Therapeutic concepts

Proposing a new regulatory pathway for combination therapies

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“Nichts ist so beständig wie der Wandel”

Heraklit von Ephesus (etwa 540 - 480 v. Chr.)

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Table of contents

List of abbreviations

AFSSAPS	Agence française de sécurité sanitaire des produits de santé
AGREE	Appraisal of Guidelines for Research and Evaluation
ADR	Adverse drug reaction
AIMDD	Active implantable medical devices directive
AMG	Arzneimittelgesetz (Medicinal Product Act, German Drug Law)
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (Federal Office of Consumer Protection and Food Safety)
CDx	Companion diagnostic
CHMP	Committee for Medicinal Products for Human Use
CML	Chronic myelogenous leukaemia
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CRF	Code of Federal Regulations (USA)
CTD	Common Technical Document
CYP	Cytochrome P450
DCP	Decentralised Procedure

DELBI	Deutsches-Leitlinien-Bewertungsinstrument (German tool for appraisal of clinical practice guidelines, German adaption of AGREE)
DNA	Deoxyribonucleic acid
EBM	Evidence-based medicine
EC	European Commission
EEA	European economic area
EU	European Union
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GKV	Gesetzliche Krankenversicherung (German statutory health insurance)
HER	Human Epidermal Growth Factor 2
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IMDRF	International Medical Device Regulators Forum
IQWiG	Deutsches Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (German Institute for Quality and Cost-Effectiveness in the Health Care Sector)
IVD	In vitro diagnostic
IVDD	In vitro diagnostic directive
MA(H)	Marketing authorisation (Holder)

MDD	Medical devices directive
MDR-TB	Multidrug-resistant tuberculosis
MRP	Mutual Recognition Procedure
NB	Notified Body
NIH	National Institutes of Health (USA)
NYHA	New York Heart Association
ODA	Orphan Drug Act (USA)
OOPD	Office of Orphan Products Development
PMA	Premarket approval
PMN	Premarket Notification
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
RMS	Reference Member State
SGB V	Sozialgesetzbuch (German Social Code, Book 5)
SmPC	Summary of Product Characteristics
SNP	Single nucleotide polymorphism
SOC	Standard of care
TB	Tuberculosis
UDI	Unique Device Identification
WHO	World Health Organization

1 Abstract

Medicinal products are a special good. Under the right circumstances, they can help by preventing, alleviating and curing diseases and even save lives. On the other hand, medicinal products under the wrong circumstances can have serious consequences by remaining either ineffective or causing adverse effects that may range from mild discomfort to fatal reactions. In order to protect society from possible harms special regulations are required for a secure handling of medicinal products. In addition to country specific medicines regulations the EU has developed its own legal framework for medicinal products over the years to harmonize the requirements across the European countries. The requirements for market authorisation for products for human use are set in Directive 2001/83/EC. Besides this Directive, several other regulations exist on European or Member State level that ensure high standards and safety in the development, testing, manufacturing, trade, advertising and use of medicinal products. The entirety of the regulations concerning medicines are intended to protect society, to identify the right circumstances under which medications are beneficial and to ensure an overall high quality of the products.

The scope of this thesis is to explain potential limits of the current system and suggest a possible new approach to overcome certain limits by expanding the current legislation. It gives an overview on the current regulatory system, particularly the requirements for market authorisation of medicinal products for human use.

A particular limit of the existing regulation that was identified in this thesis is the remote possibility of the approval of combination therapies, meaning therapy in which more than one medication is used. Usually, active agents are evaluated in terms of their individual safety and efficacy. For exceptional cases, guidelines and regulations exist for the approval of specific combinations, such as fixed combinations, which includes two or more active agents within a single pharmaceutical form. The free combination of individual medications or other medical products is however currently not reflected in the legal framework. Yet combinations of different medicinal products are widely use in the medical

practice and are in fact essential for the treatment of several diseases but this is not taken into account in the approval process. Thus, a gap between treatment reality and regulatory approval exists. A possible approach for closing this gap is presented in this thesis: the introduction of "therapeutic concepts". Therapeutic concepts describe the marketing authorisation of a treatment regime consisting of a combination of two or more individual medicinal products for a defined condition or a combination of a medicinal product and a companion device that is compulsory for diagnosis or decision-making whether the medicinal product in question is appropriate for treatment that have been developed and studied together. Products included in the therapeutic concept may or may not have been marketed prior to the approval in the therapeutic concept. Therapeutic concepts can be regarded as an integrative approach based on the current framework. The approach would be an addition to the present legislation to meet existing needs. Compared to fixed combinations the free combinations of a therapeutic concept would offer additional benefits, such as better dosage adjustment based on the individual patient's need.

At present, combinations of medicinal products in certain conditions are for example described in medical guidelines. However, medical guidelines differ greatly in quality from each other, having the status of recommendation and cannot be equated with a market authorisation. Defined regulations for a market authorisation of combinations based on evidence obtained from clinical studies provide a greater knowledge and control on combinations in use and an improved legal certainty compared to medical guidelines.

Combinations of different medicinal products have been commonly used as treatment systems, often in complex or multifactorial diseases, such as bacterial infection (e.g. tuberculosis), cardiovascular diseases or cancer. Current research focuses now on genetics-associated diseases, which also often require a complex combination of diagnostics and medicine. This field of research is referred to as personalized medicine as the patient's individual disease and metabolic markers are analysed to stratify patients into subgroups which receive a therapy based on their genetic profile that is more likely to be effective compared to an alternative medication. Due to the complexity of the treatment approach and the involvement of both medicinal products and diagnostics, which are mainly medical devices, the

field of personalized medicine would profit from approved therapeutic concepts and would be a possible area for the application of therapeutic concepts.

The link between medicinal products and medical devices, which are actually subject to different regulations, can be strengthened by therapeutic concepts. The connection between medicinal products and a diagnostic whose result determines whether the medicinal product is effective is of particular importance as both products contribute to the overall treatment outcome and should therefore be considered as a unit.

For a possible implementation of therapeutic concepts as a new regulatory approval pathway, several aspects have to be considered. The design of pivotal studies for the approval process should allow as much evidence on safety and effectiveness as possible without too many control arms in the study as this might be too time and cost-consuming and requires a high number of participants. Labelling, reimbursement and risk management are particularly challenging for therapeutic concepts. Labelling must be designed in such a way that the individual medicinal product can be identified as part of an approved therapeutic concept. Risk management und vigilance plans should be more extensive to reflect to additional risk caused by the combination.

Therapeutic concepts as a new regulatory pathway offer a regulatory change from which all stakeholders would profit and which has various possible fields of application.

2 Methods and Material

The research methodology applied for this thesis is a combination of literature research and comparison of the legislation that includes laws, guidelines, regulations and standards.

Researched literature is retrieved from publicly available online databases for medical literature. PubMed is a metadatabase developed by the National Center for Biotechnology Information (NCBI, USA) and is one of the largest and most widely used databases for biomedical literature. PubMed gives free access to the database Medline, a U.S. National Library of Medicine (NLM) bibliographic database covering literature on medicine, pharmacy, dentistry, veterinary medicine, psychology, public health, biology, biochemistry, molecular and genetic information. Medline comprises more than 22 million life science journal articles from more than 5,600 journals worldwide to date.[1]

Google Scholar is a search engine for scholarly literature in general and thus gives a broader range for search.[2] It was found to index similar literature as Medline but adds additionally own citations from other sources such as presentations, books and journals not covered by Medline or PubMed. Search strategies were adapted according to the line of research. Starting point was research on “combination therapy” to identify commonly used combinations and approaches how and why specific combinations are used. The search revealed the complex and heterogeneous nature of this subject that led to the focus on “personalized medicine” and “co-development” for further investigation.

Parallel to scientific literature the legal basis for the corresponding subjects was examined. The consideration of the legal framework provided information on the current and/or prospective regulations applicable for pharmaceuticals and medical devices. Information were gathered concerning regulations mainly in Europe and Germany as well as the USA to provide different aspects and approaches on handling pharmaceutical and health related issues. EudraLex is the collection of rules governing the medicinal products in the European Union and serves as main

[1] NIH. Fact Sheet Medline. 23 Jun 2016 [Accessed on: 26 Jun 2016]. https://www.nlm.nih.gov/pubs/factsheets/medline.html.
[2] Google. About Google Scholar. [Accessed on: 26 Jun 2016]. https://scholar.google.de/intl/de/scholar/about.html.

source for research. The ten volumes of EudraLex are also available online and deal with pharmaceuticals for human and veterinary use, marketing authorisation, clinical trials, manufacturing, and vigilance.[3] Information on country specific legislation can usually be retrieved by accessing material available from competent authorities.

Decisions of German courts for relevant issues were obtained from www.dejure.org, an internet based platform that comprises more than 1,000,000 court decisions with references to the corresponding laws.[4]

Comparison of rules and regulations over time allows conclusions on the overall developments in the area of medicinal products and reflects the progress of the scientific evolvement. In conjunction with the focus of the scientific literature and position papers by interested parties, the current needs and demands of the various stakeholders, which are drivers for change in the regulatory landscape, can be recognized. Based on the results of the literature and regulation research the proposed approach presented in this thesis was developed.

[3] European Commission. EU legislation – Eudralex. [Accessed on: 26 Jun 2016]. http://ec.europa.eu/legislation/index_en.htm.
[4] Dejure. Was ist dejure.org eigentlich? [Accessed on: 26 Jun 2016]. https://dejure.org/verzahnung.

3 Regulations and authorisation of medicinal products

3.1 National and international regulations

Various national and international regulations and laws regulate the principles for manufacturing, approval and marketing of human medicinal products. The European Union has harmonized the pharmaceutical legislation by several regulations in the past years. The most important European regulation regarding human medicinal products is Directive 2001/83/EC relating to medicinal products for human use. The directive has been implemented in the national legislation of each member state. In Germany, the corresponding law is the German Drug Law (Arzneimittelgesetz (AMG)) from 1976 and amendments.

3.2 Approval and authorities

Before a finished medicinal product may be placed on the market in the European Union, a governmental authority to evaluate whether the drug is safe, effective and meets the necessary pharmaceutical quality must first examine it.

Article six of Directive 2001/83/EC of the European Parliament and the Council states

> *No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive […].*

Hence, prior to marketing a medicinal product in the European Union, the pharmaceutical entrepreneur of the product must apply for a marketing authorisation issued by a competent authority. According to §4 AMG, the pharmaceutical entrepreneur is the holder of the approval or registration of the medicinal product. The pharmaceutical entrepreneur is also any person who places medicinal products on the market under their own name. A competent authority must issue the approval of the medicinal product. In Germany, the competent authority for the approval of human medicinal products is the BfArM, which is an independent federal higher authority within the portfolio of the Federal Ministry of Health (Bundesministerium für Gesundheit). The Paul-Ehrlich-Institut (PEI) is responsible for serums, vaccines, allergens test, test sera, test antigens, and blood preparations. The Federal Office of Consumer Protection and Food Safety

(Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) approve veterinary drugs (BVL). The European Commission grants a marketing authorisation for the entire EEA after assessment procedure and positive recommendation by the European Medicines Agency (EMA) in London.

3.2.1 Criteria for approval

The medicinal product to be approved must necessarily meet three criteria

- Efficacy
- Safety
- Quality

Only those products that meet these three essential criteria are granted market access.[5]

The efficacy of the product should be demonstrated by pre-clinical and clinical data. It must be proven that the product is effective under the defined specification. Therefore, the product should be tested in clinical studies in its intended use in a selected population with an appropriate dose regimen. Efficacy means the ability of the product to treat the condition it is intended for in the label.

The assessment of a drug's safety is based on its relative benefit-risk ratio. This implies that for a product with a high benefit, for example for serious, life-threatening diseases or in diseases with little or no treatment alternatives, a higher risk may be tolerated than in drugs for a simple headache. Unacceptable serious adverse reactions are usually not tolerated. These reactions may be carcinogenic, genotoxic or teratogen effects; however, an unacceptable adverse reaction is always relative. Predicable adverse effects should be managed by determination of exclusion criteria and contraindications or other suitable measures.

Important criteria for the pharmaceutical quality of a drug are purity, stability and bioavailability. These parameters can be influence by the manufacturing process.

[5] BfArM. Arzneimittelzulassung. [Accessed on: 26 Jun 2016]. http://www.bfarm.de/DE/Arzneimittel/zul/_node.html

3.2.2 Common Technical Document (CTD)

To harmonize the format in which the pharmaceutical entrepreneur submits the required data the ICH introduced the Common Technical Document (CTD) format. All information regarding the drug approval is presented to the authority in order to facilitate the regulatory review process in a mandatory format. The CTD consist of five modules. Module 1 contains the regional administrative information and is not considered part of the CTD. Module 2 encloses the table of content, an introduction and also the overall quality summary, non-clinical as well as clinical overview and summaries. Module 3 focusses in the pharmaceutical and biological data of the active agent and on manufacturing processes and other quality relevant matters. Non-clinical study reports are part of Module 4, the clinical trials and the analysis of clinical data are covered in Module 5.[6] Figure 1 provides an overview on the CTD format. Article 8 section 3 of Directive 2001/83/EC (and §§22 - 24 AMG for Germany) specifies the data that are required for the application.

[6] ICH. M4 : The Common Technical Document. [Accessed on: 26 Jun 2016]. http://www.ich.org/products/ctd.html

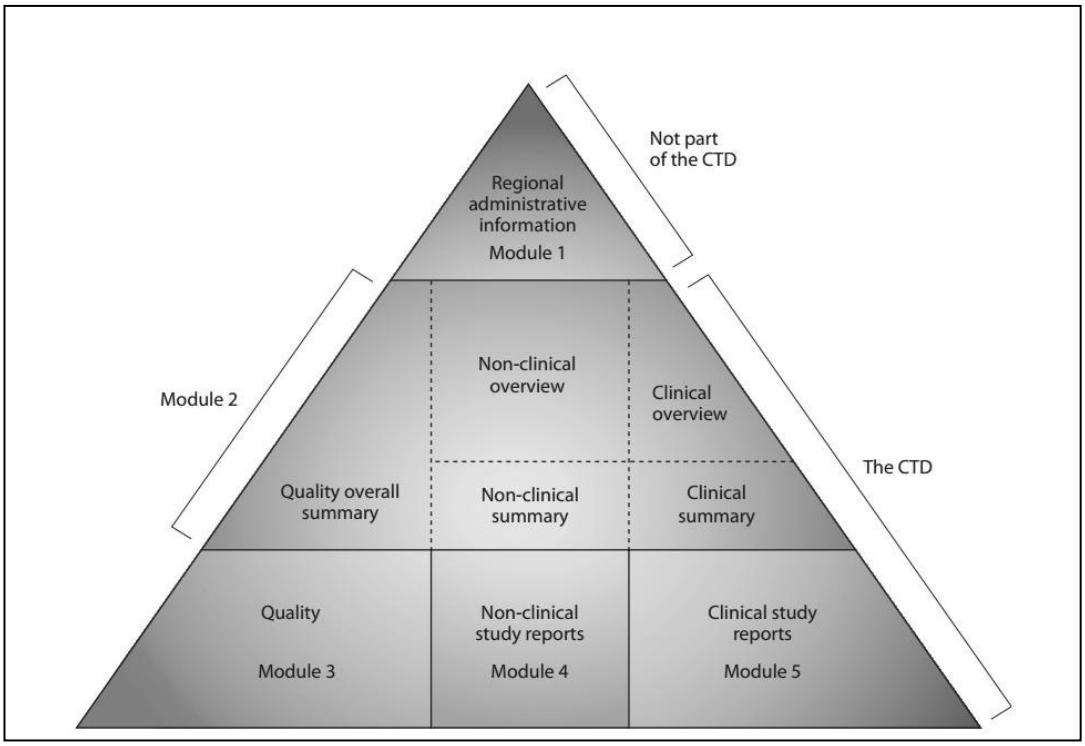

Figure 1 *CTD Triangle: The Common Technical Document, developed as part of the harmonization of the drug authorisation procedures in the European Union, the US and Japan by the ICH, is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.*[7]

[7] ICH. CTD Triangle. [Accessed on: 26 Jun 2016]. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/CTD_triangle.pdf.

3.3 Approval procedures

Different routes to obtain a marketing authorisation exist within the European Union. The requirements for approval of medicinal products were largely harmonized within the EU to allow simpler market access throughout the Union. In addition to national marketing authorisations, decentralised and centralised approaches for EU-wide approval were introduced. The national procedure allows market access for one specific Member State. Currently, there are two procedures, by which marketing authorisation for several Member States can be obtained: Mutual Recognition Procedure and Decentralised Procedure. A marketing authorisation that has been approved via the centralised procedure is valid for the entire EEA. The following sections give an overview on the different procedures.

3.3.1 National Procedure

To obtain a marketing authorisation for a human medicinal product in Germany, an application must be submitted to the BfArM or the PEI if it is serum, vaccine, antigen or blood preparation. The marketing authorisation is only valid for this particular national market. A national procedure is only possible when a centralised procedure is not compulsory (see 3.3.4).

3.3.2 Mutual Recognition Procedure (MRP)

The MRP is only feasible for products with an existing national MA in a Member State. The pharmaceutical entrepreneur may then choose to apply for MA in further Member States (Concerned Member State) using the identical application. The Member State in which the first marketing authorisation has been granted serves as the Reference Member State (RMS) and is responsible for issuing an Assessment Report that evaluates the safety, efficacy and quality based on the application. The Assessment Report is made available to the CMS. MA in the CMS is granted subsequently within 90 days, unless a serious risk to public health is identified and raised by the CMS. The identification of such a risk leads to a negotiation phase in the CMD(h) (Coordination Group for Mutual Recognition Procedures and Decentralised Procedures). When an agreement cannot be reached, the CMDH will evaluate the case by arbitration.[8]

[8] BfArM. MRP. [Accessed on: 26 Jun 2016]. http://www.bfarm.de/DE/Arzneimittel/zul/zulassungsverfahren/MRP/_node.html.

3.3.3 Decentralised Procedure (DCP)

In contrast to MRP, the Decentralised Procedure is only possible if no national marketing authorisation has yet been granted and the pharmaceutical entrepreneur aims to obtain national marketing authorisations in several Member States. The pharmaceutical entrepreneur may choose the Reference Member State. An identical application is submitted simultaneously to the RMS and all other Concerned Member States. The RMS prepares a preliminary draft assessment report that can be commented by the CMS. In a second assessment phase, the report is evaluated within 90 days. Similar to the MRP serious risk to public health may be raised by any Member State involved in the procedure. The consequences are the same as in the MRP; the CMD(h) negotiates to find a mutually acceptable solution. When an agreement cannot be reached, the CMDH will evaluate the case by arbitration.[9]

3.3.4 Centralised Procedure (CP)

In most cases, the pharmaceutical entrepreneur is free to choose the procedure to gain approval for a product. However, for a number of products, the centralised procedure is required in the European Union. The products that are obligated to enter the market via the CP are defined in Regulation (EC) no. 726/2004. These include advanced therapy medicinal products and monoclonal antibodies as well as human medicines with novel agents for the treatment of AIDS, diabetes mellitus, cancer, neurodegenerative diseases, autoimmune diseases and other immune dysfunctions, viral diseases and orphan drugs. The centralised procedure differs from the other non-central procedures, as the same institution does not perform the scientific evaluation and the authorisation. A national competent authority in all non-centralised procedures conducts both assessment and marketing authorisation. In the CP, the application for MA is submitted to the European Medicines Agency (EMA) in London. The scientific committee for human medicinal products (CHMP) of the Agency carries out the assessment procedure. The CHMP consists of expert representatives from regulatory authorities of all Member States. The Committee will present their evaluation to

[9] BfArM. DCP. [Accessed on: 26 Jun 2016]. http://www.bfarm.de/DE/Arzneimittel/zul/zulassungsverfahren/DCP/_node.html.

the European Commission. Based on the findings of the EMA assessment the European Commission grants the marketing authorisation for the entire EEA. For products that have been approved under the CP, a European Public Assessment Report is published to inform the public in a summary about the product.[10]

Table 1 *Summary of authorisation procedures in Europe*

Procedure	Available for	MA valid in
National Procedure	All products not within the scope of Reg (EC) no. 726/2004	Only Member State applied to
MRP	Products with existing MA in one Member State	Several Member States, first in RMS, subsequently CMS
DCP	Products with no existing MA in any Member State	Several Member States, simultaneously in RMS and CMS
CP	Mandatory for all products within the scope of Reg (EC) no. 726/2004; Optional for other products	Entire EEA

3.3.5 Other marketing authorisation procedures

Additionally to the procedures described above, other procedures exist according to Regulation (EC) no. 726/2004. These methods are only used for a small number of special cases.

- Compassionate Use (Regulation (EC) no. 726/2004 Article 83)
  Compassionate use means the supply of an unlicensed product to a group of patients with serious or fatal diseases, for whom no satisfactory alternative therapy with an authorised product is available. The medicinal product is either subject of an application for a marketing authorisation or clinical trials.

- Conditional marketing authorisation (Regulation (EC) no. 507/2006)
  The conditional marketing authorisation may apply in cases where there is a specific unmet patients' medical need. Under these circumstances, a marketing authorisation can be granted before complete data are available.

[10] EMA. Central authorisation of medicines. [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp.

It is presumed that the product has a positive benefit risk ratio that justifies the incomplete data on the clinical part of the application. The conditional MA is grated for one year and is subject to specific obligations. Clinical trials are required to be completed and after providing finalized data to support the positive benefit-risk-ratio, then the conditional MA can be transferred to a regular MA.[11]

- Marketing authorisation under exceptional circumstances (Regulation (EC) no. 726/2004 Article 14 (8))

  In specific cases where an applicant can demonstrate that it is not possible to assemble all required data on efficacy and safety under normal conditions for various reasons a MA with special obligations may be grated. Specific procedures regarding the safety of the product must be introduced. The authorisation is reviewed annually to assess the risk-benefit ratio.[12]

3.4 Limits and chances of the current regulations

The goal of the European regulations is to achieve and maintain a harmonized system that provides a satisfactory framework for all stakeholders. The involved parties in the pharmaceutical regulations include many different groups such as regulatory agencies and authorities, pharmaceutical industry, development facilities, medical research, users and of course patients. The current regulations are designed to accomplish a balanced system in which the interests of all stakeholders are reflected. Thorough non-clinical and clinical testing of new products should protect patient safety. Nevertheless, innovation and new therapies shall be able to access the market in an appropriate timeframe so that investments in research and development pay off.

[11] EMA. Guideline on the Scientific Application and the Practical on the Conditional Marketing Authorisation for Medicinal Products for Human Use Falling Within the Scope of Regulation. 25 Feb 2016 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf.

[12] EMA. Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004. 15 Dec 2005 [Accessed on: 26 Jun 2016] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf

New developments in the medical field are however diverse and not always easy to predict. The ever-changing circumstances must therefore be carefully observed in order to keep the system and its stakeholders at balance. When new or better developments in science and medicine arise, they should be reflected in the legislation so that the legal situation is not lagging behind. The regulatory framework must therefore ensure that it will not inhibit the scientific progress, as this would have extensive consequences in the end for all stakeholders. Innovative therapies and procedures might have to face great difficulties in entering the market, despite a possible benefit, when it is outside the scope of the current regulation and the regulatory framework offers no approach for the particular innovation. If innovation cannot be sufficiently promoted, it will affect both the industry as well as the patients negatively. At the present pace of medical progress, for example in the field of genetic research, it can be expected that situations that are not covered by the legislation will occur more often. The current system will therefore probably turn out more often to be too rigid in future. For instance, the approval of free combination therapies is not possible with the present framework, which provides only the approval of individual substances, or a fixed combination of substances. More flexibility in the system could change the existing and future limitations and turn them into an opportunity. As the medical field advances, the regulatory framework should adapt to those developments as to maintain its high standards and to keep up with recent development as well as to offer solutions for different scenarios.

New approaches to grant a more flexible system do not require an entirely new regulation. Including or adding new pathways can enhance the existing regulations. A first example that shows that the existing regulatory system has reached its limits but attempts to adapt to a more flexible approach has been presented in 2012. Adaptive licensing was introduced as a new pathway for marketing authorisation. The EMA has started a pilot project in 2014 for this new approach. This demonstrates that the EMA and other regulatory bodies have identified the necessity to extent the current system in order to meet new needs to close the gap between regulations and medical reality.

The example of the adaptive pathway illustrates that new approaches can be set out based on the current system. Continuous development and adaptation of the

regulatory framework to the scientific opportunities is essential for all those involved. The current system gives the change to overcome many possible limitations and should overcome them in the interest of patients.

