ratio. In this final balance of risk, burden, and benefit, the benefits must clearly outweigh.

The benefit-risk analysis and assessment is based on the collection and review of data and the literature. The clinical evaluation is based on clinical data from

recognized literature databases, FDA and BfArM notifications,[15] personal data from PMS, or data from competing companies.

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[15]BfArM notifications, FDA reports on problems (Manufacturer and User Facility Device Experience, MAUDE database), clinical trial results being published, e.g., in PubMed (only clinical data from "peer-reviewed" publications can be considered), feedback from the field.