3.4.1 EMA Adaptive Pathway (Adaptive Licensing)

It becomes more and more obvious that the current marketing authorisation procedures do not fit for all scenarios. To keep up with the medical and scientific progress and with newly identified needs, it is important to adjust the regulatory framework to new conditions. One of the many limitations of the current frameworks is it binary decision process. Once a pharmaceutical obtains a marketing authorisation it becomes available to hundreds and thousands of patients more or less overnight while only being available to patient in trials under controlled conditions before. This problem and a possible solution scenario were addressed in 2012 by suggesting a new pathway: adaptive licensing.[13]

Adaptive licensing was introduced as an approach to give more flexibility to the current system. In today's regulatory system, safety and efficacy of a new pharmaceutical product is being tested and evaluated in randomized clinical trials (RCTs) under controlled conditions with a selected patient population. The results of the clinical trials are presented in the dossier to the authorities where safety and efficacy of the product are assessed to decide whether or not a marketing authorisation shall be granted. From the moment of marketing approval, the product's safety and efficacy is considered appropriate when used within the scope of its label and the product is accessible for public and a wide group of prospective patients. Most of the patients that receive the product after authorisation are no longer part of controlled studies; the product is therefore used under everyday conditions with less restriction in the patient population than in the RCTs, including multi-morbid patients or patients receiving poly-medication. The effectiveness of the product (the beneficial effect of the drug), rare adverse reactions and possible new contraindications can be observed from this point of the drug's life-cycle. Therefore, in reality the learning process about the medicinal product is not finished with the day of approval. New knowledge from broader

[13] Eichler H-G, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther. 2012;91(3):426–37.

usage may hence lead to label changes, such as restrictions or expansion of the indication. The day of approval is therefore rather a point in time ("magic moment") in which the proof for safety and efficacy is considered sufficient even without having an absolute knowledge and new evidence will be gathered. Instead of having this "magic moment" in which the product switches from unapproved (still under investigation) to approved (safety and efficacy are considered satisfactory), adaptive licensing proposes a way to extend a product's application sequentially to achieve several aims. First, patients with a high medical need would have earlier access to a therapy. Secondly, more evidence about the product under realistic and uncontrolled conditions is gained. Under the current regulatory framework, specific high medical needs are already taken into account. The conditional marketing authorisation (see 3.3.5) grants faster access to a new therapy in a field with a particularly high demand. Under the conditional marketing authorisation pathway, incomplete information regarding the clinical data requirements is available. However, the higher risk resulting from the lack of information is acceptable in circumstances with serious, life-threatening diseases with unsatisfactory therapeutic alternatives. Adaptive licensing aims to satisfy the unmet medical needs without granting a full marketing authorisation. After initial licensing, new data are collected for further risk assessment. To establish adaptive licensing, the development and licensing process needs to be determined in advance. In the current marketing authorisation procedure, clinical trials are performed under controlled conditions. Thus, all patients receiving the drug are monitored regularly. After receiving marketing authorisation, the number of patients in RCTs decreases soon, while the number of patients receiving the drug under real world conditions without any particular surveillance increases rapidly (see Figure 2 (a)). The time course is different for adaptive licensing. The process starts with patients in RCTs as well. Before starting clinical trials, it shall be planned with the regulatory authorities what data need to be obtained to allow a first risk and efficacy assessment. If the evaluation indicates a positive safety and efficacy balance, an initial license is granted. It should be clear that at the time of the initial license the clinical data are incomplete. Therefore, the initial license should be granted earlier than a normal marketing authorisation, as the RCTs are still on going. The initial license is not a full, normal marketing authorisation but allows the prescription of the drug under certain limitations to well-defined

patient populations outside of RCTs. These patients would still be under certain surveillance but are taking the medication under less controlled conditions. All patients, whether or not they are part of RCTs, are monitored, and the observations contribute to effectiveness and safety information. When data from clinical trials and observational studies are complete to allow a concluding evaluation a full authorisation for the product is issued (see Figure 2 (b)). The current authorisation process and proposed adaptive licensing are compared in Figure 2, showing the patient groups of the process and the period.

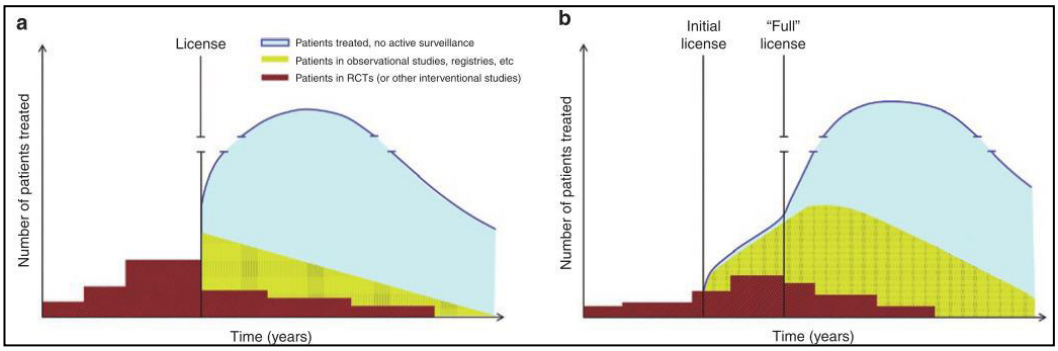

Figure 2 *Time course of (a) current marketing authorisation and (b) adaptive licensing. The time from start of RCTs to initial license in the adaptive licensing model is shorter than in the current process. Patients outside of RCTs gain earlier access to the product in AL before a full license is issued. Current MA process only includes patients in RCTs only in the pre-licensing phase leaving effectiveness studies to the post-licensing phase.*[13]

The definition for adaptive licensing proposed by Eichler et al is as follows:

> *Adaptive licensing is a **prospectively planned, flexible approach** to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to **maximize the positive impact of new drugs** on public health by **balancing timely access for patients** with the need to assess and to provide adequate evolving information on **benefits and harms** so that **better-informed patient-care** decisions can be made.*[13]

The EMA adopted the proposed approach using the basis of currently existing regulatory procedures. A pilot project started in 2014 under the name adaptive pathways to demonstrate that the approach considered the drug's life-span from clinical development, approval, reimbursement and clinical practice.

> *The concept of adaptive pathways foresees either an initial approval in a well-defined **patient subgroup with a high medical need** and subsequent widening of the indication to a larger patient population, or an **early regulatory approval** (e.g. conditional approval) which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on the medicine's use in patients.*[14]

EMA is now gathering experience on the pathway and tries to identify eligible candidates for the program. The Agency has released a list of criteria for potential candidates who shall provide:

- an iterative development plan, either by gradual expansion of the target population (e.g. starting from a population with a high medical need) or by progressive reduction of uncertainty after initial authorisation, based on surrogate endpoints;
- an ability to engage HTAs and other downstream stakeholders, with proposals for how their requirements can be met;
- proposals for the monitoring, collection and use of real-world post-authorisation data as a complement to randomised clinical trial data.[14]

[14] EMA. Adaptive pathways. [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp.

The next years will show if the adaptive pathway will become a new authorisation approach and will be implemented in the regulations. The approach certainly demonstrates the need for new and innovative ways to adapt the regulatory framework to modern experience and new knowledge in medicine. When the medical need gets more and more specific, pathways to satisfy these specific requirements are necessary. Adaptive licensing is one of those pathways, but others are needed for different situations. Therapeutic concepts are such a new and different approach that would allow more flexibility in the field of combination therapies.

4 Therapeutic concepts: Proposal of a new regulatory approach for combinations

4.1 Definition and scope of therapeutic concepts

The introduction of the Adaptive Pathway shows that the regulatory framework for drug authorisation needs constant development and changing to adapt to new challenges.

There are several other aspects in drug authorisation, that are reflected unsatisfactory in the regulatory framework. In the current status of drug development and drug approval, only one agent at a time is reviewed and approved by authorities. Yet, it is common knowledge that for certain diseases a variety of drugs and medical devices are used in combination to treat a condition. Combinations of medicinal products are very frequently used in the medical practice but the legislation for combinations is lagging behind when compared to single drug authorisation. Combinations of medicinal products have a long history, and it is likely that with the current research the use of medical combinations will even extent. With the evolution of personalized medicine, research is just beginning to recognize the many different biological and genetic aspects of diseases. This knowledge can be used in drug development and therapy. Having a more detailed understanding of the cellular pathways provides better chances to target drug therapy. Because the body is a complex biological system, it is in many diseases not enough to inhibit only one cellular pathway, as alternative routes can be activated as a response to such inhibition that leads to therapy resistance. To develop targeted therapy a complete understanding of the biochemical response to drugs and disease is needed. Then, drug combinations can be designed to address multiple cellular pathways and resistance mechanisms. Personalized medicine and genomic research are an important part of the development towards the targeted drug combination therapy.[15] Today, some of the most serious diseases, such as Hepatitis C, HIV infections and many types of cancer require a combination of drugs for the treatment. Other treatments rely on

[15] Woodcock J, Griffin JP, Behrmann RE. Development of Novel Combination Therapies. N Engl J Med. 2011;364(11):985–7.

the outcome of a diagnostic test. The diagnostic test should hence be considered to be part of the treatment regime.

Therefore, a gap between treatment reality, research and approval practice exists. The limits of single drug authorisation are reached. New pathways for the authorisation of combinations need to be introduced. The next logical step in the regulatory framework is the co-approval of combination therapies based on targeted approaches, which so far does not exist. The approach introduced in this thesis recommends this additional new way of drug approval to overcome this gap. The development and approval of novel therapeutic concepts would be a consistent step towards a better health care. A clear regulatory pathway towards an approval of drug combinations could help agencies, health care professionals and patients to gain safer therapies and clear recommendations for medical practice.

To distinguish between an approved combination regimen and the frequently used term "combination therapy" that refers to a general therapy consisting of a therapy with multiple medicinal products or other treatment options, a new term is introduced for the approved combination therapy: **"Therapeutic concept"**.

The definition for a therapeutic concept as it is introduced and used in this work is the following[16]:

Therapeutic concept:

A therapeutic concept is the approval of a treatment regimen, consisting of two or more, marketed or not yet marketed, medicinal products <u>or</u> one or more medicinal products and a companion diagnostic/medical device, if it is required for a safe and effective use of the regimen, that have been developed and studied together for a specific condition and patient population.

[16] Krollmann KB, Schweim HG. Zulassung von „therapeutischen Konzepten" / Der nächste Schritt zu einer „personalisierten" Medizin. pharmind. 2015;77(5):650–3.

A therapeutic concept therefore clearly differs from the other options for drug combination (such as fixed combinations) which are introduced in Chapter 4.2. Unlike guidelines, authorisation of therapeutic concepts would not be a recommendation based on experience but is a clear statement that this combination has been studied as an intended combination.

The following options for combinations to fall under the scope of therapeutic concepts exist:

1. Combination of two or more medicinal products
2. Combination of one or more medicinal product with a companion diagnostic.

The drugs used in a therapeutic concept shall not be a fixed combination, nor shall they be required to come in one single package but can be marketed and dispensed separately.

The combination used in a therapeutic concept shall be intended to be adjusted to individual patient's needs. The separated administration of the components provides the opportunity to administer the medication in an appropriate dosage to prevent side effects and increase efficacy and compliance. Individual dosing can be handled more easily when the components are not part of a fixed combination.[16,17]

As companion diagnostics are nowadays often a vital tool for diagnosis and selection of treatment, therapeutic concepts shall provide the opportunity to include companion diagnostics in an approved therapy. That means that two products which currently fall under different legislations (medicinal products and medical devices) would be combined for specific cases under the medicinal product legislation.

[17] Schweim JK, Schweim HG. Status quo and future developments of combinations of medicinal products. Synergy. 2014;1(1):70–5.

4.2 Fixed combinations and combination packs

Now, several possibilities provide assistance when and how drug combinations are indicated. These are

- Medical guidelines
- Combination packs
- Fixed combinations

While medical guidelines are usually initiated by medical societies and are based on review of clinical data, combination packs and fixed combinations are regulatory terms and describe pharmaceutical products approved by a competent authority.

Development and importance of medical guideline are outlined in Chapter 4.3.

In the definition of the EMA, a combination pack

> *„consists of more than one medicinal product, or more than one pharmaceutical form of the same medicinal product, presented under a single (invented) name and in a single product package (e.g. box, blister pack), where the individual products/forms are intended for simultaneous or sequential administration."*[18]

An example for a combination pack is ZacPac, which consists of three different active substances, namely pantoprazol, amoxicillin and clarithromycin.[19] ZacPac is indicated for treatment of *Helicobacter pylori* infection (refer to Chapter 4.4.2). The combination pack is a comfortable choice for the patient, as the right amount of tablets is provided for the treatment unit and it is less likely for the patient to forget taking one of the tablets, thus combination packs can improve the patient compliance. The downside of such combination packs is the relative high price compared to generics of the single active substance.

[18] EMA. Guideline on the non-clinical development of fixed combinations of medicinal products. CHMP/EWP/240/95 Rev. 1. 19 Feb 2009 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf.

[19] SmPC. Takeda ZacPac. March 2016 [Accessed on: 26 Jun 2016]. http://www.fachinfo.de/suche/fi/004930.

In contrast to a combination pack, a fixed combination is defined as the combination of active substances within a single pharmaceutical form of administration. The EMA states

> *"the proposed combination should always be based on valid therapeutic principles. Fixed combination medicinal products have been increasingly used to benefit from the added effects of medicinal products given together. In addition, it is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product. Potential advantages of fixed combination products may also include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy."*[18]

Fixed combinations are found commonly for many different indications. Cardiovascular diseases often require multiple active substances, and for patient convenience many fixed combinations are on the market in this area (e.g. Atacand plus with candesartan and hydrochlorothiazide[20]). To cover all the individual needs of the patients a wide range of different combinations with different content of active substances need to be marketed. Even though these combinations are easy to use for the patient, as they only need to take one rather than two or more pills a day, fixed combinations are as inflexible as their name already indicates. A change in the dosage of one active substance, for example, is quite complex to implement. There are also certain restrictions and limits to fixed combinations. They can only be developed under certain conditions, for example, only if the active ingredients can be taken concurrently. Furthermore, the duration of action of each active substance should correspond with the administration interval.

[20] SmPC. AstraZeneca Atacand PLUS. May 2016 [Accessed on: 26 Jun 2016]. http://www.fachinfo.de/suche/fi/002608.

4.3 Medical guidelines

Besides the regulatory possibilities for combinations of medications such as fixed combinations and combinations packs other non-regulatory approaches exists that provide guidance for the use of combinations in specific disease patterns, namely medical guidelines (German: "Leitlinie"). Medical guidelines support physicians in the therapeutic decision making by suggesting therapeutic approaches that can include combinations based on evidence and experience in the medical field. The guidance given in published medical guidelines can be regarded as an aid and necessity as to close the existing gap between the limited regulatory combination possibilities and medication practice, even though this is not their main purpose. However, the information presented in medical guidelines cannot be viewed equivalent to authorised combinations from the legal perspective.

The primary objective of medical guidelines is the improvement of quality in health care by applying evidence based and economically appropriate therapies. They are created to present the current state of scientific knowledge to optimize the medical care. Furthermore, they should help avoid unnecessary and obsolete methods of medical practice. Another task is to inform the public.[21]

At first, the term "medical guideline" otherwise also called "clinical practice guideline" (hereafter referred to as guidelines), needs to be defined. The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)), founded in 1962, is the publisher of many medical guidelines and represents more than 160 medical societies in Germany. The association gives advice about fundamental medical questions, not only to their member organizations, but also regarding political concerns and represents Germany in the WHO Council for International Organizations of Medical Sciences CIOMS.[22] The question of medical guideline definition is answered as following:

[21] Ollenschläger G. Leitlinien in der Medizin – scheitern sie an der praktischen Umsetzung ? Der Internist. 2001;42(4):473–83.
[22] AWMF. Wir über uns. [Accessed on: 26 Jun 2016]. http://www.awmf.org/.

> *"Guidelines are systematically developed statements reflecting the current state of knowledge and meant to support doctors and patients in making decisions concerning appropriate care for specific health problems. Guidelines are important and effective instruments for quality development in health care. Their primary objective is to improve medical care by disseminating current knowledge. Guidelines […] formulate clear recommendations for treatment backed up by a clinical weighting of the power and applicability of the study results. Guidelines can be understood as "treatment and decision corridors" which can or should be deviated from in justified cases."*[23]

Guidelines are developed to improve health care and describe the best clinical practice. Evidence-based medicine is one of the main principles that ought to be reflected. Clinical practice guidelines are part of all fields of medical practice. It begins with how to diagnose patients, which test and screening might be necessary. They might then be helpful to establish a patient's medical therapy, either by drugs, surgery or other possibilities. Moreover, guidelines may offer advice, on how surgical procedures can be performed, how long patients should stay in hospital and many other questions that rise in clinical practice.[24] However, guidelines are not intended to be used as a "cookbook" that provides every step in patient care. It is the clinician's responsibility to interpret the use of the guideline for an individual patient.

Medical guidelines aim to help several stakeholders. First, they are one of the most important sources for doctors and health care professionals for decision-making. Especially for the most common diseases, such as asthma, high blood pressure or diabetes, guidelines are a great tool, as they mostly consider the current status in medicine. Guidelines are furthermore meant for the public to inform about therapy options. Patients or other interested persons can access most guidelines on the internet free, giving them a chance to discuss those options with their physician and informing them about treatment alternatives. The third

[23] AWMF. Introduction: What are guidelines? In: AWMF Guidance Manual and Rules for Guideline Development. p. 5. Version 1.0. 06 Nov 2012 [Accessed on: 26 Jun 2016]. http://www.awmf.org/leitlinien/awmf-regelwerk/awmf-guidance.html.
[24] Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ. 1999;318(7182):527–30.

stakeholder for whom guidelines are of great interest is the health care system. Guidelines are always intended to present economic aspects of different treatment or diagnosis methods as well. A more detailed overview about potential benefits and harms is given in subsection 4.3.1.

However, despite all good intentions guidelines are repeatedly criticized. It is questionable whether the ambitious goal of improvement of care, consistency, efficiency and cost reduction are actually achieved. A poor implication into practice often stands in the way.[25] A proper implication of high quality guidelines in the health care sector over the next years is therefore an important task.[26] Furthermore, there is criticism that the guidelines assume an ideal, average patient, not an individual patient where certain conditions are to be considered, such as co-medication, age and medical history.[27] The number of guidelines with a high degree of systematic development (S3) is small. They usually only exist for very common diseases since evidence for less frequent illnesses is often not sufficient for a systematic guideline process. The financial aspect is certainly a reasonable approach, but therapy should not be withheld from patients for economic reasons. The right balance between cost-effectiveness and the selection of effective interventions must be found.[28]

[25] Chant C. The conundrum of clinical practice guidelines. Can J Hosp Pharm. 2013;66(4):208–9.
[26] Ollenschläger G, Thomeczek C, Weinbrenner S, Nothacker M, Rohe J, Schaefer C. Das Ärztliche Zentrum für Qualität in der Medizin 1995 – 2010: 15 Jahre Förderung von Evidenzbasierter Medizin , Patientenorientierung und Patientensicherheit. Gesundheitswesen. 2012;74:407–9.
[27] Hurwitz B. Legal and political considerations of clinical practice guidelines. BMJ. 1999;318:661–4.
[28] Ulsenheimer K, Biermann E. Leitlinien - medico-legale Aspekte. Anästh Intensivmedizin. 2008;49:105–6.

4.3.1 Benefits and harms of medical guidelines

As described above, guidelines are meant for different stakeholders in the health care sector, most importantly health care professionals, physicians in particular, patients and payers. The different impact, both positive and negative to these groups will be reviewed in this part.

Health care professionals

There are various potential benefits and harms for physicians in medical guidelines. The most obvious benefit for health care professionals is a clear guidance on how to handle specific situations and illnesses. A guideline of high quality can most certainly improve quality of care when a clear decision-making pathway is defined. Available treatments should be compared and distinctions among interventions should be explained. Doctors can learn about new or more effective interventions, giving their patients the best possible care while making cost-effective decisions, too. Furthermore, attention is called to treatment alternatives, which are outdated, ineffective or harmful, obsolete medication or surgery creates high costs in the health care system and makes patients suffer longer from their illness, due to higher failure rates, side effects, and longer hospitalization. Consequently, guidelines are an essential tool to keep physicians and other health care professionals updated on the current medical evolvements. It is nonetheless of uttermost importance that doctors do not only rely on the actual guideline, but also keep themselves posted by reading other medical literature, as one must not expect that guidelines always present the current status. Guidelines need to be updated, in some cases more frequently than in others, and it has to be kept in mind, that a six months old guideline can already be out-of-date. Health care professionals have to be able to independently evaluate the information given in the guideline to identify an obsolete or flawed one. Only a vivid dialogue between guideline developers, health care professional and other stakeholders can preserve high quality guidelines. Additionally, the guideline developing progress and discussion helps to find gaps in evidence and assess the quality of studies that are included in the guideline. If lack of evidence is found, efforts can be made to close the knowledge gap and improve health care.

Guidelines are a good basis for doctors to justify their decision and may strengthen their position towards patients, payers and administrators. In case of being charged with error of treatment, guidelines can provide legal protection, if used properly. (For further legal considerations, see Chapter 4.3.3)

Despite all the benefits, guidelines are not always easy to handle. Implementation of the given medical advice is described challenging by some physicians, they find guidelines time-consuming and some guidelines cannot be simply realized in medical practice. Physicians are moreover confronted with contradicting guidelines when working in fields where several aspects need to be considered before starting therapy, such as cardiovascular diseases, which are often associated with metabolic syndrome. It may occur that different scientific societies give opposing opinions on how an illness should be treated.

Guidelines may have a negative impact on reimbursement practice. Payers may not cover interventions, which are not mentioned in a guideline, for whatever reason, anymore. For doctors, who do not have any alternative options for a patient, this might be a significant hurdle.[24]

Patients

One of the main and most important benefits for patients that guidelines provide is a better treatment outcome. When physicians follow the right recommendations in the guideline, treatment will be more likely to be successful due to choosing a therapy that has proofed to be the best available option. In a high quality guideline, different therapies have been compared in numerous patients giving enough evidence to draw a conclusion. On the other hand, treatment options that have proven to be inefficient are discarded, sparing patients unnecessary therapy, which would only result in side effects and time loss without improving the patient's health. The intention of guidelines is to harmonize the treatment of a certain disease in a way that patients, regardless of where they are treated, would be cared for in an equal matter. This ambition is more difficult to reach. While it may be possible to harmonize therapy in one region or even one country it is almost impossible to achieve harmonization on an international level, keeping in

mind that different drugs are on the marked in every country and the medical background and traditions vary.

Another benefit that medical guidelines offer to patients is drawing attention to new findings. If a new method or drug is highly recommended by a guideline, this can help patients gain access to those, since it becomes more likely for them to be reimbursed.

Patients are given the opportunity to get informed about their care by using patient's leaflets that are usually handed out with a clinical practice guideline. This seems to be a challenge for patients to learn about their conditions and the opportunities that are available. It might help involve the patient in the treatment process, which can improve the therapeutic success. Then again, the information given to the public might as well cause confusion. For instance, when doctors do not chose the best-recommended therapy for any reason, perhaps because the patient has a specific condition that makes a less recommended treatment the better option in this case, the patient might not understand this. This can cause distrust and in consequence leads to worse results.

However, confusion and distrust are not the major problem for the patient. The greatest harm lays in outdated or inflexible guidelines. Outdated guidelines that do not represent the current medical knowledge result in a less effective, suboptimal, or even worse, harmful therapy. Guidelines of low quality might offer wrong recommendations, which is obviously a risk. A further threat for the patients is the inflexibility of some clinical practice guidelines or doctors that take the recommendations as a one-size-fits-all approach. Leaving out individual characteristics of a patient by strictly following a guideline from top to bottom will give some patients an inappropriate care.[24]

Health care system

It has already been described that guidelines can make new interventions the best available care, replacing other older and ineffective approaches. Reimbursing the best care helps the health care system by granting the patients access to superior treatments thus improving public health. The health care system mainly benefits from the economic point of view. Guidelines can standardize health care and

suitable implementation of guideline recommendations in clinical practice reduces costs. Of course, cost reductions can only be realized with systematically developed guidelines in which economic matters and medical issues are equally included. Therefore, payers should verify a guideline's content before reimbursing new services. Otherwise, important resources and money might be wasted.[24]

Table 2 *Summary of potential benefits and harms of medical guidelines*

	Benefits	**Harms**
Health care professionals	Clear guidance for clinical decision-making	Flawed or outdated guidelines with incorrect information
	Improved quality of care	Time consuming use
	Attention for harmful or ineffective treatments	Difficult to implement when guideline does not meet clinical demands
	Legal protection in some respects	Reimbursement questionable when intervention is not recommended
Patients	Improved health care outcome	Inflexibility
	Standardized care	Treatment with incorrect or outdated recommendations
	Information	Disturb patient-doctor relationship
Heath care system	Cost reduction	Waste of resources
	Standardized care	

4.3.2 Development and quality of guidelines

Guidelines are "systematically developed statements"[24] and are to be developed according to standardized principles. The AWMF has published a guidance to help developers maintain quality standards based on DELBI and AGREE criteria. DELBI (Deutsches-Leitlinien-Bewertungsinstrument, German tool for appraisal of clinical practice guideline) is the German adaption of the international AGREE (Appraisal of Guidelines for Research and Evaluation) instrument that is a tool for the assessment of medical guidelines. DELBI and AGREE can be used by developers and users to evaluate the quality of a clinical practice guideline.[29] According to the AWMF guidance, development or revisions of guidelines usually begins with finding a subject or scope. The subject of a guideline should always be of importance for the health care sector. The selection of subjects should be comprehensible and of justified medical necessity. Various reasons can explain the need for a guideline. These include for instance the prevalence of a certain health care aspect, potential of improvement or optimization and great differences in care. Even when an illness's prevalence is not very high, the need for a new guideline may be justified by a poor standard of care. Furthermore, economic factors as well as ethical and social aspects play a role in the selection process. New technologies can be introduced by guidelines.[23] The guideline should always have a clear clinical question that it intends to answer without having a scope that is too broad. It needs to be defined which topics ought to be covered by the guideline in order to give reasonable and practical advice that can be implemented in the clinic.

The groups involved in the guideline working process should represent as many appropriate stakeholders as possible. This can include several organizations, scientific medical societies as well as users and patients of the target audience. Professionals who are familiar with the methodological approach and evidence-based medicine (EBM) are an important part of the development group. In general, a multidisciplinary group is more likely to prevent biases that might occur in imbalanced groups; moreover, this later on improves the chances of

[29] The AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003;12(1):18–23.

better implementation and acceptance.[30,31] From the beginning, the group should be aware of the systematic process it chooses. In Germany, different classifications are known that describe the degree of systematic development: S1, S2k, S2e and S3. S3 guidelines present the highest systematic development, whereas S1 is the lowest that is formed by expert recommendation without a systematic research. S2e guideline ("e" = evidence) is developed using systematic research, while S2k ("k" = consensus) is based on a structured consensus of a representative body. The highest standard S3 combines all elements; it may include expert opinions but a systematic performed research and formal consensus is compulsory.[32] The choice of classification for which the guideline is aimed is dependent on how much effort is suitable and implementable.

Table 3 *S-classification of medical guidelines according to AWMF.*

S1	S2k	S2e	S3
Informal consensus or expert recommendations	Consensus-based	Evidence-based	Evidence- and consensus based
low ←	degree of systematic development		→ high

To ensure high quality, it is suggested to hold on to DELBI and AGREE specifications for the actual development process. For S2e and S3 a systematic review of available literature is inevitable. Literature includes not only clinical trials and studies and their reviews and meta-analysis, but also other guidelines to screen for possible contradictions or adaptions that can be made. The literature obtained by research is to be categorized by level of evidence with a classification

[30] Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)-Ständige Kommission Leitlinien. Zusammensetzung der Leitliniengruppe: Beteiligung von Interessengruppen. In: AWMF-Regelwerk Leitlinien. p. 10. 1st edition. 09 Nov 2012 [Accessed on: 26 Jun 2016]. http://www.awmf.org/leitlinien/awmf-regelwerk.html.
[31] Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ. 1999;318(7183):593–6.
[32] Muche-Borowski C, Kopp I. Wie eine Leitlinie entsteht. Z Herz-Thorax-Gefäßchir. 2011;25(4):217–23.

system (i.e. levels of evidence of Oxford Centre for Evidence-based Medicine[33]). According to the evidence situation the strength of the guideline recommendation must be indicated, for example by using the AWMF code, in which A stands for a strong recommendation, B representing a recommendation (weaker compared to A) and 0 meaning recommendation open.[23]

4.3.3 Legal considerations

In this section, mainly the German legislation will be reviewed. Nevertheless, the findings presented here will most likely apply for most legal environments.

A guideline, by definition, is not legally binding and following is not mandatory. In German:

> *"Die „Leitlinien" sind für Ärzte rechtlich nicht bindend und haben daher weder haftungsbegründende noch haftungsbefreiende Wirkung."*[34]

This also applies to medical guidelines. The AWMF states that guidelines are not legally binding for health care professionals and therefore have neither liability nor liability claim liberating effect.

Guidelines have different impact on social law and liability law. The question is whether guidelines actually present something new looking from a legal perspective regarding liability or if they are rather a methodological approach to describe the duty of care according to German Civil Code Section 276 (§ 276 BGB).[35] Guidelines are to be understood as guidance, they cannot adequately determine an error in treatment.[28,36] An error in treatment is characterized by the deviation from the standard of care at the particular time of the patient's treatment.[37] Guidelines may be useful for determining those standards, however, are often not sufficient in a particular case. Guidelines may be outdated, may not apply to the corresponding case or do not present all known treatment alternatives;

[33] Centre for Evidence-based Medicine. Oxford Centre for Evidence-based Medicine - Levels of evidence (March 2009). [Accessed on: 26 Jun 2016] http://www.cebm.net/index.aspx?o=1025.
[34] AWMF. Leitlinien. [Accessed on: 2015 Dec 06]. http://www.awmf.org/leitlinien.htm.
[35] Ratzel R. Qualitätssicherung, Leitlinien und Recht. Geburtsh Frauenheilk. 2006;66(S 2):Q8–Q14.
[36] Dierks C. Juristische Implikationen von Leitlinien. Dtsch Med Wochenschr. 2003;128:815–9.
[37] Bundesministerium für Gesundheit. Behandlungsfehler. [Accessed on: 26 Jun 2016]. http://www.bmg.bund.de/themen/praevention/patientenrechte/behandlungsfehler.html.

therefore, expert opinion discussing the guideline is usually necessary in court.[38] This is confirmed in a judgment of the higher regional court (Oberlandesgericht (OLG)) Naumburg, Germany. The Court does not see guidelines as binding instructions, due to differences in quality, legitimacy and topicality. They cannot represent the individual treatment case.[39] The Federal Court of Justice (Bundesgerichtshof (BGH)) came to a similar decision in 2008, indicating that guidelines are non-binding.[40] Likewise, the OLG Köln saw a deviation from a guideline not necessarily as an error in treatment; the individual case must be considered.[41] A violation of guidelines is also no grave error in treatment, and therefore does not necessarily shift the burden of proof away from the complainant.[42] Nevertheless, it will be difficult in some cases to justify the deviation from a high quality guideline, thus meaning for doctors to make sure a current, appropriate guideline is always used. If not, it should be well documented why other measures have been taken. Some experts claim that the uncertain legal status of guidelines leads to a lower acceptance of those in the medical profession.[21] Then again, it should be warned against trying to establish guidelines as legal standards. This would restrict the freedom of medical therapy and cause uncertainty.[43] The character of an orientation aid, as defined by the AWMF, should be retained since the quality differences are still striking

Legal liability aspects affect not only physicians and patients. The guideline development process requires greatest care and skills. Nevertheless, there is no guaranty for an absolutely accurate guideline despite all control. Critical questions concerning the development course arise:

[38] Hart D. Ärztliche Leitlinien - Definitionen, Funktionen, rechtliche Bewertungen. Medizinrecht. 1998;1:8–16.
[39] OLG Naumburg. Urteil vom 19.12.2001; Az: 1 U 46/01.
[40] BGH. Beschluss vom 28.03.2008; Az: VI ZR 57/07.
[41] OLG Köln. Urteil vom 18.08.2010; Az: 5 U7/10.
[42] OLG Stuttgart. Urteil vom 22.02.2000; Az: 14 U 62/00.
[43]Clade H. Medizinische Leitlinien: Entscheidungshilfen für Arzt und Patienten. Dtsch Arztebl. 2001;98(6):A288–A290.

- Who initiated the clinical practice guideline process and selects those involved in the discussion and creation?
- Which criteria determine content and evidence?
- How is the development financed?
- Are (employees of) pharmaceutical companies allowed to participate financially or through collaboration?
- Who is liable for the accuracy, e.g. in the event of a faulty dosage?
- Can companies sue guideline developers should their drug or therapy not be included despite existing evidence?

In general, authors of a guideline or the scientific society can be sued for wrong statements and conclusions. The AWMF can be made responsible for dispensing flawed guidelines and should withdraw questionable guidelines from circulation, but again, liability is a case-by-case decision. These considerations should be kept in mind as criticism of guidelines comes up from time to time. For instance, questions about pharmaceutical industry involvement recently hit the lay press, when the *Spiegel* magazine reported that new drugs are added too quickly to a guideline caused by industry pressure.[44] The producers of guidelines need to be aware of their important yet responsible task, which is a great tool of information for all health care stakeholders when done in the right way.

Despite the non-binding nature of guidelines, they are referred to in several sections of SGB V and are thus represented as an important part of social legislation. This includes, for instance, the general practitioner-centred care, in which treatment is to be carried out according to evidence-based guidelines for primary care that have been tested in practice (§ 73b Abs. 2 Nr. 2 SGB V). Furthermore they are mentioned in § 137f Abs. 1 Nr. 3 and Abs. 2 Nr. 1 SGB V (structured treatment programs for the chronically ill) as well as § 139a Abs. 3 Nr. 3 SGB V (IQWiG will evaluate evidence-based guidelines for the epidemiologically important diseases). As already discussed, guidelines can influence social law by initiating reimbursement of services and thus serve as a control tool in health care. However, there is only an indirect and no formal

[44] Kuhrt N. Pharmaindustrie soll Leitlinien beeinflusst haben. In: Spiegel Online. 24 Mar 2013 [Accessed on: 26 Jun 2016]. http://www.spiegel.de/wissenschaft/medizin/leitlinien-werden-zunehmend-durch-pharmahersteller-beeinflusst-a-890556.html.

connection between guidelines and the services and treatments reimbursed by the GKV (statutory health insurance). Quality and effectiveness of services have to comply with the general state of medical knowledge and take account of medical progress (§ 2 Abs. 1 S. 3 SGB V) but must also be practical and economical (§ 12 Abs. 1 S. 1 SGB V, § 70 Abs. 1 SGB V). Guidelines can provide information about these terms and start a reimbursement discussion.

In conclusion, medical guidelines present a good orientation for all stakeholders but are also often reason for criticism and uncertainty. They may be a helpful aid regarding the choice of combinations of medicinal products. However, not every combination described in guidelines is actually advisable. More reliability for doctors therefore would be desirable and could be created by the approval of therapeutic concepts in some cases.

4.4 Targeted drug combinations

The combination of drugs is as old as medicine itself. It is commonly acknowledged that combinations are the better choice compared to monotherapy in many diseases. Combinations therapy is in some diseases even the standard of care and monotherapy in these cases would be considered as treatment error. These therapies with several pharmaceuticals are often found in diseases where the patient population is clearly defined.

Some classic examples of these diseases with combination therapy are described below. The reasons why drug combinations in many diseases are the better alternative are diverse. The most common reasons include

- Biological rational

  A biological rational could be the prevention of resistance in antibiotic therapy. Serious diseases caused by bacteria, such as tuberculosis, with a high risk of resistance are therefore treated with several antibiotic agents to minimize the risk (see chapter 4.4.1). Other biological rationales are for example the addition of an agent to a drug that would prevent side effects.
- Differentiation in the cause of the disease

  A disease can have different causes but cause the same symptoms. Gastritis, for example, can be caused either by gastric hyperacidity or by the bacterium *Helicobacter pylori*. The treatment of the disease's origin results in different treatment of the symptoms, and requires in case of *H. pylori* infection a combination of several agents (see chapter 4.4.3)
- Stratification or subgroup analysis

  Subgroup analysis of a certain (combination) therapy might reveal that the therapy works especially well in a particular patient subgroup. This happened in case of the so-called "race-drug" BiDil (chapter 4.4.3).

This shows that a need for regulation in the field of combinations thereof. The examples indicate that the need for regulation in the field of combinations is obviously present.

4.4.1 Tuberculosis

Worldwide, tuberculosis (TB) is one of the most common infectious diseases and the second leading cause of death caused by infections. The WHO indicates 1.5 million deaths by tuberculosis and 6 million new cases in 2014.[45] One-third of the world's population is estimated to be infected with TB; however, only 10% of infected people develop the disease.[46,47] The causative agent of tuberculosis is mainly *Mycobacterium tuberculosis,* which was discovered by Robert Koch in 1882.[48] *M. tuberculosis* is a rod-shaped bacterium that has a relatively long generation time of 18-24 h. The bacterium has the ability to become dormant in macrophages, a state in which it does not dived and has low metabolic activity. It is also resistant to chemotherapy in this state.[49] The cell wall of *M. tuberculosis* is quite unusual. Staining using the Gram technique is of little avail, an acid-fast stain can be used instead. Mycobacteria resist Gram staining as their cell wall contains high amounts of branched lipid substances that are linked to arabinogalactan forming mycolic acids. The characteristic cell wall structure is responsible for the bacterium's resistance against most known anti-infective medications.[50] As an obligate intracellular pathogen, *M. tuberculosis* prefers tissue with high oxygen levels. Hence, infection of the lungs is most common.[51] Symptoms of pulmonary tuberculosis include chest pain and prolonged cough, which may contain blood. In a smaller number of cases, TB may also occur in other parts of the body (extrapulmonary tuberculosis). Fever, weight loss and night sweats are general symptoms of TB infection.[51,52] TB is transferred via droplet infection. Microscopy of active TB patients' sputum is used to diagnose the presence of the bacterium.

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[45] WHO. Introduction. In: Global tuberculosis report 2015. p. 1. [Accessed on: 26 Jun 2016] http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1.
[46] Chan ED, Heifets L, Iseman MD. Immunologic diagnosis of tuberculosis: a review. Tuber Lung Dis. 2000;80(3):131–40.
[47] Brzostek A, Pawelczyk J, Rumijowska-Galewicz A, Dziadek B, Dziadek J. Mycobacterium tuberculosis is able to accumulate and utilize cholesterol. J Bacteriol. 2009;191(21):6584–91.
[48] Koch R. Die Aetiologie der Tuberculose (Nach einem in der physiologischen Gesellschaft zu Berlin am 24. März gehaltenem Vortrage). Berliner klin Wochenschr. 1882;19:221–30.
[49] Gengenbacher M, Kaufmann SHE. Mycobacterium tuberculosis: success through dormancy. FEMS Microbiol Rev. 2012;36(3):514–32.
[50] Mutschler E, Geisslinger G, Kroemer HK, Ruth P, Schäfer-Korting M. Arzneimittelwirkungen.10th ed. Stuttgart. Wissenschaftliche Verlagsgesellschaft; 2012. p. 781ff.
[51] Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011;2;378(9785):57–72.
[52] Müller A. Klinische Aspekte der Tuberkulose. Pharm Unserer Zeit. 2012;41(1):27–34.

Therapy of tuberculosis always aims to minimize the risk of resistance. Therefore, treatment with a combination of antibiotic substances is of utmost importance as well as the patient's compliance to therapy. Treatment with only one agent would select mutated resistant pathogens. In combination therapy, the drugs used in the regimen have different modes of action to target all *M. tuberculosis* populations. Isoniazid and rifampicin are bactericidal against replicating bacteria in neutral pH. Rifampicin also has a sterilizing effect on pathogens with very low metabolic activity that only have very short metabolically active phase. Pyrazinamide acts on slowly proliferating pathogen located in acidic environment. Ethambutol diminishes the risk of resistance.[53]

In uncomplicated cases, a six-month therapy as shown in Table 4 is the standard of care. For the first two months four substances are administered daily, the following four month the number is reduced to two drugs daily. Success rates of this combination are more than 85% in Germany.[52]

Table 4 *Most commonly used tuberculosis protocol in Germany. In the six months treatment protocol, a combination of four antibiotic substances is given once daily for the first two months followed by four months period of two antibiotic substances, also administered once daily.*[53]

	Medication	**Daily dose [mg/kg bodyweight]**	**Max. dose/day [mg] (depending on body weight)**	**Dosing regimen**
Intensive phase	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol	5 10 25 15	200/300 450/600 1500/2500 800/1600	2 months 1-0-0
Continuation phase	Isoniazid + Rifampicin			4 months 1-0-0

[53] Schaberg T, Bauer T, Castell S, Dalhoff K, Detjen A, Diel R, et al. Empfehlungen zur Therapie, Chemoprävention und Chemoprophylaxe der Tuberkulose im Erwachsenen- und Kindesalter. Pneumologie. 2012;66:133–71.

Despite the high response rate in the industrial world it is important to stratify patient based on the resistance of the bacterial strain they are carrying, pulmonary or extrapulmonary TB, co-infections (e.g. HIV) and other characteristics such as pregnancy or alcoholism (as TB drugs are potentially hepatotoxic) to provide best care while reducing the chance of side effects. Two examples illustrate the importance of patient stratification on individualization of therapy:

- Multidrug-resistant tuberculosis (MDR-TB), TB resistant to at least isoniazid and rifampicin, affects about 480,000 patients worldwide in 2014.[54] These patients must be identified and treated more intense as mortality rate in these cases is particularly high. In cases of a diagnosed or strongly presumed resistant TB, an individualized approach must be sought. Therapy must consider the possibility of cross-resistance and should include drugs that are most likely to be effective. Injectable treatment is typically necessary. The WHO provides tables that list different groups of second-line TB drugs that should be used in individualized treatment regimens.[53,55]
- A major problem in TB treatment remains the co-infection with HIV. In some parts of Africa of all TB infected patients 80 % are also HIV-positive, while the overall worldwide co-infection percentage is around 15 %.[53] Potential for interaction between TB drugs antiretroviral treatment is considered high, especially for rifampicin. Drugs for the patients should therefore be selected based on the least possible interaction chance. As death rates among HIV-positive TB patients are considerably higher than in HIV-negative it is essential that patients receive HIV treatment as well as TB therapy.[53,56]

[54] WHO. What is multidrug-resistant tuberculosis (MDR-TB) and how do we control it? Oct 2015 [Accessed on: 26 Jun 2016]. http://www.who.int/features/qa/79/en/.
[55] WHO. Treatment of drug-resistant tuberculosis. In: Treatment of Tuberculosis Guidelines. 4th edition. p. 85. 2012. [Accessed on: 26 Jun 2016] http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.
[56] WHO. Co-management of HIV and active TB disease. In: Treatment of Tuberculosis Guidelines. p. 65-70. 4th edition. 2012 [Accessed on: 26 Jun 2016]. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.

Due to the complex and tedious therapy, it is especially difficult to gain control of the disease in developing countries. Agencies like FDA, EMA, the German Robert Koch-Institut and organizations such as WHO make a huge effort to collaborate and find a common approach to fight this deadly infection. Yet, it is a long way to go.

A little progress in the fight against ever more increasing resistance was made in December 2012, when the FDA approved a new drug, Sirturo (bedaquiline), under the accelerated approval program for treatment of multidrug-resistant pulmonary tuberculosis when other alternatives are not available. Like other TB drugs, Sirturo should be used in combination with other TB-fighting drugs.[57] Sirturo is the first new medicine for TB treatment in almost fifty years.[58] On July 25th, 2013, the EMA recommended to refuse marketing authorisation for Delamanid, another new drug that was supposed to treat MDR-TB. The CHMP initially found "*that the benefits of Delamanid […] had not been sufficiently shown"*[59] however, the product was approved as an orphan medication soon after.[60]

[57] FDA. FDA news release. 31 Dec 2012 [Accessed on: 26 Jun 2016]. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm.
[58] Hohmann-Jeddi C. Keine Entwarnung bei Tuberkulose. PZ. 2013;44:44.
[59] EMA. Questions and Answers - Refusal of the marketing authorisation for Delamanid (delamanid). 26 Jul 2013 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002552/WC500146651.pdf.
[60] EMA. EPAR summary for the public. Deltyba delamanid. Apr. 2014 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002552/WC500166235.pdf.

4.4.2 Helicobacter pylori

Stomach ulcers and gastritis were generally treated until the end of the 1980s with antacids, substances that neutralize or reduce stomach acidity. In 1983, a report in "The Lancet" describing "unidentified curved bacilli on gastric epithelium in active chronic gastritis" revolutionized the treatment of gastritis and stomach ulcers.[61] The bacterium was found in patients with chronic gastritis. The authors of this article, Barry Marshall and Robin Warren, were awarded the Nobel Prize in in Physiology or Medicine 2005 for the discovery of the bacterium that was initially named *Campylobacter pyloridis* and later renamed *Helicobacter pylori*.[62] The identification of this particular bacterium suggested that ulcers and gastritis may underlie different mechanisms of pathogenesis other than gastric hyperacidity or stress and further research supported this. Today, it is widely accepted that *H. pylori* is one of the main causes for ulcers and other diseases of the upper gastrointestinal tract, including cancer which is why *H. pylori* was classified as a type 1 carcinogen by the WHO in 1994 as it is a risk factor for the development of gastric cancer.[63] More than half of the global population is infected with this organism with a higher prevalence in developing than in industrialized countries.[64,65] The majority of infected persons, however, will remain asymptomatic.[66]

The organism cannot survive for a long time in the acidic environment of the stomach. Hence, it has evolved a mechanism to avoid the acidic environment to colonize the stomach anyway. It does that by using its flagella swimming into mucus layer towards the epithelial cells where the pH is higher. In addition, the

[61] Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet. 1983;1(8336):1273–5.
[62] Nobelprize.org. The Nobel Prize in Physiology or Medicine 2005. [Accessed on: 26 Jun 2016]. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/.
[63] WHO/IARC. Infection with Helicobacter pylori. IARC Monogr Eval Carcinog Risks Hum. 1994;61:177–240.
[64] Kist M, Glockner E, Suerbaum S. Pathogenese, Diagnostik und Therapie der Helicobacter-pylori- Infektion. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2005;48(6):669–78.
[65] Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med. 2002;347(15):1175–86.
[66] Bytzer P, Dahlerup JF, Eriksen JR, Jarbøl D, Rosenstock S, Wildt S. Diagnosis and treatment of Helicobacter pylori infection. Dan Med Bull. 2011;58(4):1–5.

bacterium generates high amount of urease that produces carbon dioxide and basic ammonia, which increases the pH in the surrounding area.[67,68]

Invasive and non-invasive methods for *H. pylori* detection exist. Non-invasive procedures are antigen detection in stool or the carbon-urea-breath-test. For the breath test, patients are orally given ^{13}C-labelled urea. The high urease activity of the bacterium cleaves urea producing ammonia and labelled carbon dioxide that can be detected in the breath.[64] Once *H. pylori* is shown to be present the first-line therapy for eradication is a triple therapy consisting of a proton pump inhibitor (PPI) and two antibiotics. There is a choice of several suitable PPIs, omeprazole (20 mg), esomeprazole (20 mg) and pantoprazole (40 mg) are the ones most commonly used. In the Italian triple therapy, clarithromycin and metronidazole are used as antibiotics; the French therapy metronidazole is replaced by amoxicillin.[69] In Germany, as already mentioned, a combination pack containing pantoprazole (40 mg), amoxicillin (1000 mg) and clarithromycin (500 mg) for a seven-day therapy with the brand name ZacPac is approved.[19] Quadruple therapies use a PPI, metronidazole, tetracycline and a bismuth salt. A bismuth free quadruple therapy (concomitant therapy) exists as well; both quadruple therapies have demonstrated superiority when compared to standard therapy.[69] Current research indicates that eradication rates achieved by triple therapy have lost efficacy over the years and are now less than 80% due to the development of antibiotic resistance primarily to clarithromycin.[70] A new approach of combining all previously used substances is the sequential therapy. This protocol administers the antibiotics not simultaneously but in a sequence and has initially suggested higher eradications rates than triple therapy (84.3 %)[71] but newer studies indicate

[67] Amieva MR, El-Omar EM. Host-bacterial interactions in Helicobacter pylori infection. Gastroenterology. 2008;134(1):306–23.
[68] Smoot DT. How Does Helicobacter pylori Cause Mucosal Damage? Direct Mechanisms. Gastroenterology. American Gastroenterological Association; 1997;113(6):S31–S34.
[69] Fischbach W, Malfertheiner P, Jansen PL, Bolten W, Bornschein J, Buderus S, et al. S2k-Leitlinie Helicobacter pylori und gastroduodenale S2k-guideline Helicobacter pylori and gastroduodenal ulcer disease. Z Gastroentero. 2016;54:327–63.
[70] Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon ATR, Bazzoli F, et al. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. Gut. 2012;61(5):646–64.
[71] Gatta L, Vakil N, Scarpignato C. Global eradication rates for Helicobacter pylori infection : systematic review and meta-analysis of sequential therapy. BMJ. 2013;347(f4587):1–14.

non-superiority of the sequential therapy and is no longer recommended in the German guideline.[69,72]

Table 5 *Most commonly used H. pylori first-line eradication protocols in Germany*[69]

Name	Medication	Dosing
Italian triple therapy	PPI + clarithromycin (250-500 mg) + metronidazole (400-500 mg)	7 -14 days 1-0-1
French triple therapy	PPI + clarithromycin (500 mg) + amoxicillin (1000 mg)	7 -14 days 1-0-1
Quadruple therapy	PPI + bismuth potassium salt (140 mg) tetracyclin (125 mg) + metronidazole (125 mg)	10 days
Concomitant therapy	PPI + clarithromycin (500 mg) + amoxicillin (1000 mg) + metronidazole (400-500 mg)	7 days 1-0-1

Thanks to the discovery of *H. pylori*, patients with ulcer and gastritis now receive a differentiated diagnosis for the cause of their medical condition. Based on this diagnosis, an individual therapy can be provided which takes into account different pathogenesis of peptic ulcer and gastritis.

[72] Hsu PI, Wu DC, Chen WC, Tseng HH, Yu HC, Wang HM, et al. Randomized controlled trial comparing 7-day triple, 10-day sequential, and 7-day concomitant therapies for Helicobacter pylori infection. Antimicrob Agents Chemother. 2014;58(10):5936–42.

4.4.3 BiDil – the "race drug"

The product BiDil is an in many respects remarkable example of an attempted targeted combination drug. The FDA approved the drug in 2005 for treatment of heart failure for patients that "self-identify as black".[73] Interestingly, two active substances were combined in this product, which usually play a minor role in the treatment of heart failure. It consists of two vasodilators, hydralazine hydrochloride and isosorbide dinitrate (ISDN). Both compounds have long been available generically. Hydralazine receives only little attention in the German guidelines for heart failure.[74] The vasodilatory effects of ISDN are mainly used in the treatment of angina pectoris. The FDA first rejected BiDil in 1997 since the data for the tested population, that included all races, could not show the drug's efficacy convincingly. The company was advised by the FDA to review their data. A post hoc subset analyses indicated that the drug works better in black patients, while no benefits were observed for white patients. A new clinical trial called A-HeFT (African-American Heart Failure Trial) with self-identified African-Americans who suffered from NYHA class III or IV heart failure was conducted.[75,76] In this study, BiDil succeeded to show efficacy through the reduction of deaths by 43 % and a 39 % decrease in hospitalization compared to standard of care and was authorised on the basis of these figures by the FDA. Approving a drug for a specific race, based on patients' self-identification, was an unprecedented regulatory situation. The FDA declared the approval as *"[...] a step toward the promise of personalized medicine"* and emphasized that the drug combination is a treatment from which not all patients benefit but only a few.[73]

After being approved, the drug and its intended use were cause for many discussions. Especially the self-identification of patients was criticized as a poor surrogate for stratification. "Self-identified black" is a purely subjective

[73] FDA. FDA Approves BiDil Heart Failure Drug for Black Patients. 23 Jun 2005 [Accessed on: 26 Jun 2016]. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108445.htm.
[74] Bundesärztekammer, Kassenärztliche Bundesvereinigung, AWMF. Nationale VersorgungsLeitlinie Chronische Herzinsuffizienz. Aug 2013 [Accessed on: 26 Jun 2016]. http://www.awmf.org/uploads/tx_szleitlinien/nvl-006l_S3_Chronische_Herzinsuffizienz_2013-abgelaufen.pdf.
[75] Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Ferdinand K, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. N Engl J Med. 2004;351(20):2049–57.
[76] Krimsky S. The short life of a race drug. Lancet. 2012;379(9811):114–5.

stratification that is scientifically untenable. It was never discovered why the drug seemed to be more effective in black patients. A causal link between a target structure and effect was never found and no genetic markers could be identified. It has been much debated that race does not automatically corresponds to a certain genetic heritage from which the drug's effect can be derived. Furthermore, the pivotal study raised concerns. The study was conducted with black patients only without any involvement of other ethnic groups as a control, thus the extent of the benefits of black patients against white patients was not determined, said critics.[76,77,78,79]

The FDA answered to those critical concerns and justified the agency's decision as a reasonable conclusion based on data from clinical studies. They emphasized that there had been two well-controlled, randomized trials prior to the pivotal study that led to the approval in which black as well as white patients were represented. No clinical benefit for the white population was indicated by these two studies so that the study design for A-HeFT with exclusively black population was considered rational. Confronted with the accusation about the missing knowledge why the drug works better in black patients, the FDA argued that this is not a legal requirement. It is essential to show that a drug works according to its claim but not why it works that way. The lack of knowledge about why the drug is more effective in African-Americans is not a sufficient reason to deny a group of patients access to a drug from which they clearly benefit. The FDA was also astonished that so much criticism arose from the fact that BiDil was approved as a race-specific drug. For many years now, it is a requirement to include all sorts of different groups in drug testing trials such as patients of different ages, sexes and even races since it is commonly known that drugs work differently among patient groups. A drug's effect and metabolism differs for example in man and women or elderly patients and younger ones. Therefore, it is not remarkable that a drug

[77] Duster T. Medicalisation of race. Lancet. 2007;369(9562):702–4.
[78] Coons SJ. Have we witnessed the rise and fall of race-specific drugs? Clin Ther. 2009;31(3):620–2.
[79] Kahn J. Misreading race and genomics after BiDil. Nat Genet. 2005;37(7):655–6.

shows a better effect in one race compared to another and that this characteristic is considered in the approval.[80]

Despite all the concerns, the approval of BiDil was of great economic interest for the marketing authorisation holder, NitroMed, because the drug's patent was extended by 15 years through the approval as race-specific drug, which would have otherwise expired in 2007.[77] The economic expectations for the drug were initially large, 750,000 patients and annual sales of $825 million were expected,[81] but sales fell significantly short of expectations because sceptical physicians and patients did not adapt the drug very well.

Despite the limited success of the drug, it is an example how products, which have already been in the marked for some time, can enter new therapeutic fields by identifying subgroups. It may help old medicines gain new economic power and relevance in therapy.

[80] Temple R, Stockbridge NL. BiDil for heart failure in black patients: The U.S. Food and Drug Administration perspective. Ann Intern Med. 2007;146(1):57–62.
[81] Saul S. U.S. to Review Heart Drug Intended for One Race. In: New York Times. 13 Jun 2005 [Accessed on: 26 Jun 2016].
http://www.nytimes.com/2005/06/13/business/13cardio.html?pagewanted=all&_r=0

5 Applications of therapeutic concepts

Combination of medications can be realized using fixed combinations, combinations packs or evidence displayed in medical guidelines. Despite the benefits of these alternatives there are several disadvantages connected with that as well. These are mainly the missing dosage flexibility in fixed combinations and the varying degree in quality and absence of authorisation in medical guidelines. Many diseases however require combination therapy such as tuberculosis or helicobacter. In other cases combinations seem to be beneficial for defined patient groups (see Chapter 4.4). Especially when a disease mechanism is very well known and a patient population can be defined in which this pathology is present, combinations can serve as a valuable tool in therapy. Therapeutic concepts can compensate the disadvantages of other combination alternatives described above by having a flexible yet authorised arrangement.

Therapeutic concepts are rather complex due to the various possibilities of combinations and the fact that the products of the combination shall be marketed independently, which poses an elevated risk compared to single drug treatment. Hence, therapeutic concepts are particularly interesting in distinctive and well-defined patient groups whose pathologic pathway is well understood to reduce unexpected risks. One potential field of application for therapeutic concepts would eventually be personalized medicine. This field of research is based greatly on genomic approaches and strives to identify the reaction of patient groups towards specific treatments. The research in this area is likely to discover new cellular pathways and optimized therapies derived from this knowledge. The new findings expected in this area can lead to an increased use of combinations with a scientific rational to target therapy to multiple cellular pathways thus making it superior to single drug treatment. Personalized medicine is therefore particularly noteworthy for therapeutic concepts and is therefore presented in further detail in the following sections.

5.1 Personalized medicine

Drugs are usually administered based on the experience that it provides a sufficiently high probability that it will help the patient in his suffering. However, not every drug works equally well in every patient. A drug that helps one patient may fail in the next patient. The probability that a certain drug will be effective is different for each patient. This is true for almost any drug to varying degrees. Studies show that the response rate of patients to a certain pharmacological intervention can be extremely low. Response rates in Alzheimer's therapy for example can be as low as 30 %, efficacy rates for depression or schizophrenia may reach around 60 %. Even COX-2 analgesics only show efficacy rates of 80 %.[82] Reasons for the response rate are numerous and can include inappropriate dosing or lack of compliance in addition to physiological causes. The situation is similar for adverse reactions. Not every patient experiences a drug's adverse reactions. If side effects occur, they may have varying severity. It is usually impossible to predict which patient benefits from a drug and which will suffer from side effects.

The development of personalized medicine strives to change the predictability of these outcomes since several years. It means to increase the likelihood of effectiveness and reduce the adverse effects for selected drugs based mainly on genetic and biological markers. Currently it is not possibly to determine the chances of efficacy for all therapeutic classes, in fact there is only a small percentage of therapeutics for which evidence based prediction is now possible. The presence of personalized medicine is founded on the growing knowledge about cellular signalling pathways, which can be used in drug development. A more detailed insight into the cellular pathways and a complete understanding of the biochemical response to drugs provides better chances to target drug therapy.[15]

In the last decade, personalized medicine has raised great anticipation for the medicine of the future and has in fact become a synonym for modern medicine. No clear definition for the phrase actually exists and it is interpreted quiet differently among various interest groups. The definition of the NIH Talking

[82] Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001;7(5):201–4.

Glossary of Genetic Terms however can be regarded as consensus for most stakeholders.

> *Personalized medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen. Personalized medicine is being advanced through data from the Human Genome Project.*[83]

Personalized medicine strives to deliver the right drug to the right person at the right time and at the right dose; tailoring the medicine to the patient is based on genetic information. Pharmacogenomics and personalized medicine are often used interchangeably.[84,85]

Personalized medicine means to identify a patient subgroup that exhibits a certain clinical characteristic. Personalized medicine is in fact not a medicine personalized for one individual patient. The personalization takes into account only personal markers, mostly of genetic origin, but not actual personal circumstances. The individual differences of patients with respect to heritage, social environment and way of life are not considered, even though these are also relevant factors for diagnosis and treatment outcomes. Personalized medicine means a purely scientific stratification and not a personalization on an individual social basis. It is rather "stratified" than "personalized". Terms like "targeted medicine" or "stratified medicine" that are used as well are more indicative of the approach.

Treatment with a personalized medicine drug often requires testing of a certain marker prior to treatment. Which marker test is required depends on the drug that is intended to be used and its mechanism of action. Most markers are of genetic nature but can concern different aspects of genetics such as:

[83] NIH. Personalized Medicine. In: Talking Glossary of Genetic Terms [Accessed on: 26 Jun 2016]. http://www.genome.gov/glossary/index.cfm?id=150.
[84] Hamburg MA, Collins FC. The Path to Personalized Medicine. N Engl J Med. 2010;301–4.
[85] Henney AM. The promise and challenge of personalized medicine: aging populations, complex diseases, and unmet medical need. Croat Med J. 2012;53(3):207–10.

- Variations in metabolism (e.g. cytochrome P450-enzymes)

  Depending on the individual expression of the metabolic (CYP-) enzymes substances can be metabolized faster, slower or not at all. Differences in metabolic enzymes may influence the effectiveness of drugs in different ways. For example, a pro-drug cannot be transferred in adequate quantity into the active form when the corresponding enzyme is insufficiently available. Furthermore, a too slow degradation of active substance or metabolites may cause an accumulation, which in turn could lead to a higher risk of adverse effects.
- Gene mutations

  Mutations in genes can be associated with a higher risk of cancer. Certain mutations are target of personalized medicine and the pharmaceutical will only be effective when the corresponding mutation is present.
- Other (non-genetic) biomarkers

Based on the test result it can be determined whether the patient should receive the “personalized medicine” or conventional treatment. Figure 3 shows an example of a possible stratification scenario. A larger group of patients with the same diagnosis (e.g. lung cancer) undergoes a test to determine molecular differences. If, in case of lung cancer, a mutation of the EGRF (epidermal growth factor receptor) gene is present the group of patients with the mutation a different treatment will be administered than to the group that shows no mutation, thus creating two subgroups with one receiving the “personalized treatment” with the promise of a higher treatment success.

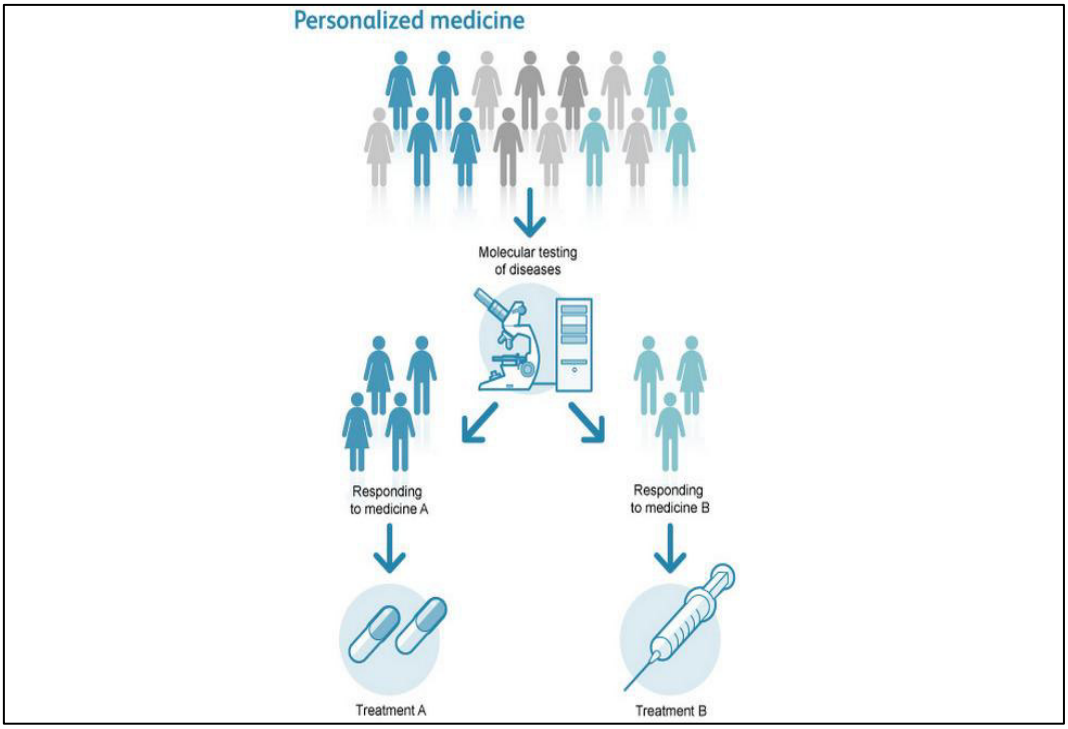


Figure 3 *Personalized medicine: A patient cohort is tested for a specific marker in order to stratify the group into subgroups. Depending on test results, the groups receive different treatment, the one that is most likely for them to be effective.*[86]

The very first articled found on PubMed database concerning personalized medicine was published in 1999 by R. Langreth and M. Waldholz in The Oncologist called ”The new era of personalized medicine”[87]. This article was the first to discuss the pharmaceutical industry’s efforts towards so-called “niche-busters” (drugs that are successful in a smaller subpopulation of patients) instead of continuing looking for one-size-fits-all blockbuster drugs and the vision of tailor-made drugs based on individual genetic makeup. Several big pharma companies had started to invest the genetic diversities hoping to find genetic markers that would help to determine whether a drug works in a patient or if it is likely to cause adverse reactions.

[86] Pfizer. What is Personalized Medicine? [Accessed on: 25 Jul 2015]. http://www.pfizer.ie/personalized_med.cfm
[87] Langreth R, Waldholz M. New era of Personalized Medicine. Oncologist. 1999;4(5):426–7.

Two criteria must at least be met to raise the industry's interest in developing drugs for personalized medicine:

1. An economically interest market must exist.
   Costs for developing a targeted medicine differ from those of conventional drug development. The duration of time and cost consuming clinical trials may be shortened through prior patient stratification as the evidence of effectiveness can be more easily provided, which leads to faster access to market time and longer patent protection time. However, the patient population receiving the drug once approved is significantly smaller than of a one-size-fits-all. A high therapeutic efficacy compared to alternative therapies justifies higher market prices on the other side.[88]
2. Identification of the subgroup must be feasible.[88] This means that the detection of the patient markers must be both technically feasible and the expenses are not too high.

One of the first approved drugs in the area of personalized medicine was trastuzumab (trade name: Herceptin) by Genentech, a monoclonal antibody that is only to be used when the patient overexpresses the Human Epidermal Growth Factor 2 (HER2), a receptor protein which is encoded by the HER2/neu gene. Before starting treatment, it is mandatory to examine the patient's HER2 status in the laboratory as the monoclonal antibody only has beneficial effects when the receptor is overexpressed.[89] It gained approval from the FDA in 1998, the European market authorisation was granted in 2000. Since 2010, the product is also approved for the treatment of stomach cancer. A test detecting the gene amplification for HER2/neu is mandatory before administering the drug to the patient. Since the mid-90's more and more drugs require determination of biomarkers before starting treatment (see Table 7)

[88] Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nat Rev Drug Discov. 2007;6(4):287–93.
[89] Kato R, Hasegawa K, Ishii R, Owaki A, Torii Y, Oe S, et al. Human epidermal growth factor receptor-2 overexpression and amplification in metastatic and recurrent high grade or type 2 endometrial carcinomas. Onco Targets Ther. 2013;6:1065–71.

Personalized medicine can be interpreted very differently by the existing fields in medicine. There is no definition yet what personalized medicine is about, statements on definition range from a purely biomarker-oriented approach in disease treatment to the personal needs of an individual patient, which leaves much space for interpretation. It can be said that the diseases that personalized medicine focusses the most on, according to the number of published articles and approved products, are cancer, diabetes, autoimmunity diseases and cardiovascular pathologies. Even though the first drugs were approved over ten years ago, regulators, industry and the medical sector are still just starting to find a good approach on this topic. There are a huge number of working parties on pharmacogenomics and personalized medicine by agencies (*Pharmacogenomics Working Party* (PgWP) by CHMP, Interdisciplinary Pharmacogenomics Review Group (IPRG) by FDA), universities or industry.

There is also a huge public interest in this topic, news magazine such as *Spiegel* have featured various detailed articles about hopes and concerns of an individualized therapy in the past years.[90]

Personalized medicine does not only promise a targeted treatment in case of illness but also envisions that diseases can be detected even before their manifestation and can then be treated preventively. Genetic data measures for individual patients or patient groups, such as families, could be used to react as soon as possible with available prevention strategies when a certain marker is present. Prevention strategies may include several options, such as medication or change of life style. An inherited genetic mutation that indicates a high risk for a specific type of cancer may even lead to surgery in order to reduce the risk of this cancer, such as for example an oophorectomy in women with proven BRCA1/2 (BReast CAncer) mutation who have an elevated risk of ovarian cancer.[91] In cases where no adequate prevention is available, the investigation of the genetic status at an early stage can lead to quicker selection of an appropriate therapy with less try-and-error approaches.

[90] Grill M, Hackenbroch V. Das große Versprechen. In: Der Spiegel 32/2011. 2011;32:124–8.
[91] Marchetti C, De Felice F, Palaia I, Perniola G, Musella A, Musio D, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Womens Health. 2014;14(1):1–6.

Personalized medicine means not only to determine which is the right medication for the patient but can also determine in some cases which is the wrong choice for the patient. Biomarkers that predict the patients risk for serious adverse reactions exist for several drugs. For example, serious hypersensitivity reactions are a feared side effect in the treatment of HIV infections with abacavir. The manufacturer of abacavir demonstrated in a clinical trial that this reaction was strongly associated with the presence of the HLA-B*5701 (human leukocyte antigen-B) allele which had a prevalence of 5.6 % in the patient population. A screening for this biomarker prior to abacavir treatment significantly reduced the appearance of the hypersensitivity reaction. Prospective screening for the HLA-B*5701 allele is mandatory to protect these patients from the serious adverse effects of the drug.[92,93] Other examples for biomarkers that similarly determine a patient's likeliness to response adversely to a drug are listed in Table 7.

A further goal of personalized medicine is to increase patients' therapy compliance. Compliance describes the degree to which a patient correctly follows the therapeutic intervention that a health care professional has prescribed and can referred to as adherence. Compliance is influenced by a large amount of factors and has a major share in the success of any therapy concluding that non-compliance on the other hand has a huge part in therapy failures. WHO has reported in 2003 that 50 % of patients with chronic diseases are non-compliant.[94] Non-compliance can be affected by a variety of reasons. Onset of adverse reaction or the fear of such or absence of the perception of the therapy effect often causes non-compliance. Other explanation may include poor understanding of the treatment regime and benefit, lack of communication with the physician, costs, complicated dosing or multi-medication and comorbidity. Treatment failure and hospital admissions due to non-compliance result not only in negative health effects but also in high costs. Improving compliance is therefore an important issue and personalized medicine might indeed offer an approach in some cases. A

[92] Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358(6):568–79.
[93] Becquemont L, Alfirevic A, Amstutz U, Brauch H, Jacqz-Aigrain E, Laurent-Puig P, et al. Practical recommendations for pharmacogenomics-based prescription: 2010 ESF-UB Conference on Pharmacogenetics and Pharmacogenomics. Pharmacogenomics 2011;12(1):113–24.
[94] WHO. The magnitude of the problem of poor adherence. In: Adherence to long-term therapies: Evidence for action. p. 7. 2003. [Accessed on: 26 Jun 2016]. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.

biomarker based diagnostic and therapy can increase the participation in health care decision for both physicians and patients and support communication and compliance as the patients receives a positive feedback regarding safety and efficacy of a therapy. By dosage adjustment or not prescribing critical drugs side effects can be prevented, this increases the compliance.[95,96]

In conclusion, the goal of personalized medicine is to improve quality of life by means of better choices of therapy and less adverse reactions as well as to improve the cost-effectiveness of therapy by faster choosing of a therapy and by improving patients' understanding and compliance of those therapies.

However, personalized medicine has still several obstacles to overcome. Some major challenges are not yet addressed. Today, there is no sufficient evidence, that personalized medicine is superior in the long term than the standard of care. The identification of relevant genetics is rather slow. Even if a genetic variant is identified, its clinical significance on risk prediction or treatment success is questionable.[97] Comparative warfarin sensitivity trials, for example, showed little benefit of the sensitivity test over careful patient monitoring.[98] For mutations that are associated with an elevated risk of cardiovascular diseases in women, a study showed that the predictive power of the mutation presence of chromosome 9p21.3 does not give additional information on the risk.[97,99] There is also a high demand for evidence of promised cost-effectiveness of personalized medicine. Only by providing evidence, payers will agree to invest in personalized medicine therapies. The economic evaluation of genome-based therapy presents itself as very complex, as many different factors contribute to it and long term cost savings are

[95] Deutscher Bundestag 16. Wahlperiode. Potenziale der individualisierten Medizin. In: Technikfolgenabschätzung Zukunftsreport Individualisierte Medizin und Gesundheitssystem. p. 7f. 17 Feb 2009 [Accessed on: 26 Jun 2016]. http://dip21.bundestag.de/dip21/btd/16/120/1612000.pdf.
[96] Downing GJ. Key aspects of health system change on the path to personalized medicine. Transl Res. 2009;154(6):272–6.
[97] Garber AM, Tunis SR. Does Comparative-Effectiveness Research Threaten Personalized Medicine?. N Engl J Med. 2009;360(19):1925–7.
[98] Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, Nicholas ZP, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation. 2007;116(22):2563–70.
[99] Paynter NP, Chasman DI, Buring JE, Shiffman D, Cook NR, Ridker PM. Cardiovascular Disease Risk Prediction With and Without Knowledge of Genetic Variation at Chromosome 9p21.3. Ann Intern Med. 2009;150:65–72.

difficult to determine.[100] Essentially, cost-effectiveness needs to be determined for each condition and each therapy individually. Even for personalized medicine, therapies that are applied often, the evidence for cost-effectiveness is still not complete. For example, trastuzumab is found to be cost-effective only under certain circumstances (HER2-positive patients under 65 years of age).[101] No overall cost-effectiveness evidence for genome-based therapies is yet available.

Personalized medicine in summary offers various opportunities for modern medicine. Due to the complex nature of personalized medicine several obstacle are however yet to overcome before all the promises can be implemented practically. While some genetic based diagnostics and treatment have already proven their value to health care, others remain uncertain. Personalized medicine remains a heterogeneous research area, which, like conventional medicine, will result in successful medical treatment options as well as in those that will fail to meet the demands.

[100] Shabaruddin F, Payne K, Fleeman N. Economic evaluations of personalized medicine: existing challenges and current developments. Pharmgenomics Pers Med. 2015;8:115.
[101] Diaby V, Tawk R, Sanogo V, Xiao H, Montero AJ. A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. Breast Cancer Res Treat. 2015;151(1):27–40.

Table 6 *Summary of aims and challenges of personalized medicine*

Goals and Visions	vs.	Problems and Challenges
Prevention rather than reaction		Lacking evidence for superiority to SOC
Less try-and-error, faster choice of best therapy		Proper biomarker identification must be available
Less ADRs		Lacking evidence for cost-effectiveness
Improving compliance		Possible genetic discrimination
Better cost-effectiveness		Disregarding social environment
Improving Quality of life		Shift of priorities: Less conventional treatment and research?

5.1.1 Biomarkers

In the concept of personalized medicine biomarkers play an essential role. It has already been described that the presence or absence of a certain patient's characteristic is crucial for the effectiveness of specific medicines. Measurable indicators of those characteristics are called biomarkers. A genomic biomarker is defined by the ICH as

> *"[...] a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions."*[102]

Examples of those characteristics are measurement of gene expression or function, single nucleotide polymorphisms (SNPs) in DNA or RNA splicing variations. The FDA does not only see genetic information as biomarkers but also all sorts of other

> *"[...] characteristic[s] that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention. A biomarker can be a physiologic, pathologic, or anatomic characteristic or measurement that is thought to relate to some aspect of normal or abnormal biologic function or process. Biomarkers measured in patients prior to treatment may be used to select patients for inclusion in a clinical trial. Changes in biomarkers following treatment may predict or identify safety problems related to a drug candidate or reveal a pharmacological activity expected to predict an eventual benefit from treatment."*[103]

Biomarkers, that are assumed to improve therapy or predict an outcome, are found every day but it is vital to find those that will actually proof significant in clinical

[102] EMA. Note for Guidance on definitions for genomic biomarkers, phamacogenomics, pharmacogenetics, genomic data and sample coding categories. (EMEA/CHMP/ICH/437986/2006). Nov 2007. [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf.

[103] FDA. DDT Glossary. 01 Sep 2015 [Accessed on: 26 Jun 2016]. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284395.htm.

use. The regulatory system needs to meet the requirements to ensure a safe and effective medical treatment.

The EMA recommends involving biomarkers very early in clinical research and trials to judge the biomarker's influence on prediction and treatment (ICH topics E15 and E16). Retrospective studies can be challenging since they lack the power of well-planned prospective trials. Nevertheless, even retrospective analysis can save a drug that otherwise would probably struggle to get an approval. An example for such a scenario is the product BiDil. As already discussed, the product was rejected by the FDA at first, but later analysis revealed that the combination had a statistically better effect in Afro-Americans than in Caucasians and so the FDA approved it for that purpose. Thus, a very easy to find "biomarker" helped placing a drug on the market for some patients' benefit (compare Chapter 4.4.3).

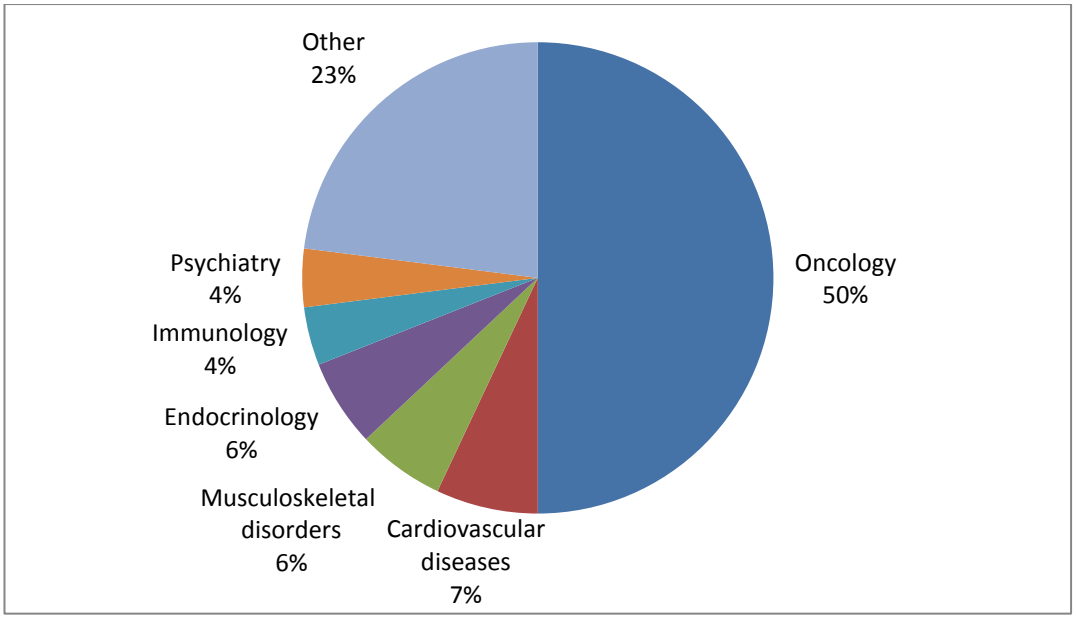


Figure 4 *Use of biomarkers in clinical trials 1970-2011.*[104]

Diagnostics, especially in-vitro diagnostics (IVD), in context of personalized medicine are not very much in focus, at least in the European Union. The FDA has worked out an approach to deal with drug/diagnostic combinations. If an IVD

[104] The Boston Consulting Group, vfa. Die Personalisierte Medizin In: Medizinische Biotechnologie in Deutschland. p. 27. Jun 2011. [Accessed on: 26 Jun 2016]. http://www.gtai.de/GTAI/Content/EN/Invest/_SharedDocs/Downloads/Extern/Industries/vfa-report-on-medical-biotechnology-2011.pdf.

is needed for the safe and effective use of a drug, the specific companion diagnostic needs to undergo clinical trials and FDA approval, otherwise the drug will not receive market authorisation. In the European regulatory framework, IVDs are subject to the IVD directive 98/79/EC. Since most of the IVD that are needed for personalized medicine drugs do not belong to List A or B in Annex II the conformity assessment procedures lays in the responsibility of the manufacturer. This bears a high risk, because no independent third party (Notified Body) is involved. To minimize risks due to weak performances of IVDs, the European Union should raise the standards and requirements for IVD. A first improvement could be the evaluation of the test by a reference laboratory or stricter phrasing in the SmPC on how tests, for example when looking for an overexpressed receptor, should be performed, and more information about how they were done in the clinical trials. The diagnostics issue is surely one that the EC and the EMA will have to work on in order to increase the value of personalized medicine.

5.1.2 Personalized medicine drugs

The drugs approved for personalized medicine are often based on mandatory or recommended testing for certain genetic markers ("Biomarkers"). The outcome of the test determines whether the drug in question will be effective for the patient or will show if the patient has a high risk for a serious adverse reaction. Table 7 gives an overview on some of the most prominent examples for personalized treatments approved in Germany and Europe. Most of the medicinal products are used in oncology. The table shows that personalized medicine is in great need of validated diagnostic tools that help to determine if the listed medications are beneficial for the patient in the specific situation. If the diagnostic give a false positive or false negative result the patient may be treated with an ineffective product. A correct test result is therefore indispensable. As a test exists for most drugs that are considered personalized medicine, therapeutic concepts provide an opportunity to include the corresponding diagnostic in an authorised treatment combination.

Table 7 *Selected drugs approved for personalized medicine in Germany and biomarkers associated with effectiveness or adverse reaction of the drug. Test are conducted to determine either the effectiveness of the medication or a patient's likeliness to suffer from severe adverse effects.*[105]

Active ingredient	Indication	Test mandatory or recommended*	Subject of test/Outcome	Test result indicates
Abacavir	HIV/Aids	Mandatory	Presence of HLA-B*5701 allele, which is strongly associated with hypersensitivity reactions, only to be used in HLA-B*5701 negative patients.	Adverse drug reaction
Arsenic trioxide	Oncology/ APML	Mandatory	Presence of PML/RAR alpha gene, only to be used in patients with positive test result	Effectiveness
Azathioprine	Immuno-suppressant	Recommended	Absence or low activity of the enzyme TPMT causes higher risk for bone marrow suppression	Adverse drug reaction
Carbamazepine	Epilepsy	Recommended	Presence of HLA-B*1502 allele, which is associated with fatal skin reactions, only to be used in HLA-B*1502 negative patients	Adverse drug reaction
Cetuximab	Oncology/ Colorectal cancer	Mandatory	Presence of wildtype KRAS gene, only to be used in patients carrying the wildtype	Effectiveness

[105] vfa. In Deutschland zugelassene Arzneimittel für die personalisierte Medizin. http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/individualisierte-medizin.html (Accessed on: 03 Feb 2016).

* according to Fachinfo/SmPC of product.

Active ingredient	Indication	Test mandatory or recommended*	Subject of test/Outcome	Test result indicates
Crozotinib	Oncology/ALK (NSCLC)	Mandatory	Presence of ALK gene, only to be used in patients with positive test result	Effectiveness
Erlotinib	Oncology/Lung cancer	Mandatory (since 08/11)	Presence of EGFR mutation/overexpression, only to be used in patients with positive test result	Effectiveness
Fulvestrant	Oncology/breast cancer	Mandatory	Presence of hormone receptor-positive breast cancer cells, only to be used in positive tested patients	Effectiveness
Imatinib	Oncology/AML and CML	Mandatory	Presence of Philadelphia chromosome, only to be used in positive patients	Effectiveness
Ivacaftor	Cystic fibrosis	Mandatory	Presence of G551D mutation in CFTR gene, only to be used in patients with positive test result	Effectiveness
Lomitapid	Homozygous familial hyper-cholesterolemia	Recommended	Genetic evidence of homozygous familial hypercholesterolemia	Effectiveness
Maraviroc	HIV/Aids	Mandatory	Presence of CCR5 receptor (HIV tropism), only to be used in patients with positive test result	Effectiveness

Active ingredient	Indication	Test mandatory or recommended*	Subject of test/Outcome	Test result indicates
Natalizumab	Multiple sclerosis	Recommended (since 06/11)	Test for Anti-JCV antibodies, JCV may cause progressive multifocal leukoencephalopathy	Adverse drug reaction
Tamoxifen	Oncology/breast cancer	Recommended	a) Presence of hormone receptor-positive breast cancer cells, only to be used in positive tested patients b) Test for expression ratio of HOXB13, IL17BR genes to determine recurrence risk of cancer, based on results mono or combination therapy	Effectiveness
Trastuzumab	Oncology/breast and stomach cancer	Mandatory	Presence of HER2 overexpressing tumour, only to be used in patients with positive test result	Effectiveness
Vemurafenib	Oncology/ melanoma	Mandatory (since 02/12)	Presence of BRAF-V600 mutation, only to be used in patients with positive test results	Effectiveness

The complete list of drugs that are considered personalized medicine contains 47 approved substances in Germany to date (February 2016). Of the 47 substances, 36 are used in oncologic therapies, which corresponds to 77 % of these drugs.

A test to either check for the products effectiveness or an adverse reaction is mandatory for 39 medications (83%). This data show how important diagnostic test are for a safe and effective use. Therefore is must be ensured that the diagnostic actually gives correct results.

5.1.3 Development of personalized medicine

The idea of tailoring the right medicine to the right patient at the right time is as old as medicine itself. In a time where people had no understanding for basic human physiology, let alone DNA, doctors already tried to find the best cure for their patients. One of the most well-known physicians of ancient time was Hippocrates (c. 460 BC – c. 370 BC). He understood that he was not treating conditions but an individual person suffering from this condition. Today, the often-quoted statement, "*It is more important to know what sort of person has a disease than to know what sort of disease the person has*"[106] by Hippocrates is one of the highest credos in personalized medicine. However, it was not until 1866 before the first scientific proof about a person's individual characterization was postulated by Gregor Mendel.[107] His experiments with pea plants and their hybrids led to Mendel's Laws of Inheritance and made him "the father of modern genetics".[108] Another turning point in understanding biological differences between individuals was the discovery of blood types and the characterization with the ABO system described by Karl Landsteiner (1868-1943) in 1901.[109] This finding showed for the first time very undoubtedly that there is no such thing as a "one-fits-all" medicine; receiving blood from a person with the wrong blood type had mostly disastrous results, which made Landsteiner's discovery a lifesaver for many patients. Only a few years later, Sir Archibal Garrod reports about an

[106] Fosarelli P. Medicine, Spirituality, and Patient Care. JAMA. 2008;300(7):836–8.
[107] Mendel G. Versuche über Pflanzenhybriden. Verhandlungen des naturforschenden Vereines in Brunn. 1866.
[108] Hackett S, Feldheim K, Alvey M. Genes and genius: the inheritance of Gregor Mendel. DNA Cell Biol. 2006;25(12):655–8.
[109] Tan S, Graham C. Karl Landsteiner (1868–1943): Originator of ABO blood classification. Singapore Med J. 2013;54(5):243–4.

"inborn error in metabolism": alkaptonuria.[110] This disease can be diagnosed by a person's urine, which, after exposure to air, turns dark. Later in life, patients suffer from arthritis caused by accumulation of homogentisic acid in the tissue. Garrod studied several families and found alkaptonuria to be of autosomal recessive inheritance, thus linking genetic inheritance and susceptibility to a certain disease.[111] The demonstrated examples were all important milestones in the formation of personalized medicine. However, one of the most important discoveries was yet to come, the molecular model of a base-paired DNA presented by Watson and Crick in 1953.[112] DNA and genetics gained a high amount of interest in the scientific world. Researchers focused more and more on this field and therefore developed a great variety of tools and technology to investigate. In the late 1950's, different findings suggested a relation between genetics and drug reactions. Werner Kalow and a colleague found patients with an uncommon susceptibility to the muscle relaxant suxamethonium resulting in prolonged apnoea. They had not only the patients' blood, but also that of their family members' and other test persons analysed. In 1956, he published the results proposing the idea that there must be at least two different types of human serum-cholinesterase.[113] Another adverse drug reaction (ADR) was bringing more attention to drug – genetics interactions. Primaquine is an agent that has been used to treat malaria since the 1940's. One side effect was intravascular haemolysis in some patients, which can be fatal.[114] It was later shown that this was due to a glucose-6-phosphate dehydrogenase deficiency.[115] Both events draw attention to the fact that genetics can affect drug metabolism, and raised the question what other adverse drug reactions were possibly caused by related genetic mechanisms. The concept of the field of pharmacokinetics was basically established, but it took a few more years until the actual term for the genetically caused reactions to drugs

[110] Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. 1902 [classical article]. Yale J Biol Med. 2002;75(4):221–31.
[111] Phornphutkul C, Introne WJ, Perry MB, Bernadini I, Murphy MD, Fitzpatrick DL, et al. Natural History of Alkaptonuria. N Engl J Med. 2002;347(26):2111–21.
[112] Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature. 1953;171(4356):737–8.
[113] Kalow W. Familial incidence of low pseudocholinesterase level. Lancet. 1955;268:576–7.
[114] Myint HY, Berman J, Walker L, Pybus B, Melendez V, Baird JK, et al. Review: Improving the therapeutic index of 8-aminoquinolines by the use of drug combinations: review of the literature and proposal for future investigations. Am J Trop Med Hyg. 2011;85(6):1010–4.
[115] Carson PE, Flanagan CL, Ickes CE, Alving AS. Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes. Science. 1956;124(3220):484–5.

came up. Friedrich Vogel was the first to use the word pharmacogenetics in 1959.[116] Today, pharmacogenetics refers to many different aspects of genetic differences in metabolic pathways. That includes ADRs caused by drugs, a therapeutic effect that can only be achieved in patients with a specific gene variation, as well as the testing for genetically caused diseases or for both drug safety and efficacy. In the 1960's the cytochrome P450 (CYP) family was discovered, and was soon found to be of great importance for drug metabolism and occasionally also for activation of prodrugs. Cytochrome P450 are a large group of monooxygenases that plays a very important role in the metabolism and therefore in the biotransformation of drugs. Cytochrome P450 enzymes occur in all life forms. In humans, the highest concentration of these proteins is found in the liver. Polymorphism in the CYP enzymes may lead to either a reduced or increased metabolism of a substance, which results either in too little or too high concentrations of a drug, causing side effects or failure of therapy.[117] Learning about the impact on drug therapy due to genetic differences between individuals was an important step towards a better and safer health care. However, in the time of the discoveries mentioned above having a person tested for their genetic variation was almost impossible and very costly. In 1990, the US National Institutes of Health (NIH) and international partners, aiming to fully sequence the human DNA and help researchers to understand more about genes, founded the Human Genome Project and in 2003, it was announced that the full DNA sequence was available. The location of all of the approximately 20,500 genes can now be identified.[118] Having all those information and a completely new set of tools to investigate patients' genome was a huge step also in medical practice. It did not take long for the first "personalized" agent to come into the market, in fact, even before the Human Genome Project ended. Trastuzumab (Herceptin) gained marketing authorisation in the United States in 1998. Just months after trastuzumab launching an article in The Wall Street Journal appeared, reporting

[116] Gurwitz D, Motulsky AG. "Drug reactions, enzymes, and biochemical genetics": 50 years later. Pharmacogenomics. 2007;8(11):1479–84.
[117] Mutschler E, Geisslinger G, Kroemer HK, Ruth P, Schäfer-Korting M. Arzneimittelwirkungen.10th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft; 2012. p. 24f.
[118] National Human Genome Research Institute. An Overview of the Human Genome Project. 11 May 2016 [Accessed on: 26 Jun 2016]. http://www.genome.gov/12011238.

about a new approach of the pharmaceutical industry, trying to tailor drugs to patients based on their genetics; the term "personalized medicine" was coined in this very article. The industry's hope to develop safer and more potent drugs using gene research is portrayed.[87] Today, research moves faster with every day, the information that was obtained results in more and more biomarkers for prevention and therapy, new technology, and deeper insights into drug - gene interaction. The challenge is to use the mass of information in a way that health care truly profits from new discoveries.

5.1.4 Ethical considerations

The concept of personalized medicine does not only bring new problems to the regulatory framework but also poses a challenge in many different aspects. Despite scientific and economics aspects, ethical criteria must be considered. There is always criticism that personalized medicine raises more hopes that it can fulfil.[119] The phrase "personalized medicine" creates a misleading image for patients, who expect a person-centred care rather than the very scientific genome-based approach. Biomarkers pop up everywhere and are described for almost all common diseases. The problem is that the majority of them are not of great value for therapy. Each biomarkers creates a hope of altering the way medicine can cope with a certain condition, but this is only true for very few of them. After all this research, "*there are (only) around 50 drugs that actually have genetic tests as part of their labelling*" said former FDA Commissioner Hamburg.[120] This illustrates one of the ethical problems that come along with personalized medicine. The question remains whether all the investments, work and research put into this part of medicine pay off. It might very well be that only very few patients profit from this research while a great number of people suffering from common diseases, e.g. high blood pressure, where genetic research is unlikely to improve a therapy or prediction, will not benefit. Some people remark that putting too much effort into personalized medicine will disregard research on basic care of widespread diseases so that in the end despite all the efforts we will come to a negative outcome for society.

[119] Wald NJ, Morris JK. Personalized medicine: hope or hype. Eur Heart J. 2012;33(13):1553-4.
[120] Margaret A. Hamburg. Remarks at the National Press Club Speaker Luncheon. 06 Oct 2010 [Accessed on: 26 Jun 2016]. http://www.fda.gov/NewsEvents/Speeches/ucm229195.htm.

With more and more "personalized" treatment, the amount of genetic data available on a person will increase ever more. As the exact handling of this information is relatively unclear, the possibility of genetic discrimination based on available genetic data exists. People with a high possibility of developing certain diseases may be discriminated in health insurance or in employment decisions.

Personalized medicine is continuously criticized for using the term personalized without being truly personalized. The type of treatment is based on a person's genetic but not on the person's personal environment. Socioeconomic factors such as access to education, lifestyle or income are not taken into account but only scientific aspects.[121] Higher education, income and social status are generally associated with better health. Access to clean water, air and safe housing and work places also influence health. Individual behaviours like smoking, physical activities and diet also contribute to the individual's health status.[122,123] These truly personal factors may have a significant impact on the individual disease development and treatment outcome, in some cases even more than genetic factors.

Another huge ethical issue is very rarely discussed. Biomarkers and diagnostics promise to pick the right patient at the right time for the right therapy. One can easily see that this cannot be true for all patients. There will never be a guaranty that test, biomarker and laboratory work one hundred percent accurate every time, thus producing false negative or false positive results. On the one hand, there will be those patients that are chosen for a therapy who will not benefit even though a test predicted that they would. Those patients will probably suffer from side effects but not profit from the therapy. On the other hand, there will be those patients who receive a wrong negative outcome of the test. They are refused therapy since they seem unlikely to respond. Health care providers will not want to waste time and money on such a patient with the costly biomarker based

[121] Horwitz RI, Cullen MR, Abell J, Christian JB. (De)Personalized Medicine. Science. 2013;339(6124):1155–6.
[122] Braveman PA, Cubbin C, Egerter S, Chideya S, Marchi KS, Metzler M, et al. Socioeconomic status in health research: one size does not fit all. J Am Med Assoc. 2005;294(22):2879–88.
[123] WHO. Health Impact Assessment (HIA). The determinants of health. [Accessed on: 26 Jun 2016]. http://www.who.int/hia/evidence/doh/en/.

therapy but instead use an alternative treatment, one that in reality is the one less likely to be of use for the patient. With a rising number of decisions based on tests and biomarkers, the number of patients that are refused therapy based on this "evidence" will go up as well. These considerations should not be left out when discussing the vicissitudes of personalized medicine.

5.1.5 Pharmacovigilance

Pharmacovigilance, the on-going and systematic monitoring of the safety of a medicinal product in order to discover its adverse effects, to assess and understand risks and take appropriate action to minimize those risks, is an important and compulsory aspect of a drugs life cycle. Personalized medicine promises a safer therapy by excluding patients with a high risk of adverse events. The ability to identify the right patient subgroup should therefore be in the focus of safety assessments. Special attention should be paid to pharmacovigilance in personalized medicine, as it is associated with additional risks compared to common medicines. These additional risks include the misuse of personalized medicine products for "wrong" patients, meaning those patients who should not receive the drug because they do not fit the inclusion criteria. In common "one-size-fits-all" drugs, this risk is practically not present. The misuse might lead to serious adverse events or even death. Administering therapy to the wrong patients could derive either from a false positive results of a test or because no test was conducted due to ignorance about the necessity of the test or limited resources. The impact of false positive test results and the resulting unintentional misuse should be carefully evaluated in the general risk-benefit analysis. A high number of treatments of false positive patients who experience serious adverse events can indicate that the corresponding test is not accurate enough. In order to understand the necessity of certain test a high education level concerning genetics and pharmacogenomics is required. The lack of appropriate resources applies especially to developing countries where it is not feasible to conduct complicated or costly exclusion testing.[124] Therefore, in developing countries special precautions and vigilance plans should be maintained.

[124] Lunshof JE., Pirmobamed M., Gurwitz D. Personalized medicine: Decades away? Pharmacogenomics. 2006;7(2):237–41.

Pharmacovigilance cannot only be used to assess adverse events but can also be a tool to identify new beneficial aspects of a drug, resulting in development of new therapies, expanded indications[125] or a better-defined patient population. Investigating underlying mechanism of action and growing understanding of genomics can thus be an important part of personalized medicine pharmacovigilance.

[125] Boguski MS, Mandl KD, Sukhatme VP. Drug discovery. Repurposing with a difference. Science. 2009;324(5933):1394–5.

5.2 Orphan drugs: a regulatory challenge for personalized medicine?

5.2.1 Orphan drug regulations

Orphan diseases, or rare diseases, are diseases that affect only a small minority of patients, which means by definition no more than 5 out of 10,000 in the European Union; prevalence in other parts of the world is not considered. Patients often have a high level of suffering, as it can take years to get a diagnosis. Approximately 80 % of rare diseases are of genetic origin.[126,127] Many of these rare diseases affect only an extremely small number of patients, while other rare diseases, such as cystic fibrosis, affect a much larger group of patients. More than 55 million people suffer from an orphan disease in Europe and the US.[128]

The first initiative concerning orphan diseases was the Orphan Drug Act (ODA) that was passed in 1983 in the United States to provide better health care to those who suffer from rare illnesses. The FDA defines a rare or orphan disease as a condition, which affects less than 200,000 patients in the US, which is a slightly different definition than the European. Research for the approximately 6,000 – 8,000 rare diseases[126] is costly and due to the limited number of patients unlikely to be profitable. Efforts of pharmaceutical companies therefore were little prior to 1983, only 10 drugs have been placed onto the market in the decade before the ODA. The ODA proposes economic incentives to increase the industry's willingness for developing drugs for rare diseases. Incentives in the US include seven years of market exclusivity, fee exemptions from FDA fees, free FDA scientific advice and tax credits. The impact of the Orphan Drug Act seems remarkable: From 1983 until today, the FDA Office of Orphan Products Development (OOPD) has designated more than 2,000 compounds as orphan drug and more than 400 of those have been approved.[129,130,131] Other countries followed

[126] EURORDIS. About Rare Diseases. [Accessed on: 26 Jun 2016]. http://www.eurordis.org/about-rare-diseases.
[127] Melnikova I. Rare diseases and orphan drugs. Nat Rev Drug Discov. 2012;11(4):267–8.
[128] The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat Abstract. European regulation on orphan medicinal products: 10 years of experience and future perspectives. Nat Rev Drug Discov. 2011;10(5):341–9.
[129] FDA. Developing Products for Rare Diseases & Conditions. 30 Mar 2016 [Accessed on: 26 Jun 2016]. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm.
[130] Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nat Rev Drug Discov. 2010;9(12):921–9.

implementing an orphan drug regulation to their legislation; Japan in 1993, the European Union in 2000. Similar to the FDA Office of Orphan Products Development a European equivalent responsible for orphan drug designation within the EMA exists, the Committee for Orphan Medicinal Products (COMP). The COMP is composed of one member from each Member State, three patients' organizations representatives nominated by the European Commission, three members nominated by the European Commission on the recommendation of the EMA, non-voting members from Iceland, Norway and Liechtenstein, one EC representative and general observers. Designation in the EU includes 10 years of market exclusivity and reduction of agency fees. The regulation led to an increased number of drugs for rare diseases, to date there are more than 70 approved orphan drugs in the Community.[128,130,132]

The following criteria must be met in order to gain orphan drug designation according to Article 3 of Regulation (EC) No 141/2000 on orphan medicinal products:

- Condition is life-threatening/ seriously debilitating/ serious and chronic and
- Affects no more than 5 in 10,000 persons in the Community or no sufficient return without incentives and
- No approved satisfactory method of treatment or of significant benefit for affected persons

> *„1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:*
>
> *(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing*

[131] Brewer GJ. Drug development for orphan diseases in the context of personalized medicine. Transl Res. 2009;154(6):314–22.
[132] Orphanet Report Series. Lists of medicinal products for rare diseases in Europe. In: Orphanet Report Series. p. 3ff. Apr 2016 [Accessed on: 26 Jun 2016]. http://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf.

> *of the medicinal product in the Community would generate sufficient return to justify the necessary investment;*
>
> *and*
>
> *(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition."*[133]

In the US legislation, a medicinal product is qualified for orphan drug designation by the limited number of patients and profitability while the European legislation additionally considers the unmet medical need as defined in Article 3 (b) of a product, which is the main difference between US and EU designation criteria.[130] The US also only grants seven years of market exclusivity.

Market exclusivity (Article 8 of Regulation (EC) No 141/2000) is an important part of an approved orphan drug. However, it does not create a monopoly in its indication. According to the regulation, other products that are not similar to the first in terms of chemical structure or mechanism of action can be granted orphan drug status in the same indication. Likewise, a drug similar to the already authorised orphan drug can be approved when it is superior to the first one, providing a better safety profile or is more effective. Other derogations are the marketing authorisation holders consent to a second applicant (Article 8, paragraph 3 a) and lack of supply (paragraph 3 b). In addition, the market exclusivity may be reduced to 6 years, should the product be sufficiently profitable that maintaining exclusivity is not justified (paragraph 2).

Drugs can be designated as orphan drug at any stage of development. While the decision about orphan drug designation is based on the review and recommendation of the COMP, the approval of the drug is processed by the CHMP. Orphan drugs are to be authorised by the centralised procedure according to Regulation (EC) No 726/2004. The same rules for marketing authorisation

[133] The European Parliament and the Council of the European Union. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Article 3. Off J Eur Union. 2000;L 18:1–5.

applications apply for orphan drugs as for any other drug.[134] That means clinical trials are necessary to prove the drug's safety and efficacy. For the majority of approved orphan drugs it is feasible to perform full clinical studies despite the small number of patients. Therefore, most orphan drugs are authorised on normal routes, marketing authorisation "under exceptional circumstances" or "conditional approval" is rather rare (compare Chapter 3.3.5).[12,128]

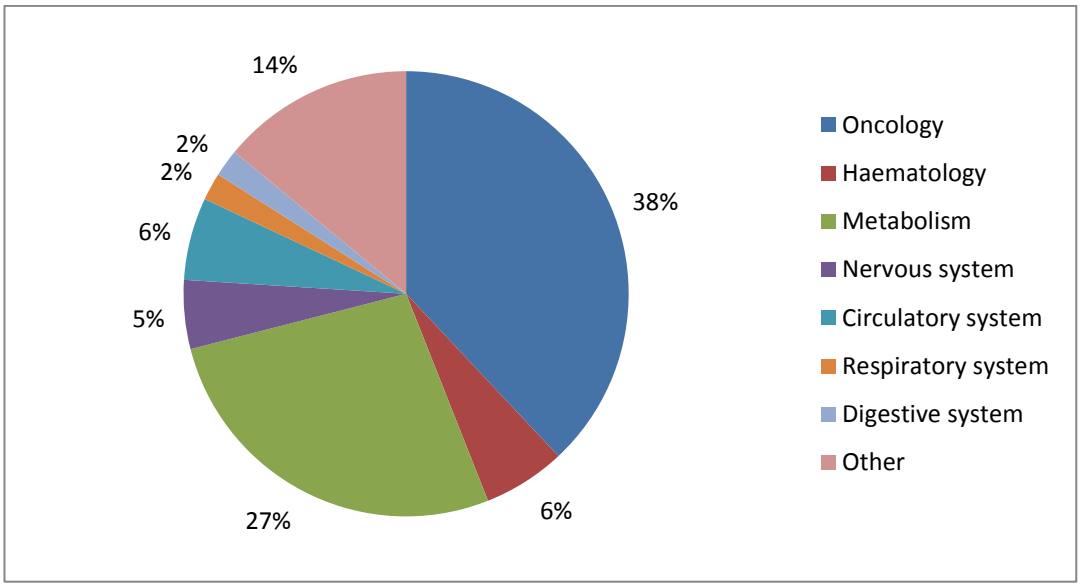


Figure 5 *Proportion of orphan drugs approved in the European Union in different therapeutic indications as of 2008 (based on the ICD-10 system for classifying diseases).*[135]

Figure 5 shows the share of orphan medicines in various indications. Most orphan drugs that have been approved and marketed in the EU are used to treat rare types of cancer. Their share in the market is almost 40 %. The reason for this is partly the high unmet medical need; on the other hand, a greater knowledge usually exists for rare cancers in contrast to many other rare diseases and the biological and molecular differentiation methods improve rather rapidly.[135] Drugs for metabolic diseases are also present in a high extent.

[134] Putzeist M, Mantel-Teeuwisse AK, Llinares J, Gispen-De Wied CC, Hoes AW, Leufkens HGM. EU marketing authorization review of orphan and non-orphan drugs does not differ. Drug discovery today. 2013;18(19-20):1001–6.
[135] Enzmann H, Lütz J. Förderung von Arzneimitteln für seltene Leiden durch die Europäische Gemeinschaft. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz. 2008;51(5):500–8.

5.2.2 Personalized medicine – from blockbuster to niche-buster to orphan?

On first glance, it looks as if orphan drugs and personalized medicine do not have much in common with each other. The major difference between drugs for personalized medicine and those for orphan diseases is the scientific knowledge and the economic interest. In personalized medicine, sub-groups of well-studied conditions are treated. The pathogenesis of those diseases is usually well understood. In contrast, orphan diseases are mostly at a much lower level of expertise and medical knowledge. Due to the high heterogeneity and great research effort, these diseases gain little economic interest.[130]

Today, the majority of drugs that are used are developed to fit as many patients as possible. This can be referred to as a "one-size-fits-all" approach, which allows the pharmaceutical industry to reach as many patients as possible. Sales of drugs like that can exceed the one billion dollar mark per year on a global level; those are so-called "blockbuster drugs". Although these drugs are prescribed to millions of patients, not all patients benefit from them. Depending on the indication and drug, it is estimated that the overall effectiveness is often below 80 %, but in some cases the response rate is even lower. A study from 2001 analysed major drugs for important diseases and their efficacy. It was shown for example that selective serotonin re-uptake inhibitors (SSRI) antidepressants have an average response rate of 62 %, which means that 38 % of all patients do not benefit from therapy. For some cancer drugs efficacy seems to be as low as 25 %, leaving 75 % of patients that do not respond to therapy. The highest efficacy rate found in this study was 80 % for COX-2 inhibitors.[82]

One can imagine that future research, driven by the current high interest in personalized medicine and the ever-increasing knowledge about molecular pathways, will reveal more about a diseases' mechanism and the role of genes. In certain cases, this might lead to "sub-conditions" or more patient sub-populations that eventually become a fully acknowledged condition of their own. Knowing more about the molecular mechanism of these sub-conditions, it will be possible to create drugs that are targeted for this particular mechanism. In consequence, this also means that the one-size-fits-all approach will no longer work in many cases, as the target population that receives this drug will be smaller than before. However, it also means that the response rate to the therapy is likely to be higher

than in conventional therapy, as only a selected population receives this therapy. Some of the drugs that were developed for a specific sub-population have evolved into so-called "niche-busters" in analogy to blockbuster drugs, whose annual revenue is similarly high. An example is imatinib, an anticancer agent that is marketed in Europe under the trade name Glivec. Imatinib, an inhibitor of tyrosine kinase Bcr-Abl was initially approved as a therapy for chronic myelogenous leukaemia (CML). Reciprocal translocation between the Abelson (Abl) tyrosine kinase gene at chromosome 9 and the **b**reakpoint **c**luster **r**egion (Bcr) gene at chromosome 22 leads to the Philadelphia chromosome. The resulting Bcr-Abl tyrosine kinase is constitutively elevated. Imatinib decreases the protein's activity by inhibiting ATP binding to the kinase.[136,137] With only 55,000 patients, imatinib's 2006 revenue was more than $2 billion.[88] This impressive number shows how high efficacy of a drug justifies a higher price and makes it economically interesting. Medicine for orphan diseases can also achieve commercial success. Cerezyme (imiglucerase) is used for the treatment of Gaucher disease, the most common of the lysosomal storage disease that is caused by a deficiency of β-glucocerebrosidase. This lysosome-localized enzyme cleaves glucosylceramide into glucose and ceramide. With the reduced activity of β-glucocerebrosidase, glucosylceramide accumulate primarily in macrophages. Manifestation of Gaucher disease includes in most cases enlarged spleen and liver and patients may suffer from thrombocytopenia and painful skeletal disorders. Gaucher disease is considered an orphan disease yet Cerezyme is not a designated orphan drug due to the fact that it was authorised in Europe in 1997 prior to the orphan drug regulation.[138] In 2009 with fewer than 6,000 patients, the annual revenue was almost at $1.8 billion.[139] These examples show how even therapy for small patient populations can achieve high revenues which is especially true if the

[136] Kurzrock R, Kantarjian HM, Druker BJ, Talpaz M. Review Philadelphia Chromosome – Positive Leukemias : From Basic Mechanisms to Molecular Therapeutics. Ann Intern Med. 2003;138(10):819–31.
[137] Mutschler E, Geisslinger G, Kroemer HK, Ruth P, Schäfer-Korting M. Arzneimittelwirkungen. 10th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft; 2012. p. 899.
[138] EMA. EPAR summary for the public. Cerezyme. Oct 2010 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000157/WC500024108.pdf.
[139] Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. Drug Des Devel Ther. 2012;6:81–106.

disease is severe and the treatment is the only one available or very effective. These criteria justify a high price and a greater chance of reimbursement that increased the industry's interest in some niche and orphan indication.

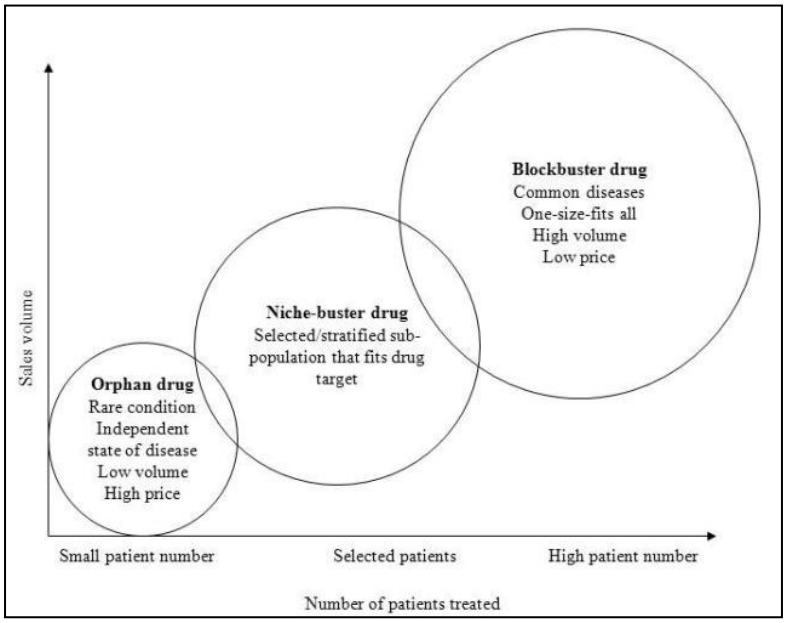


Figure 6 *Visualization of the general distribution of orphan drugs, niche-busters and blockbusters with regard to their sales volume and patient number.*

The question is whether the prospect of launching an economically successful niche or orphan drug brings major changes to the regulatory system. Will there be more drug approvals of orphan drugs and less one-size-fits-all blockbuster drugs? Currently a lot of discussion is going on whether there will be a shift from blockbuster to so-called niche-buster drugs that are specified for a smaller, more defined group of patients,[140,141] that would possibly also effect therapeutic concepts, when they have been identified for a smaller patient subset. It can be envisioned that this development will even go further and create more conditions that only a handful of patients suffer from, leading to more orphan diseases and a higher amount of requests for orphan drug designation. However, the "condition" for which an orphan drug is intended to be used must be a well-recognized disease. It is not possible to simply down-slice indications depending on the severity and course of a disease or its intensity variants. These are not sufficient

[140] Dolgin E. Big pharma moves from "blockbusters" to "niche busters". Nat Med. 2010;16(8):837.
[141] Collier R. Bye, bye blockbusters, hello niche busters. CMAJ. 2011;183(11):697–8.

features to gain orphan drug designation. Characteristics of a condition for which orphan drug resignation is sought must clearly differ from other similar conditions and their treatment.[135] Personalized medicine might be able, however, to identify diseases in which specific, targeted therapies are more successful than earlier, especially in the field of oncology where research is most intense. If the prevalence of that condition is rare enough in the European Community chances are that the industry can benefit from orphan incentives and the number of orphan drug designations will rise. The question is, whether this would be a threat to the regulatory and health care systems or a chance to improve medical care since financial barriers for research are reduced and if such a development is within the intention of the orphan drug regulation.

To answer these questions, it might be helpful to look at other approved orphan products that are controversially discussed, namely those products that have an orphan designation, but whose active ingredient has already been known before. The blockbuster drug sildenafil (Viagra, Pfizer) additionally holds an orphan drug designation for the rare disease pulmonary arterial hypertension and is marketed under the trade name Revatio since 2005. The well-known compound ibuprofen is a designated orphan drug approved in 2004 for the treatment of neonatal patent ductus arteriosus (Pedea). Both compounds were already known prior to their orphan drug designation and commonly used in other indications; sildenafil for erectile dysfunction, ibuprofen is mainly used for pain relief, fever reduction and as an anti-inflammatory agent. Even before Revatio was approved, the compound sildenafil was already used off-label to treat pulmonary hypertension;[142] ibuprofen as well was already in use for treatment of neonatal patent ductus arteriosus.[143] Although it is questionable whether such an approach corresponds to the intention of the orphan drug regulation, such a development can certainly bring positive achievements. On first sight, authorising compounds that are already in use additionally as an orphan drug seems like a gift to industry that benefits from orphan incentives and possibly higher prices for the orphan drug than the off-label

[142] Tabarrok A. From off-label prescribing towards a new FDA. Med hypotheses. 2009;72(1):11–3.
[143] Swartz EN. Is indomethacin or ibuprofen better for medical closure of the patent ductus arteriosus? Arch Dis Child. 2003;88(12):1134–5.

used product with only little research effort.[144] On the other hand, orphan research can profit from research on blockbuster and other existing drugs. If, for example, Viagra had not been approved, its therapeutic benefit in pulmonary hypertension may have never been found or even if it was found further investigation and research may not have been carried out, as it would not have been profitable. Many references concerning safety and efficacy issues had already been available due to off-label prescription.[142] This could be helpful in the planning of clinical trials for the orphan indication, and could speed up the approval process, which would make the drug faster available to patients. In this way, the research for orphan diseases can benefit from the experience and knowledge of more common diseases. The same applies vice versa: study of homozygous familial hypercholesterolemia led to the development of statins.[145] Findings of personalized medicine research can also be beneficial for orphan cancers or other rare diseases. If new patient sub-populations can be identified who will profit from a new and targeted therapy with better response, this is definitely within the meaning of the orphan regulation. Of course, there is always the risk that the attractive incentives for orphan products are utilized, for example, by obtaining more orphan indications for the same product or developing non-orphan drugs.[146] However, at present, the risk of exploitation seems rather low. The number of orphan drugs approval the past years in Europe is illustrated in Figure 7, in. So far, 2014 was the year with the most orphan drug authorisations, to be precise 15 new approvals.[132]

[144] Dooms M, Pincé H, Simoens S. Do we need authorized orphan drugs when compounded medications are available? J Clin Pharm Ther. 2013;38(1):1–2.
[145] Gericke CA, Riesberg A, Busse R. Ethical issues in funding orphan drug research and development. J Med Ethics. 2005;31(3):164–8.
[146] Wellman-Labadie O, Zhou Y. The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? Health Policy. 2010;95(2-3):216–28.

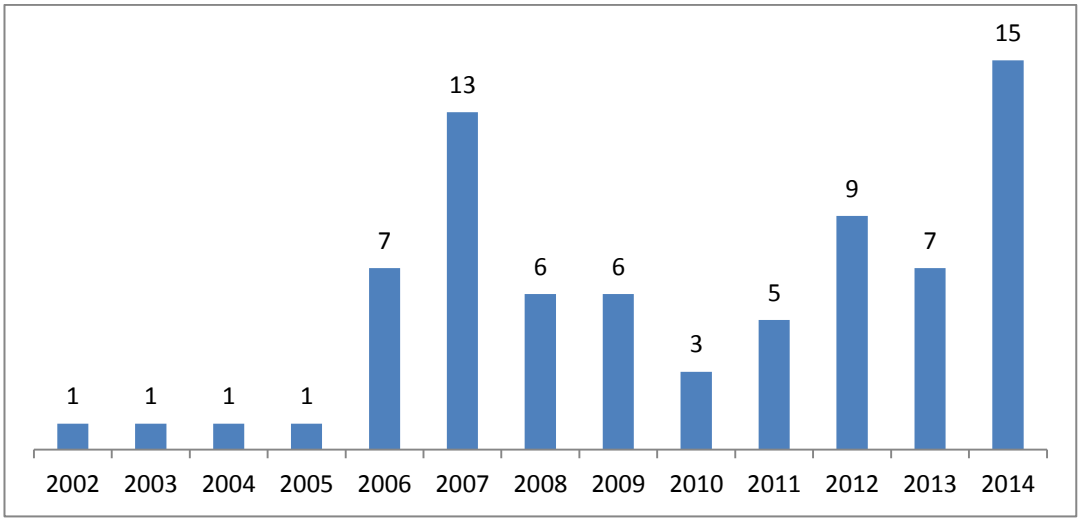


Figure 7 *Number of approved orphan drugs in Europe by year of marketing authorization.*[132]

It remains to be seen if the placement of orphan drugs onto the market will actually rise in the future due to new findings in personalized medicine or whether the proportion of lucrative drugs for rare cancers increases. At the end, patient care should be the highest principle of this regulation. As long as the situation of patients affected by rare diseases improves by stimulating orphan research, the regulation can be considered successful. Nevertheless, the regulation should also be critically examined again in the future to be able to make any improvements if this is deemed necessary.

5.3 Companion diagnostics

Many drugs that are part of personalized medicine require a diagnostic test to distinguish between those patients who benefit from a targeted therapy and those who do not. For this purpose, genetic testing is often performed to determine for example mutations or overexpression of certain genes. Results of these tests are crucial for further treatment. Therefore, it is extremely important that performance, safety and sensitivity of the test are reliable. Otherwise, the patient group is stratified incorrectly, which may result in individual patients receiving unnecessary therapy, which is ineffective in them and might even harm them and, on the other hand, patients who require a particular therapy that is withheld from them. The diagnostic devices that are capable of determining what therapy is suitable for a particular patient are referred to as "companion diagnostic".[147]

The legal framework of those very important diagnostic tests is rather weak; the legislation is lagging behind the technological development. Various aspects of this topic are repeatedly discussed. These are, for instance, the co-development for medicinal product and diagnostic device as well as the reimbursement situation. As different directives apply for drugs and diagnostic devices, co-development is challenging. Furthermore, the current legislation is not yet familiar with the concept of companion diagnostic. There is, to this point, no definition in the European Union of "companion diagnostic", which makes handling them quite difficult. Another problem is the question of reimbursement. Although for many drugs the SmPC requires, or at least advises, a diagnostic test, not all tests are covered by health insurances. This could pose a problem for the future development of drugs and their companion diagnostic. Only proper reimbursement policies make the research and development of these technologies economically interesting. However, now this is still an unresolved matter. Today, the evidence level of many companion diagnostic and biomarker test is not yet strong enough to justify coverage from the GKV.

[147] FDA. Companion Diagnostics. 31 Jul 2014 [Accessed on: 26 Jun 2016]. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm.

Further prospective, randomized studies must be conducted in order to increase the degree of evidence of these tools.[148] Only when the tests prove that they can be used cost-effectively and are beneficial for the patients, thus are part of evidence-based medicine, the matter of reimbursement can be adequately decided.

Another problem with drugs, that require a test for a particular characteristic prior to starting therapy, are the terms on how to apply such a test. For example, before trastuzumab can be administered, proof of the HER2 overexpression must be provided, which is actually a standard procedure for most breast cancer patients. Instead of appointing a specifically validated test to detect the overexpressed gene, the German *Fachinfo* (medicinal products professional information, SmPC) lists various methods that should be used for determination, such as an immunohistochemistry (IHC) of fixed tumour blocks for HER2 overexpression or Fluorescence *in-situ* hybridization (FISH)/Chromogenic *in-situ* hybridization (CISH) for gene amplification. The standards for laboratories that analyse the patient probes are rather imprecise. The text simply states: "*To obtain accurate and reproducible results, the testing must be performed in specialized laboratories, which can ensure validation of the test methods.*"[149] As success and failure of such therapies strongly depend on the results of diagnostic tests, such a relatively broad description of standards should be viewed critically. Testing methods and their results do vary between laboratories and between the tests that are carried out. To achieve optimal and reliable results for patients, physicians and payers, it would certainly be advantageous if a particular test, a companion diagnostic, which was developed in advance to match the specific drug therapy, would be determined in the label of the drug.

[148] Biermann J, Wasem J, Mostardt SW. Interdisziplinärer Workshop. Notwendiges Evidenzlevel und verfügbare Verfahrenswege der Erstattungsfähigkeit von prognostischen und prädiktiven diagnostischen Tests: Probleme und Lösungsvorschläge. 2013 [Accessed on: 26 Jun 2016]. http://hdl.handle.net/10419/83046.
[149] Roche. Fachinformation Herceptin i.v. Feb 2016 [Accessed on: 26 Jun 2016]. http://www.fachinfo.de/suche/fi/004044

In an ideal framework for the future, regulations and development of drugs and companion diagnostics would go hand in hand. That means

1. joint development and clinical studies
2. joint approval and
3. joint reimbursement of medicinal product and companion diagnostic.

This chapter shall give a general overview on regulations of medical devices and companion diagnostics in particular. At present, a revision of the existing legal situation is in progress. Differences between the current and the proposed new situation will be examined in respect to the new technological development of companion diagnostics. In general, the EU is trying to increase safety and transparency of medical devices, and to take into account the evolvement of new technologies. In addition to the European regulations, the US FDA's view concerning companion diagnostics is presented.

5.3.1 Current diagnostics regulation

Existing legislation of medical devices consists of three directives:

- Directive 90/385/EEC on active implantable medical devices (AIMDD)
- Directive 93/42/EEC on medical devices (MDD)
- Directive 98/79/EC on in vitro diagnostic medical devices (IVDD)

Directive 98/79/EC on in vitro diagnostics (IVDD) came into force on December 7, 2003. The Directive defines 'in vitro diagnostic medical device' as

> *"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:*
>
> - *concerning a physiological or pathological state, or*
> - *concerning a congenital abnormality, or*
> - *to determine the safety and compatibility with potential recipients, or*
> - *to monitor therapeutic measures."*[150]

The Directive distinguishes five categories of IVDs:

1. High risk devices listed in Annex II List A
2. Moderate risk devices listed in Annex II List B
3. Devices for self-testing intended to be used by lay persons in a home environment
4. Devices for performance evaluation, meaning studies in laboratories for medical analyses
5. All other devices not listed in Annex II and not intended for self-testing.[151]

[150] The European Parliament and the Council of the European Union. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Article 1. 1998. OJ L 331 7.12.1998, p. 1–37.

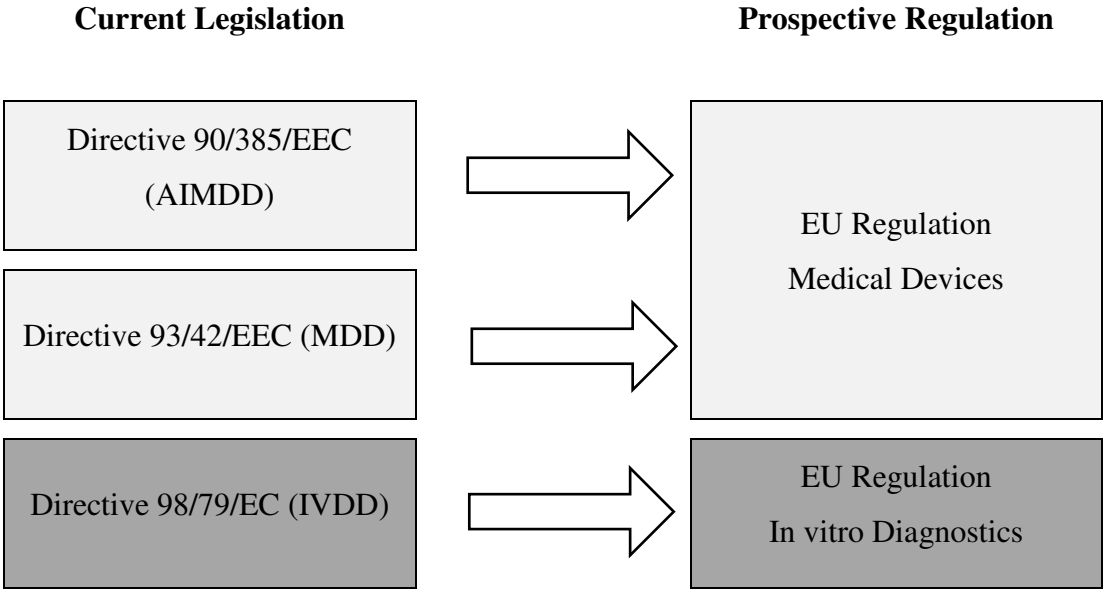
Annex I lists all the requirements that a device that falls within the scope of the Directive must meet. These requirements are known as Essential Requirements.

5.3.2 Prospective diagnostic regulation

In the past 20 years, the European Union has grown and consists now of more Member States as the original directives came into force. Globalization and the enormous progress of technology and health care in the field of devices and diagnostics made a revision inevitable.[152]

On September 26, 2012, the European Commission has unveiled drafts for a new medical device regulation and a new regulation on in vitro diagnostics, which are to replace the existing Medical Devices Directives (90/385/EEC on active implantable medical devices, 93/42/EEC on medical devices and 98/79/EC on in vitro diagnostics). The regulations are scheduled to enter into force in the years 2015 to 2019. In contrast to the previous directives, the new regulations are directly applicable and therefore require no more implementation by the Member States' laws. Instead of three directives the new medical device legislation will consist of two regulations, one covering in vitro diagnostics and the second one will cover both medical devices and active implantable medical devices.

[151] Dati F. The new European directive on in vitro diagnostics. Clin Chem Lab Med. 2003;41(10):1289–98.
[152] European Commission. Revisions of Medical Device Directives. [Accessed on: 26 Jun 2016]. http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/revision/index_en.htm.



According to the Commission, the change of the legal form was necessary, as the implementation of the Directives into national law was inconsistent. Monitoring of devices and diagnostics, which is so far only a national issue, will partly be taken over by the Commission.

Due to the enormous developments in technology and on the health care market, revision of the over 20 year old directives is urgently needed. The "PIP breast implants scandal" of 2010 was another driver for changing regulations. The French implant manufacturer, Poly Implant Prothèse (PIP) had produced implants of inferior quality using unapproved silicone gel with intend to defraud. The substandard implants hold a higher risk of rapture than those of good quality. Leakage of silicone can lead to local tissue irritations or inflammation. Leaked silicone may be distributed through the whole body and can accumulate in lymph nodes. Hundreds of thousands of women who had received those implants were urged to consult their doctors in order to check for ruptures. After the first defects became public, the French competent authority, Afssaps, was the first European agency to withdraw PIP implants from the market. The agency discovered the use of substandard silicone and the non-compliance with regulations and manufacturing specifications before the German Notified Body in charge, TÜV

Rheinland.[153,154] The Notified Body therefore bears part of the blame according to an initial French court decision.[155] The German court referred the case to the Court of Justice of the European Union to clarify responsibilities of Notified Body and further question in regards to the MDD and patients safety.[156] The immense media coverage of the topic and the high number of affected patients draw the politics' attention to the matter of device regulation.

5.3.2.1 In vitro diagnostics

As for medical devices, one of the most important novelties is the change of the legal form from directive to a regulation, which is directly binding for all Member States. The Regulation

> *"aims to ensure the smooth functioning of the internal market and a high level of protection of human health and safety"*

as well as to

> *"overcome […] flaws (of the current directive - author's note) and divergences and to further strengthen patient safety".*[157]

The new Regulation proposal (EC proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices) is largely based on the currently existing IVD Directive 98/79/EC yet the scope of the Regulation is clarified and extended concerning the following aspects to cover the most recent technological achievements:

[153] Lampert FM, Schwarz M, Grabin S, Stark GB. The "PIP scandal" – Complications in Breast Implants of Inferior Quality: State of Knowledge, Official Recommendations and Case Report. Geburtsh Frauenheilk. 2012;72:243–6.
[154] Niederländer C, Wahlster P, Kriza C, Kolominsky-Rabas P. Registries of implantable medical devices in Europe. Health Policy. 2013;113:20–37.
[155] Tagesschau. Brustimplantate-Skandal TÜV erhält Mitschuld. 14 Nov 2013 [Accessed on: 26 Jun 2016]. http://web.archive.org/web/20140122064124/http://www.tagesschau.de/ausland/brustimplantate118.html.
[156] The National Law Review. European Court to Clarify Responsibilities and Liability for Medical Devices. 14 Apr 2015 [Accessed on: 26 Jun 2016]. http://www.natlawreview.com/article/european-court-to-clarify-responsibilities-and-liability-medical-devices.
[157] European Commission. Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices. 26 Sep 2012 [Accessed on: 26 Jun 2016]. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012PC0541&from=EN.

- *high-risk devices manufactured and used within a single health institution, which are subject to most of the requirements set out in the proposal;*
- *tests providing information about the predisposition to a medical condition or a disease (e.g. genetic tests) and tests providing information to predict treatment response or reactions (e.g. companion diagnostics), which are considered as in vitro diagnostic medical devices;*
- *medical software, which is explicitly mentioned in the definition of IVDs.*[157]

The EC states, that the proposal intents to support innovations and competitiveness as well as faster, more cost-efficient market access.

A new requirement in the proposal of the EC is the "qualified person" on the manufacturer's side to ensure compliance with quality management and regulations. Since traceability has always been a problem with the current Directives the EC introduces a Unique Device Identification (UDI), a numeric or alphanumeric series, which IVDs are required to be equipped with, thus increasing transparency and patient safety. To further increase transparency, the European databank on medical devices (Eudamed) is to be expanded and include more information about the medical devices and made publicly available in large parts. Strengthening the competences of the Notified Bodies is one more subject to improve the system's quality. NBs are to carry out unannounced inspections.[158] Monitoring of the Notified Bodies itself will be taken out by the Member State's national authorities, and, in intervals, by a joint assessment with experts from other Member States and the Commission. A new classification system for IVDs will divide them into four risk classes (A, B, C, D) with class A being the lowest class of risk and D presenting the highest risk. This classification follows the

[158] European Commission. Commission recommendation of 24 September 2013 on the audits and assessments performed by notified bodies in the field of medical devices. Annex III. 25 Sep 2013 [Accessed on: 26 Jun 2016]. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:253:0027:0035:EN:PDF

suggestions of the IMDRF (International Medical Device Regulators Forum, an organization, which replaces the former Global Harmonization Task Force (GHTF)). Conformity assessment of class A diagnostics can be carried out by the manufacturer, unless the IVD is intended for near-patient testing, has a measuring function or is sold in sterile condition. In that case, involvement of a NB is essential. Depending on their risk class, varying degrees of Notified Body involvement is required for devices of class B, C and D. For class B and C the quality management system is revised, for class C the technical documentation of representative samples is checked additionally. Devices of class D require approval of design and quality management prior to the placement on the market.

A "real" authority based approval process, as it is established for the authorisation of medicinal products, will not yet be realized in the near future in the European Union, although this is being demanded by some stakeholder (such as the German associations of the statutory health insurance, *GKV Spitzenverbände*)[159]. The regulations are rather an evolution of the existing legal framework than a radical restructuring of the medical devices landscape. Nevertheless, the new regulations are expected to improve patient safety by strengthening the power of Notified Bodies, more competences for the EMA and the formation of the MDCG (Medical Device Coordination Group within the EMA). Industry benefits from the conditions; an approval similar to those of drugs, would be associated with higher costs than the upcoming solution, even if individual products are classified in a different product class. It is often argued that a medical device approval could slow down their market entry (due to a lack of capacity on authorities' level as well as longer, stricter and costlier trials) so that it will take longer for patients to gain access to innovations. The new Regulations should therefore be regarded as a compromise between an innovation stimulating, cost-effective system and a higher patient safety that strengthens the Commission as a supervisory body and harmonizes standards.

[159] Spitzenverband der gesetzlichen Krankenkassen. Medizinprodukte – Mythen und Wahrheit: Gemeinsames Argumentationspapier von den Spitzenverbänden der gesetzlichen Krankenkassen in Deutschland. 2013 [Accessed on: 26 Jun 2016]. http://www.aok-gesundheitspartner.de/imperia/md/gpp/bund/krankenhaus/meldungen/medizinprodukte_thesenpapier_krankenkassen.pdf.

5.3.3 Companion Diagnostics

Companion diagnostics will be covered in the proposed Regulation on in vitro diagnostic medical devices. Among other new definitions in the proposal, the important definition of companion diagnostics (CDx) was long expected. The initial proposal by the European Commission defined companion diagnostic as follows:

> *'Companion diagnostic' means a device specifically intended* ***to select*** *patients with a previously diagnosed condition or predisposition as* ***eligible*** *for a* ***targeted*** *therapy.*[157]

This first proposal of a definition by the Commission was amended in the Parliament on October 22, 2013 and gives now a narrower, more specific definition:

> *'companion diagnostic' means a device specifically intended* ***for and essential to the selection of*** *patients with a previously diagnosed condition or predisposition as* ***suitable or unsuitable*** *for a* ***specific*** *therapy* ***with a medicinal product or a range of medicinal product.***[160]

Changes in the original definition and the amended definition are pointed out in bold font. The revision of the definition responds to criticisms that saw the first definition as too soft. The definition of the Parliament seems to be less broad than the proposal of the Commission. In the revised version, it is clearly emphasized that the device does not only select patients, but that this selection must essential for the subsequent treatment, which is a narrower scope. In addition, eligible is replaced by suitable or unsuitable to specify the intended use. The rather neutral term "targeted therapy", that does not explain the kind of therapy that can be used, is reduced by the Parliament to therapy with a medicinal product or a range of products. Thus, the Parliament would like to express the fact that a device can

[160] European Parliament. P7_TA(2013) 0427 In vitro diagnostic medical devices ***I Amendments adopted by the European Parliament on 22 October 2013 on the proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices (COM(2012)0541 – C7-0317/2012 – 2012/0267(COD)). Amendment 47. [Accessed on: 26 Jun 2016)]. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+TA+P7-TA-2013-0427+0+DOC+PDF+V0//EN.

only be a companion diagnostic when the device is essential to the patient selection and that therapy of selected patients is carried out with (a) medicinal product(s). This stricter definition takes into account that the correct diagnostic is extremely important for therapy with targeted agents.

In the current legislation, where a definition of companion diagnostics does not exist, these devices usually fall under the scope of the IVDD.

Companion diagnostics are categorized in the new classification system as class C medical devices (Annex VII point 2.3) that present a high risk for the patient and a low public risk. This means that a Notified Body will be involved in the conformity assessment and examine the design of the companion diagnostic. Annex VIII of the proposal describes the examination. The Notified Body shall consult with the competent authority or the EMA regarding the suitability of the device in relation to the medicinal product concerned. Consultation with the competent authority or EMA shall also apply when changes are made to the device. Amendment of the Parliament states that companion diagnostics shall only be supplied on a medical prescription. Clinical evidence as well as vigilance and market surveillance are firmly embedded within the proposal to enhance safety and support intended use of the product.

5.3.4 FDA approach for companion diagnostics

The approach used by the FDA to handle in vitro companion diagnostics differs from the way used in Europe. Guidance for industry and FDA staff on in vitro companion diagnostic devices was released in August 2014 (draft in July 2011) to clarify the FDA's opinion on the issue.[161] The guidance addresses sponsors who are developing a product that depends on the result of a diagnostic test and developers of in vitro diagnostics that are to be used with a particular therapeutic product. Recently, with more and more therapies and medications being developed that are dependent on the result of a diagnostic test for a safe and effective use, the FDA thinks that this subject should be sufficiently regulated. Incorrect test results can lead to the treatment of patients who do not benefit from

[161] FDA. Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices. 06 Aug 2014 [Accessed on: 26 Jun 2016]. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf.

the therapy and a greater risk of adverse effects. Therefore, it is important that health care professionals can rely on test results to enhance treatment. The FDA defines a companion diagnostic as

> *"an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product."*[161]

This definition differs slightly from that of the EU as it explicitly mentions a *corresponding* therapeutic product and lacks the statement that the device is used for patient selection but specifies that it is used to provide information on a therapy. An inaccurate test can mean that the corresponding product is administered to the wrong patient or is denied the right patient. The correct interaction of IVD companion diagnostic device and pharmaceutical is therefore extremely important to identify patients who benefit and those who will not, recognize which patients might be at a higher risk for serious adverse reactions, or monitor therapy response correctly. The corresponding IVD companion diagnostic device will be reviewed by the FDA and approved or cleared, depending on the regulatory requirements of the device. The FDA has two different processes to handle medical devices:

- Premarket approval (PMA)
- Premarket Notification (510k)

Three classes for medical devices exist. Class I devices usually present a low risk and therefore in most cases no regulatory approval is required. However, class I devices and the manufacturer must be listed. Class II devices have a higher risk than Class I and Class III devices is the highest risk classification with high regulatory control.[162] Premarket approval (PMA), the most stringent type of device marketing application, is used to evaluate most Class III devices, those devices that hold a high risk such as support or sustain human life, are of substantial importance in preventing impairment of human health, or which

[162] FDA. What does it mean for FDA to "classify" a medical device? 28 Dec 2015 [Accessed on: 26 Jun 2016]. http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194438.htm.

present a potential, unreasonable risk of illness or injury.[163] Before such a device is put on the market, the manufacturer must seek approval by PMA application. PMA approval is received when the FDA believes the scientific evidence sufficiently supports the safe and effective use for its intended purpose. The application must therefore contain information about design and manufacturing process. Data of preclinical (e.g. biocompatibility) and clinical studies are required too. For devices of Class I, II or III that do not require a PMA a Premarket Notification must be submitted. Premarket Notification (PMN) is also known as 510(k), named after the CRF section for this procedure. This should be done at least 90 days before marketing. Most Class I and some Class II device are exempt from 510(k). In the 510(k) process FDA evaluates if the device is "substantially equivalent" to a legally marketed device that is not subject to PMA. Substantial equivalence is defined as "at least as safe and effective as [a] predicate". [164] That means the new device must be equivalent, not identical, in terms of "intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labelling, biocompatibility, standards, and other characteristics, as applicable." Devices that are marketed under a 510(k) are not approved like under PMA but cleared.

[163] FDA. Premarket Approval (PMA). 13 Jun 2016 [Accessed on: 26 Jun 2016]. http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm.

[164] FDA. Premarket Notification (510k). 16 Sep 2015 [Accessed on: 26 Jun 2016]. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.

Table 8 *Comparison of the FDA's 510(k)/Premarket Notification process and the Premarket Approval/Investigational Device Exemption.*[163,164]

510(k)/PMN	PMA
Most commonly used for some Class I and most Class II devices (also some PMA exempt Class III)	Mainly for Class III device
Clinical study rarely required	Clinical study required
"Substantial equivalence" to a legally marketed device must be demonstrated	Safety and effectiveness for intended use must be demonstrated
Device is *cleared* for commercial distribution by the FDA	Device is *approved* by the FDA prior to marketing

Clearance or approval of the IVD companion diagnostic device is done under device authority and will be reviewed within the context of the corresponding therapeutic product. FDA suggests co-development for novel therapeutic products and IVD companion diagnostic devices when test results are crucial for safe and effective use of the therapeutic. It will therefore be determined whether the device is well validated and meets all required standards. Apart from a few exemptions, the FDA will not approve any novel therapeutic products without having cleared or approved a suitable validated IVD companion diagnostic device first for the intended indication when the safe and effective use of said product depends on the test results.[161] Exemptions to this regulation may be, for example, pharmaceutical products for serious or life-threatening diseases. In that case, when no satisfying treatment alternative exists, approval of a particular product without an approved or cleared IVD may be possible when the benefits from the use with an unapproved or not cleared IVD outweigh the risks. However, a suitable IVD later on shall be sought to be approved or cleared. Thus, the FDA generally expects that IVD companion diagnostics are considered in the novel therapeutic product development as they intend to approve/clear both at the same time. For industry that means, IVD and drug development should go side-by-side, co-development should start as early as possible. An IVD need not necessarily be new, but can also be a modified, already existing IVD. Nevertheless, the same regulations

apply for that IVD, as its intended use with a novel therapeutic product is a major change from the one already existing.

Companion diagnostics to determine a patient's likelihood to respond a certain therapy are for example approved for Xalkori (crizotinib) and Zelboraf (verumafenib). Zelboraf is a drug intended to treat patients with late stage or unresectable melanoma. The cobas 4800 BRAF V600 Mutation test was approved along with the drug to identify patients with mutated BRAF V600E. Only patient with a positive mutation test outcome are to be treated with Zelboraf, as the drug has not been studied with BRAF protein mutation negative patients.[165] Xalkori is used for the treatment of late stage, non-small cell lung cancer. Before a patient receives the treatment it is necessary to test if the patient expresses the abnormal anaplastic lymphoma (ALK) gene, as the drug is only to be administered to selected patients with abnormal ALK gene. To determine this group of patients, the FDA approved the Vysis ALK Break Apart FISH Probe Kit approved together with the drug under its priority review program.[166] Both drugs and their test were approved in August 2011. A FDA approved device can be used only for the specific intended use. For example, a test for the detection of a mutated KRAS in colorectal cancer patients cannot simply be used to test for mutated KRAS in lung cancer. It is imperative that each test is validated for its intended use in a new process.[167]

[165] FDA. FDA approves Zelboraf and companion diagnostic test for late-stage skin cancer. 17 Aug 2011 [Accessed on: 26 Jun 2016].
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268241.htm.
[166] FDA. FDA approves Xalkori with companion diagnostic for a type of late-stage lung cancer. 26 Aug 2011 [Accessed on: 26 Jun 2016].
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269856.htm.
[167] Marton MJ, Weiner R. Practical guidance for implementing predictive biomarkers into early phase clinical studies. Biomed Res Int. 2013;2013(4):1–9.

6 Implementation: approval of "therapeutic concepts" in Europe

Therapeutic concepts combine ideas and knowledge from different areas. Particularly the developments in personalized medicine pave the way for a systematic development for authorised combinations because a patient population for which the therapeutic combination is beneficial can be determined on a scientific basis. This way, the "biological rational" that is required by guidelines and regulations on medical combinations can be met.

By introducing therapeutic concepts, diagnostics, which are indispensable for personalized medicine, can be included in an approved therapy. The pharmaceutical – diagnostic combination shall be studied in clinical trials to eventually include a test, which is demonstrably valid. Medical devices that incorporate a medicinal product are regulated under the medical device directive when the pharmaceutical constituent provides solely ancillary action for the medical device. Similar to this approach, therapeutic concepts would offer the opportunity to authorise a medical device in combination with a pharmaceutical under the medicinal product regulation, as the medical device is supportive and informative in the administration of the medicinal product.

From the beginning of their marketing, the therapeutic concept is a treatment combination, comparable with the recommendations of medical guidelines, but with a joint development and approval that support the safe application.

Additional input for the implementation of therapeutic concepts is provided by FDA guidance with recommendations for the co-development of already marketed drug in combination. Further considerations and approaches for the implementation of therapeutic concepts are outlined in the following sections.

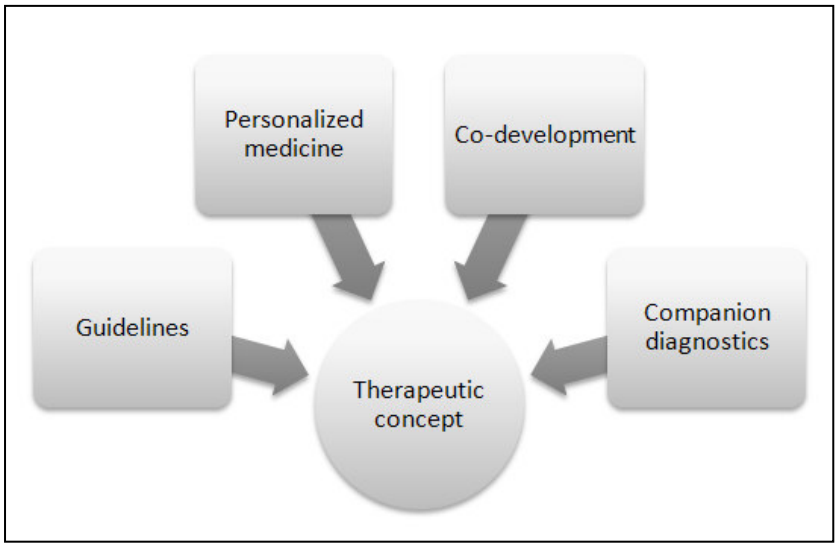


Figure 8 *Components that influence the development of therapeutic concept: Medical guidelines, evidence and experience gained from personalized medicine and companion diagnostic research as well as current views on co-development of therapies.*

6.1 Clinical trials

Non-clinical and clinical investigations are as important for therapeutic concepts as they are for any other medicinal product and are the standard for the evaluation of benefits and risks. Exceptional emphasis must be made on the interaction of the different components of the therapeutic concept to consider possible additional risk derived from the combination, especially those of the combination of two or more pharmaceutically active substances. Non-clinical studies should be carried out jointly as far and as soon as possible. Clinical trials for therapeutic concepts must furthermore be well designed to address the additional risks and interactions arising from the combination but also the benefits of the combination in contrast to monotherapy or standard of care must be demonstrated. The FDA has issued guidance for co-development of drugs, which can serve as guidance in the design of therapeutic concepts clinical trials as well.

6.1.1 Design of clinical trials for combination use

FDA acknowledges the need for combination therapy in certain conditions and encourages co-development of drugs. They released draft guidance[168] in December 2010 concerning the co-development of novel unmarketed drugs for use in combination and a final guidance for industry on this topic in June 2013.[169] Before the FDA released this guidance, co-development of drugs for a combination regimen was rather challenging as no further assistance in this matter existed. The concept of combination treatment is not new of course but the FDA guidance gives precise requirements and recommendation on how the development should proceed. Regulatory, scientific and medical aspects are addressed. Having a guidance that highlights the importance of drug combinations helps to speed up drug development and reduce costs. It also helps patients gain earlier access to treatment.[170]

The guidance states, that for many serious diseases such as cancer, infections and cardiovascular diseases *"combination therapy is an important treatment modality"*. Growing understanding of pathophysiological mechanisms helps improving treatment responses using drug combinations. New therapeutic approaches based on this knowledge can be used to our advantage. Due to a higher risk of those combinations compared to single drug use alone combinations should only be developed for serious diseases. Knowledge of the individual active compounds in the combination is lower than that of only one active ingredient developed for the treatment. Therefore, the data concerning the safety profile, effectiveness and dose-response are less informative. The FDA therefore specifies the conditions under which co-development is reasonable. Criteria for developing such new combinations are very similar to the ones mentioned in the EMA guideline on fixed combination.

[168] FDA. Guidance for Industry Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination. Draft. Dec 2010 [Accessed on: 26 Jun 2016]. https://www.c-path.org/pdf/FDADraftGuidanceCoDevelopment.pdf.
[169] FDA. Guidance for Industry Codevelopment of Two or More New Investigational Drugs for Use in Combination. June 2013 [Accessed on: 26 Jun 2016]. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm236669.pdf.
[170] FDA guidance helps facilitate drug co-development. Lancet Oncol. 2011;12(2):109.

- The combination is intended to treat a serious disease or condition
- There is a strong biological rationale for use of the combination (e.g. inhibition of different pathways, lower doses of drug can be administered to decrease toxicity, resistances are reduced)
- A full non-clinical characterization of the activity of both, the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents. A non-clinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.
- There is a compelling reason why the new investigational drugs cannot be developed independently (e.g. risk of resistance, limited activity when used as monotherapy).[169]

Furthermore, the procedure for clinical development is described in the guidance. The main objective in Phase 1 studies is to determine safety and pharmacokinetics of both the individual drugs and the combination. Whenever feasible, all pharmacokinetic parameters of the individual drugs should be investigated. If it is not possible to characterize the drugs individually in humans, non-clinical studies should be conducted. Phase 2 should further demonstrate the contribution of each individual new investigational drug in the combination, provide evidence of the combination's effectiveness and adjust the dose(s). When possible a factorial study design is desirable to obtain as many information about the drugs and their combination.

Three scenarios are conceivable for phase 2 studies:

1. *Each new investigational drug alone has activity and they can be administered separately*

To obtain the most information about safety and effectiveness the individual drugs alone should be compared to the combination and standard of care (SOC).

2. *The individual new investigational drugs in the combination cannot be administered separately*

In cases where the individual drug cannot be administered separately for pharmacological or ethical reasons (e.g. ineffectiveness of the individual drug or rapid development of drug resistance) only the combination should be studied.

3. *When administered separately, one new investigational drug in the combination is active and one is inactive*

The minimally active compound requires Phase 1 safety studies but not a further individual drug Phase 2 study.

The study designs suggested by the FDA for each scenario are given in Table 9.

Table 9 *Study design of Phase 2 studies in co-development of two unmarketed drugs according to FDA. A and B indicate the different active compounds of the combination.*

Scenario	Study design	Remarks
1	A v. B v. AB v. SOC or placebo	SOC can be added to each arm, when it is a known effective, not palliative, therapy
2	AB v. SOC	SOC can be added to AB, when it is a known effective, not palliative, therapy, comparing to placebo + SOC
3	A^{*} v. AB^{+} v. SOC or placebo	

*active drug, $^{+}$ inactive/minimally active drug

The study design of phase 3 confirmatory studies depends on the results of phase 2 studies. If the data suggest that the combination is superior to individual use and the role of each new investigational drug can be demonstrated, it is feasible to compare the combination to standard of care or placebo. If data for the contribution of each individual drug cannot be provided, a factorial design similar to scenario 1 or 3 (see above) would apply. However, these are case-by-case decision depending on previously obtained results.

The industry welcomed the guidance as it helps them to meet regulatory and scientific requirements in modern drug development. Especially the proposed study design for phase 3 studies helps to conduct more efficient trials as different situations in the drug development process can be handled flexibly. When the contribution of each drug of the combination is demonstrated in phase 2 a two arms study design for the combination is suggested. Prior to the publication of the guidance, a three or four arms study with the individual drugs and the combination was usually required. Therefore, industry benefits from more efficient clinical studies in terms of time and costs because trials will not have to have multifactorial design investigating three (four) arms, placebo, combination and single agent(s), but only two arms comparing combination to placebo or standard of care.[15,171] Shorter development times mean faster market access and patient access. Consequently, patients benefit greatly from the guidance's outline.

A major disadvantage is of course a smaller knowledge about the single agents in the combinations, which leads to a higher risk factor. This uncertainty can only be accepted when treating serious diseases with little treatment alternatives. For this reason, a strong focus on safety aspects is present in the FDA guidance.

The FDA guidance is a good starting point for introduction of therapeutic concepts. Especially the study design of non-clinical and clinical development is a solid basis.

However, the guidance only concerns novel unmarketed drugs. Nevertheless, it can be expected to be found that also drugs that are already marketed can be beneficial in certain combination therapies for specific indications. Therefore, the

[171] Nature Review. Regulatory watch: FDA guidance on co-developing investigational drugs. Nat Rev Drug Discov. 2011;10(2):86.

FDA guidance takes a step into the right direction but does not go far enough yet. Therapeutic concepts on the other hand would take the next step and would cover combinations containing compounds that are already marketed to improve the safety of combinations use of these compounds.

6.2 Benefits and challenges

Reassessment of the current approval processes is vital for a continuous improvement of the entire system. New approaches are advantageous when they provide benefits for at least one interested group. In the regulatory system of the health care sector, several stakeholders have to be considered before new processes are introduced namely the industry, patients, payers, health care professionals and regulatory authorities. A new regulatory pathway towards therapeutic concepts would influence all stakeholders, thus the potential benefits of the proposed regulation are discussed as well as possible difficulties. The question in regard to the advantages and disadvantages is who would benefit from therapeutic concepts compared to other combination possibilities such as medical guidelines and fixed combinations and which changes arise for the different stakeholders.

- Industry

  Therapeutic concepts would pose an entirely new challenge for the pharmaceutical industry. However, therapies in which several medicinal products or medical devices are involved are standard in many cases nowadays and a certain interest in the regulation of combinations is present. A defined regulation on therapeutic concepts would offer guidance for the industry for the development of such. After identification of targets, the clinical testing could become more efficient if clear rules would exist. Possible clinical trial scenarios are described in Chapter 6.1.1 which would provide fewer costs and smaller trials if only the superiority of the combination must be proven against placebo or standards of care and not in a three-armed study. That results in faster access to market for combinations under the therapeutic concept approach. A further possible benefit for industry would be the marketing of already marketed drug in

new indications as a combination therapy. If an already marketed product is found to be more effective in a certain combination with other products, this could expand the indication of the product and might results in new marketing possibilities and increasing profits.

- Patients

  One of the biggest benefits that patients will gain from therapeutic concepts are therapies with combinations that have been studied and developed precisely for this purpose which means higher safety for the patients and possibly less side effects due to stratification and identified contraindications. Therapeutic concepts might even be increasing compliance by giving the patient the possibility to identify oneself with the regime more when the combination is clearly stated in the labelling for a certain disease (see also Chapter 6.3).

  The patient does not have a direct benefit by simplified administration, as it is the case for fixed combinations but may profit from a more flexible dosing.

- Agencies / Regulatory authorities

  With the evolving medical knowledge therapeutic, standards change rapidly. At times, treatments become the standard of care even if they are not approved for it. This possibility is particularly given to the field of pharmacogenomics and personalized medicine because the knowledge of signalling pathways, toxicity and cell interactions is growing rapidly in this area and sensitive tests enable diagnosis that is more accurate. Combination therapies, which are novel in this particular combination can be considered as medically reasonable under the gained understanding. A treatment of this kind would not be approved but can be regarded as intended use over time nonetheless. On the other hand, an approved intended use of a product may prove obsolete due to new findings. In both cases, therapeutic concepts provide a new possibility for authorities to respond to such changes.

With the approval of therapeutic concepts, different products would be combined with one another through the marketing authorisation and must therefore be used in this designated combination for a defined indication. Medical guidelines in contrast only recommend a therapeutic combination of products, which is not directly mandatory from the legal point of view. Therapeutic concepts are therefore considered to have a more binding character than guidelines. Compared to fixed combinations therapeutic concepts offer more flexibility with respect to patient needs. As the products of the combination are available separately, even products with a narrow therapeutic range or dosing according to body surface could be approved within a therapeutic concept. Disadvantages of fixed combinations such as unequal duration of action and interactions in metabolism can be compensated with the use of therapeutic concepts with administration in intervals or dosage adjustments. The advantages of fixed combinations such as enhancement of action and better effectiveness and possible mitigation of side effects are retained.

Regulatory authorities ensure that only safe and effective products are released into the market. The same is true for the safety and efficacy of therapeutic concepts. Authorising this new regulatory approach gives the agencies the chance to strengthen their position in the control of combinations used. Should there be any concerns about the safety of a therapeutic concept that has been revealed in clinical trial or in post market surveillance or vigilance reports the authorities will be able to react fast in case of a serious risk to public health. They will be able to withdraw or suspend the marketing authorisation in order to minimize risk for the public or create a negative list for high-risk combinations.

- Payers

  Therapeutic concepts could result in savings of health care costs in the long term. Comparable to cost-effectiveness evidence in personalized medicine it will be difficult to determine potential savings in the beginning, as cost may rise first since payers would be paying for the entire therapeutic concept, including any diagnostics that would be part of the concept. However, due to more effective therapies with lower incidence of adverse reactions and associated follow-up costs the higher initial costs can be justified. Approved therapeutic concepts form a new treatment standard that might turn out as superior to other treatments already in the clinical trials prior to authorisation, which is much earlier than those combinations that are evaluated in medical guidelines. Combinations described in medical guideline are often the results of years of experience and studies with the products before they are included in a guideline. Therapeutic concepts can hence set a new standard very early in their life time cycle that might prove as cost-effective.

- Health care professionals

  For health care professionals it is always important to provide the best care to their patients. New therapeutic concepts would mean that the combination of products used is well-studied. It therefore provides more security for physician when prescribing such a therapy. An approved therapeutic concept would create a greater legal certainty as well as a more efficient treatment compared to medical guidelines especially those of lesser quality. Therapeutic concepts that consist of a drug and a medical device or diagnostic may be easier applied, as reimbursement for the entire therapeutic concept should be provided. Today, diagnostic and drug are often considered separately by payers when it comes to cost coverage so physician sometimes struggle to get the right diagnosis for their treatment choice. Compared to fixed combinations physician are able to be more flexible with the therapy and can for example adjust dosage in patients with renal or hepatic impairment.

  Despite the various opportunities offered by therapeutic concepts there are also challenges that need to be faced which are related primarily to the pre-

clinical and clinical development. It is conceivable that several pharmaceutical companies will have to work together in the development of a combination regimen, which can be regarded as a potential source of conflict. In a drug-drug combination the developers need to assess the single agents and their contribution to the overall effect and evaluate if one of the drugs shows a significantly more effective or toxic effect.[171] Results from such considerations may not only affect the development process and decisions which company will cover which part of the total costs. It will also have considerate influence on pharmacovigilance plans and risk management.

Evaluation of therapeutic concepts in which one or more drugs are to be applied in different dosage strengths depending on individual patient characteristics will be a further challenge. For industry and agencies, planning and evaluation of clinical trials that include several dosages to prove safety and efficacy can become a complex matter. It must be considered whether all strengths in the therapeutic concept offer benefits and safety.

Table 10 *Summary of benefits provided by therapeutic concepts*

Benefits of therapeutic concepts
• More flexible and individual dosing in combination therapies • More effective treatment by approved standards • Closing the gap between treatment realities and legal framework • Reimbursement of all parts of the therapeutic concept possible • More control on combinations in use for authorities • More studies on the combination use • Reduction of side effects by patient stratification, available studies and dosage adjustments • New marketing opportunities for industry

6.3 Labelling and Packaging

Labelling and packaging is an important part of any medical product. It must be made clear what the drug's intended use is and how it should be used. This applies also to drugs that are meant to be used as a therapeutic concept. Labelling must clearly state what the therapeutic concepts consists of and how the combination is used. Products belonging to the therapeutic concept do not necessarily need to be part of a combination pack, nor are they intended to be a fixed combination, thus meaning that there is no requirement for the drugs to be part of a single product package. The whole idea of the concept is to give physicians the freedom to adapt the right dose for each patient and having a combination pack would limit this freedom since it might not contain the drugs in the right dose for the patient. Additionally, for some therapeutic concepts the patient population might even be so small due to stratification that making a combination pack would be too much of an effort for industry.

Labelling of drugs that hold a marketing authorisation as a therapeutic concept presents several options depending on how the drugs of the therapeutic concept are marketed and whether they are only used in an approved combination or are as well used in other indication. Therefore, the following three scenarios are possible:

1. The drugs or drug/diagnostic combination are only to be used within the approved therapeutic concept
2. One or more compounds of the therapeutic concept are also used individually for an approved purpose but sold under the same brand name
3. One or more compounds of the therapeutic concept are also used individually for an approved purpose but sold under different brand names for individual use and use in the therapeutic concept

According to the different case scenarios different labelling option should be applied. Generally, if the marketed drug is meant to be used within a therapeutic concept it should be pointed out explicitly in the labelling. That way it can be ensured that the patient is aware this is a deliberately chosen medical concept, in which the specific combination of drugs (and diagnostic, if needed) offers advantages in therapy. For the three scenarios mentioned above three different label approaches are possible:

1. If the drugs are only marketed to be used within the approved therapeutic concept then only the use of the combination should be described in the package leaflet. The criteria for patient stratification should also be mentioned in the product information. Since the drugs of the combination can be sold separately, it should be made clear from the package leaflet that this drug is only to be used in the specific combination that has been developed and studied for.

2. If drugs of the combination are also used individually for treating other indications than that of the therapeutic concept and both uses are marketed under the same brand name there should be separate prescribing information for each intended use. Conceivable in this case

scenario would be a dual concept of the package leaflet. The fact that the drug can be used either alone or in an approved therapeutic concept should be made clear for example by having two separate columns for each intention. Intended use, contraindications, adverse drug effects and all other important information should be described separately in each column, one for the individual use and one for the therapeutic concept use. Again, a remark about the specific combination use should be made and necessary stratification processes should be described.

3. In a third possible scenario the drugs can either be used individually or in a therapeutic concept, similar to (2.) but the manufacturer might chose to market the drugs depending on their indication and use under separate brand names, one for individual use and one for the therapeutic concept. Labelling according to (1.) should be applied for the drug marketed as the therapeutic concept. For the drug marketed for individual use the general rules for labelling would apply.

It could be considered to apply a special mark on the package leaflet that indicates that this medicine is designated for the use in a therapeutic concept. In 2013, the EMA has introduced a black triangle displayed on package leaflet for medicines under additional monitoring to raise the patient's attention. The meaning of the black triangle is explained in a short sentence.[172] Similar to the black triangle mark the application of a different mark indicating the therapeutic concept, for example a "plus" (+) mark, would be possible. The mark and its explanation in the package leaflet would make patients and health care professionals conscious to the particular therapeutic situation.

[172] EMA. European Medicines Agency publishes initial list of medicines under additional monitoring. 25 Apr 2013 [Accessed on: 26 Jun 2016]. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001771.jsp&mid=WC0b01ac058004d5c1.

6.4 Vigilance and risk management

Having a new way of authorisation induces new challenges in pharmacovigilance. As has been described, combinations present a higher risk than a single agent does since knowledge about the single substances in the combination is smaller. The higher risk needs to be presented in vigilance plans. However, not all combination will hold the same risk, some combinations are riskier than others and therefore pharmacovigilance plans may vary. Different aspects should be considered when developing a risk plan, such as:

- Are one or more substances of the combination already in use? If so, can these substances be considered as high risk or low risk?
- Is it likely to administer other drugs with the combination?
- Are drugs from the combination likely to be used individually?

These are only some of the questions that need to be asked when discussing vigilance. Not all combinations will require more intense monitoring. Vigilance should therefore be a case-by-case decision and post marketing safety monitoring should best be discussed early with the agency.

6.5 Reimbursement

An important criterion for the success of any drug is the reimbursement policy. Without a proper reimbursement, most patients will not have access to certain therapies or medicines because the health insurance will not bear the costs. Therefore, early considerations about reimbursement are an essential part of any drug development.

Reimbursement practices are not harmonized within the European Union. Each Member State decides which therapies are reimbursable and determines the standards on which this decision is based. In Germany, the Federal Joint Committee (Gemeinsamer Bundesausschuß (G-BA)) is responsible for determining which health care services are reimbursed for 70 million members of the German statutory health insurance (Gesetzliche Krankenversicherung

((GKV)).[173] The G-BA is authorised by § 92 (1) 1 of the German Social Security Code V (Sozialgesetzbuch (SGB V)). The insured persons shall obtain a "*sufficient, appropriate and economical"* supply of health care services and products. Based on this definition the G-BA is able to restrict or suspend the use of certain products when it is found that there are other sufficient and more economical alternatives or when a treatment should be obsolete. This principle of efficiency was created to stabilize the health care system in the long term but it also creates a conflict potential from time to time. Patient representatives and pharmaceutical companies often find the decision not to reimburse a product questionable or unjustified. Annex III of the Guideline for Medicinal Products (Arzneimittel-Richtlinie (AM-RL)) gives an overview of the G-BA regulations on limitations and exclusions from reimbursement. Several fixed combinations can be found on this list, excluding them from reimbursement. Pharmaceutical with fixed combinations are often considered to pose a higher risk as the risk of side effects tend be higher and their interaction potential and effect on pharmacokinetics is often not extensively known. Additionally they are usually more expensive, thus less economic, than a free combination of several substances. The missing therapeutic benefit and medical need as well as the economic inefficiency, that are required in § 16 (1) AM-RL result in number of fixed combinations that are excluded by the list; for example analgesics with non-analgesic substances like phenazone with caffeine (Annex III no. 6) and anti-inflammatory drug with other substances (Annex III no. 18). However, there are exceptions to some restrictions, if a therapeutic benefit is proven. For no. 6, an exception is made for products with naloxone as such combinations have a strong pharmaceutical rational. An exception to no. 18 is the combination of naproxen (NSAID) with esomeprazole (PPI) that is marketed since 2012 under the trade name Vimovo. Studies indicate that 30 % of patients treated with NSAIDs develop dyspepsia and 10 % are affected by ulcers that might lead to serious complication.[174] Therefore, administration of PPI as prophylaxis during NSAID treatment is generally advised. The exception to no. 18 is however strictly limited

[173] GKV Spitzenverband. Wir über uns. 22 Dec 2015 [Accessed on: 26 Jun 2016]. https://www.gkv-spitzenverband.de/gkv_spitzenverband/wir_ueber_uns/wir_ueber_uns.jsp.
[174] Pues M. Analgesie inklusive Magenschutz. Pharm Ztg. 17/2012. [Accessed on: 26 Jun 2016]. http://www.pharmazeutische-zeitung.de/index.php?id=41710

to patients at high gastro duodenal risk where treatment with lower doses of NSAIDs and / or PPI is not sufficient.[17]

Annex III suggests that the G-BA is generally critical about combinations if it is a fixed dose and no therapeutic benefit is presumed. However, if it can be proven that the requirements of § 16 (1) AM-RL

1. diagnostic or therapeutic benefit
2. medical need
3. economic efficiency

are fulfilled, therapies are cleared for reimbursement by the G-BA and will be financed by the GKV.

For therapeutic concepts, reimbursement should therefore generally be possible. It must be proven that the therapeutic concept offers a benefit in therapy and an equivalent or better risk profile compared to alternatives. The purpose of therapeutic concepts is finding a reasonable combination of products that is supported by a strong biological and medical rationale. The interaction of the products has been tested in studies and trials so that accurate safety evaluation can be done. Due to the flexible dosage regime of the individual parts of the therapeutic concept the risk of under- or overdosing is significantly lower than in fixed combinations as it is based on the patient's need,. Another advantage with the approval of therapeutic concepts would be that it is more likely that the complete concept will be financed and not just parts of it. Even the necessary test, which would be part of certain concepts, can be reimbursed, because their contribution to the therapy would be sufficiently demonstrated in the authorisation procedure. In conclusion, reimbursement does not seem to be a major obstacle in the German legislation for the introduction of therapeutic concepts.

6.6 Patent protection

Research, development and clinical testing for drugs are complex and costly in terms of time and money. Patent protection is therefore essential for any drug development and a strong incentive for industry. Patents prevent that competitors benefit from original research and are therefore an important aspect for the development of therapeutic concepts. If no patent or similar protections exist, there is a risk that companies invest in extensive research for a therapeutic concept, which might afterwards be used by competitors and generic producers. Patents are incredibly useful and important for the industry, which is illustrated by the current trend in the industry. After the expiry of a drug patent, the industry often places new similar products on the market ("Me-too" product with the same structure-activity relation) that allows new patents and sales.[175]

An adequate protection should necessarily be provided as an incentive for therapeutic concepts. As therapeutic concepts present new indications and new dosage schedules for a defined patient population, "usage" patents might be applicable. The CMDh outlines "usage patent" as a claim to a new use for already known or patented drugs. Use may relate on new indications, formulations or dosage regimens:

> *'Usage' Patents claim novel 'uses' (indications, formulations, routes of administration, dosage schedules, patient populations etc.) for known / already patented active substances to the extent that the 'usage' patent satisfies the requirements for a valid patent, it confers an independent full period of patent protection in relation to the claimed invention. This can give rise to potential patent infringement in the event that a generic of an innovator product for which the initial patent protection period has expired but which is still protected by a 'usage' patent is authorised by a competent authority which would normally require the generic authorisation to conform to that of the innovator with respect to the*

[175] Hollmann K. Kombinationspräparate: Unsinn oder hilfreich bei der Behandlung? KVH aktuell. 2011;16(2):4–8.

> *summary of product characteristics and package leaflet and labelling as appropriate.*[176]

Other incentives for the protection of therapeutic concepts might include extension of the supplementary protection certificate (SPC). SPCs are granted for products such as medicinal products that require an approval. The authorisation processes may require years in which the patent cannot be used commercially, therefore a regulation has been created that allows to extent the market exclusivity by SCP. The SPC comes into force after the patents of the product is expired and extents the protection of a patented product. The maximum lifetime of an SPC is five years. However, there are already initiative in which the SPC can be extended. For example, the SPC can be extended for further six months for products for which data from an approved Paediatric Investigation Plan (PIP) are submitted. Similar approaches might be conceivable for therapeutic concepts with a major impact on public health, for example in indication in which only a few treatment opportunities exist.

[176] CMDh. Questions & Answers Usage Patent. October 2012 [Accessed on: 26 June 2016]. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh-279-2012-Rev0-2012_10.pdf.

7 Outlook und proposal of changes

The approach of therapeutic concepts applies primarily on indications with a high medical need, in which a strong rationale for combination therapy for selected patient populations exists. The approach follows the current development of increasing use and need for combinations in modern therapy. This drift is particularly obvious in the field of personalized medicine and the oncology sector where therapy with multiple products is common. Especially in these disciplines, the conditions are often life-threatening and difficult to treat. This development is currently not appreciated enough in the regulatory landscape. To adjust the existing legislation towards new paths therapeutic concepts are proposed to meet the demands.

As a first step, the EMA would have to officially introduce and define the term ‘therapeutic concept’. Implementation of therapeutic concepts would make use of the existing framework and could be achieved by introduction via EMA guideline on the regulatory path and requirements. A positive benefit-risk balance must be demonstrated and would still be the main criteria in order to obtain the marketing authorisation, as in any other authorisation route.

An outline on a prospective guideline for therapeutic concept development based on the implementation requirements discussed in this thesis is summarized in this section and issues that need to be clarified are discussed.

GUIDELINE ON THE DEVELOPMENT OF THERAPEUTIC CONCEPTS

INTRODUCTION

The introduction should outline that combinations in a therapeutic concept shall be based on valid therapeutic principles and shall be justified by a biological rational. The use of therapeutic concepts has the potential to facilitate the availability of approved combinations therapies for a defined patient population with a high medical need and a well-understood condition.

DEFINITION

The term ‘therapeutic concept’ must be outlined and defined based on the definition and explanations given in Chapter 4.1.

SCOPE

The guideline describes the relevant requirements that should be considered in the development of therapeutic concepts in order to support a safe use of the therapeutic concept in humans. The general requirements for the development and marketing authorisation also apply for therapeutic concepts, as well as relevant standards for components of the therapeutic concepts that are not medicinal product, such as diagnostics. The guideline does not apply to fixed combinations or combinations packs.

LEGAL BASIS

Legal basis for a guideline on therapeutic concepts should be Directive 2001/83/EC (as amended) as well as medical device directives whenever medical devices, especially in-vitro diagnostics, are involved in the therapeutic concept and the applicable standards. It must be clarified whether the entire concept can and must be approved under Directive 2001/83/EC including any medical devices incorporated in the therapeutic concept. This procedure would initiate a paradigm shift in the medical device legislation. It would mark the start of the approval of high-risk medical devices as is already demanded by many. By approving the in-vitro diagnostics used in a therapeutic concept the importance of the medical device in that particular treatment combination for the therapeutic success is

recognized. It must furthermore be determined if additional monitoring under the medical device regulation by a notified body will still be applicable. Considering the comparatively high risk of therapeutic concepts this may further improve the concept's safety profile.

It should be outlined under which approval procedure an authorisation can be obtained. Based on the complexity of therapeutic concepts due to the interaction of the different components of the concept a centralised procedure seems to be advisable. For therapeutic concepts with indications defined in Regulation (EC) no. 726/2004 the centralised procedure would be mandatory in any case. The centralised procedure should also be recommended for therapeutic concept combinations in which a close monitoring of the combinations is necessary, for example in therapeutic concepts with novel substances or with substances that previously shown a high risk. It should be considered if national procedure can be allowed under certain circumstances, such as therapeutic concept combinations with corresponding tradition in the concerned Member State. However, as therapeutic concepts represent an entirely new approval process, which must prove itself first, a centralised procedure is deemed the most reasonable approach.

GENERAL CONSIDERATIONS

The guideline should refer to the main questions in therapeutic concept development and should provide guidance on how to handle these issues.

These considerations include:

1. Justification of the therapeutic concept

   The concept must be based on the generally accepted terms for combinations. A scientific rationale shall be provided for the use of the combination. This may include pharmacological interactions (such as additive effects, reduction of adverse effects), genetic backgrounds (e.g. presence or absence of a particular gen), or other conclusive reasons that justify an improved efficacy profile. The potential interactions of the compounds within the therapeutic concept must be considered in non-clinical and clinical studies.

2. Possible therapeutic concept scenarios

   Combination of drugs or combinations of pharmaceutically active substances with diagnostics are possible.

   a. Combination of two or more medicinal products
   b. Combination of one or more medicinal product with a companion diagnostic

   The compounds are not part of a fixed combination or a combination pack (other guidelines apply for these combinations) but may be dispensed separately.

   The components of the therapeutic concepts can either be already approved components, a combination of new components or new actives substances or contain both, approved and new components.

3. Indication and patient profile

   The criteria for patient population and possible patient stratification for a specific therapeutic concept shall be clearly outlined and described. Wherever possible, a scientific rationale shall be presented to explain why the therapeutic concept is particularly eligible for the patient population (e.g. genomic parameters). Risk consideration regarding patient stratification should be evaluated.

4. Pre-clinical development and design of clinical studies

   Pre-clinical development and clinical trials with therapeutic concepts require extensive planning to prove the effectiveness and safety of the combination. Depending on the components of the therapeutic concepts (new or already approved components), non-clinical testing and clinical trials shall be planned according to the expected risk of the combination and the evidence already available for the combination and the individual components. Wherever feasible a two-armed study approach (combination vs. SOC or placebo) shall be accepted when the study design is selected to satisfactory demonstrate safety and effectiveness of the combination in order to not unnecessarily expose patients who are not likely to benefit

from the therapy. For new components, additional studies to evaluate toxicity, safety or effectiveness may be applicable in order to ensure a safe use.

5. Co-development

   Co-development of the concept should be given thorough consideration. In terms of safety and effectiveness, an early beginning of the co-development is desirable to investigate the possible interactions. Special focus should be given to the development of diagnostics that are required for a safe and effective use of a medicinal product to establish the appropriate clinical validity of the diagnostic.

6. Labelling requirements

   The labelling shall identify the distinctive requirements of the therapeutic concepts. It shall include explanations regarding the importance of the combination therapy, the selection of patients and the other components of the therapeutic concept. Three different scenarios are possible which shall be reflected within the labelling to allow patients and physicians to identify the status of the product.

   a. The drugs or drug/diagnostic combination are only to be used within the approved therapeutic concept, the mandatory combination should be clearly pointed out.
   b. One or more compounds of the therapeutic concept are also used individually for an approved purpose but sold under the same brand name
   c. One or more compounds of the therapeutic concept are also used individually for an approved purpose but sold under different brand names for individual use and use in the therapeutic concept.

8 Discussion

While combination therapies have been and will always be part of medicine they are however not always advantageous. To avoid the use of futile or even dangerous combinations several regulations were introduced over time. For the development and authorisation of fixed combinations, for example, a biological rationale must be present to justify the intended joint use.

However, the area of combination therapies is still lacking satisfying regulations and new options for the authorisation of combinations should be established. One possibility is the introduction of so-called therapeutic concepts, which are introduced by this thesis. In a therapeutic concept, several pharmaceutical products (and eventually diagnostics) shall be authorised in a free combination as a joint concept. In this way, a flexible therapeutic approach is approved that has undergone joint development and which can be used in accordance with the patient characteristics. This type of authorisation is a useful complement to the recent approval route that is mainly focused on single drug approval. New findings in science, however, offer many new insights that and why combinations in certain patient groups are particularly favourable and should therefore be used. Combinations have always been applied if they have proven to be useful for a particular disease or group of patients. Examples for combinations that are used since many years that are based on subgroups stratification and disease causes are the treatment of tuberculosis or helicobacter, which are discussed in this thesis. In these cases, there is a very strong biological rationale why these populations in particular are successfully treated with combinations. It is very likely that new knowledge about cellular pathways and disease origins lead to the conclusion that combinations are useful in many more cases and are thus applied more often. This knowledge is mainly based in the research performed in personalized medicine, which aims to investigate the genetic influence on diseases and cellular pathways.

Personalized medicine is presented as one of the main application areas for therapeutic concepts as several aspects that are important for therapeutic concepts are included such as patient stratification based on a scientific rationale. In addition, a high medical need is identified in this field and combinations are often

applied in the treatment. In many cases, a diagnostic is necessary for a safe and effective therapy as well. It was found that therapeutic concepts could be used as a new approach for several regulatory challenges that personalized medicine displays today. For example, biomarkers and companion diagnostics would be involved in the therapy from the outset. Providing the new possibility of therapeutic concepts combined with further research in personalized medicine and patients' stratification could possibly create new indications that would fall under the scope of the orphan drug regulation leading to more orphan drug applications. However, this is not considered a threat to the current intentions of the orphan drug regulation as patient safety and efficacy of a therapy should be prioritized.

Today medical guidelines are commonly used as a guide on how to apply combinations. Medical guidelines are however only recommendations and lack a legal basis and they are not comparable to an authorisation process. The uncertain legal status of medical guideline is thoroughly discussed. It was found that approval of therapeutic concepts would improve the uncertainties that are associated with medical guidelines. Medical guidelines are often the result of long years of experience with certain product combinations. Therapeutic concepts could accelerate the establishment of certain combinations in the standard of care compared to medical guidelines due to prospective planning of trials and scientific evaluations. As a result, approved therapeutic concepts are a compulsory therapy that offers more security for patients and physicians in regards of safety, efficacy and liability. Flexibility in treatment is an important aspect to respond to patient characteristics. Additionally approval of therapeutic concepts would provide the possibility of reimbursement of an entire concept not only parts of a necessary treatment.

A central step in therapeutic concept is the selection of an eligible patient collective. Because certain tests are needed for genome based patient stratification, the combination of medicines and diagnostic is becoming increasingly important. Therefore, diagnostics shall definitely be included in a therapeutic concept where needed in order to have a valid diagnostic tool that has been tested in the clinical development.

Many aspects and approaches for a therapeutic concept introduction already exist. FDA for example encourages co-development of products for use in combinations and gives guidance on design of clinical trials. For therapeutic concepts, the FDA approach should be extended to include not only unmarkted products but also already approved products in a combination use as well as diagnostics that are essential for the combination therapy. Introduction of the adaptive pathway by EMA shows that the European legislation has recognized that the current system is not suitable for all regulatory issues and that new innovative and more flexible ways of approval are being sought to satisfy different needs. Therapeutic concepts are a reasonable way to merge different approaches together and transform them into regulatory standards.

In order to establish therapeutic concepts as an attractive future way of authorisation sufficient incentives should be provided for industry and authorities. The benefits of the new regulation must be stated clearly and the pathway to the authorisation must be well defined for therapeutic concepts to be accepted by all stakeholders. Pharmaceutical companies need to be aware that therapeutic concepts approval exists in order to adapt to the new regulation and the role of the competent authorities and agencies such as the EMA should be well understood. A guideline issued by the EMA would provide the necessary guidance to fulfil the necessary requirements concerning sufficient safety and efficacy of the combinations. The strong focus on co-development of therapies should be emphasized. Considerations whether the EMA should provide special support for particular combinations with a major public interest should be made additionally. It should also be considered if therapeutic concepts approval will only be possible using the centralised approval procedure or if decentralised or mutual recognition procedures may also be used. Since therapeutic concepts are intended to strengthen the control of certain combinations and novel combinations introduced to the market, the centralised procedure seems to make the most sense. However, national approval could prove useful for the authorisation of old products in a new therapeutic concept, particularly if this combination already has a corresponding tradition in the concerned country.

Therapeutic concepts provide benefits in different areas, including better control of combination for both health care professionals and authorities. The combinations will be better studied, thus providing more information about possible interactions and risks, which leads to a safer use of certain combination regimens. Therapeutic concepts close the gap between treatment reality and medical practice. As discussed in this thesis, special considerations must be made concerning clinical trials, labelling, and implementation of medical devices/diagnostics into the therapeutic concept as well as vigilance strategies to address the extraordinary status of a new authorisation route.

Summary

In this thesis, the limitations and opportunities of the current regulation concerning therapy with product combinations are outlined.

It was found, that combinations are and always have been a frequently used approach in the day-to-day medical practice and the explanation why combinations are often a reasonable approach for the treatments of certain conditions are numerous. Despite several implemented procedures for the approval of combinations (fixed combinations, combination packs) not all scenarios for combination use are covered by the regulations. Amongst other things, this includes combinations administered individually in different doses, or combinations with medical devices that are indispensable for the safe and effective use of a treatment regimen.

Particularly personalized medicine exemplifies the many factors that influence modern therapy and justify the use of combinations by a scientific rationale supported by the identification of patient characteristics such as certain biomarkers. Stratification of patients allows a more effective and safer therapy. Despite gaining more importance this field of modern combination therapy is reflected poorly in the regulations and has been found to be in need of improvement. The increasing complexity of medical knowledge requires a more flexible approval system to adapt to the rising and ever changing needs.

In this thesis, the introduction of a new marketing authorisation route based on the current legal framework is proposed and the requirements for the presented approach are discussed. Introduction of so-called “therapeutic concepts” provides a new way of approving combination therapies. In a therapeutic concept several products that belong to the same treatment regimen for a defined patient collective are authorised for combination use in which the single compounds or products are administered separately on an individual basis and dosage; they are not necessarily part of a combination pack. Therapeutic concepts may combine several pharmaceutical compounds or a combination of pharmaceutical and

medical device should such be necessary for a safe administration, e.g. when the medical device is a diagnostic for a genetic makeup.

The expansion of the existing regulatory system by the approach proposed in this thesis not only reduces uncertainties in regards to combination therapies, but also brings a significant increase in patient safety.

Index of tables and figures

Tables

Figures

Publications

Krollmann KB, Schweim HG. Zulassung von „therapeutischen Konzepten“ / Der nächste Schritt zu einer „personalisierten“ Medizin. pharmind. 2015;77(5):650–3.

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