

COMPANION DIAGNOSTICS FOR PERSONALISED MEDICINES - THE REGULATORY FRAMEWORK FOR THEIR (CO-)REGISTRATION IN THE EU AND USA

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LIST OF ABBREVIATIONS

ASM	Aggressive Systemic Mastocytosis
BIMO	Bioresearch Monitoring Programm
BLA	Biological License Application, Biological License Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDx	Companion Diagnostic
CE	Conformité Européene
cGMP	current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
EC	European Commission
EMA	European Medicines Agency
FD&C	Federal Food, Drug and Cosmetic
FDA	Food and Drug Administration
FURLS	FDA Unified Registration and Listing System
HDE	Humanitarian Device Exemption
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
ITC	internal tandem duplication
IVDD	<i>In-vitro</i> Diagnostic Directive 98/97(EC)
IVDR	<i>In-vitro</i> Diagnostic Regulation (EU) 2017/746
MDA	Medical Device Amendments
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NSCLC	non-small cell lung cancer
OC	Office of Compliance
ODE	Office of Device Evaluation
ONC	Office of the National Coordinator for Health Information Technology
OOPD	Office of Orphan Products Development
OSB	Office of Surveillance and Biometrics
PM	Personalised Medicine
PMA	Premarket Approval
PMI	Precision Medicine Initiative

LIST OF ABBREVIATIONS

QMS	Quality Management System
QS	Quality System
QSR	Quality System Regulation
RSI	Request for Supplementary Information
SmPC	Summary of Product Characteristics
SRIA	Strategic Research and Innovation Agenda
SSED	Summary of Safety and Effectiveness Data

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1. INTRODUCTION TO COMPANION DIAGNOSTICS FOR PERSONALISED MEDICINES

The first section of this thesis defines the terms “Personalised Medicine” (PM) and “Companion Diagnostic” (CDx) as they are used in this work. The following sub-sections introduce the concept of PM and CDx and initiatives to promote them in both the European Union and United States of America.

1.1 TERMS AND DEFINITIONS

1.1.1 AN ATTEMPT TO DEFINE PERSONALISED MEDICINE

Since the 1960s the concepts of personalised medicine have been acknowledged and the term personalised medicine was first introduced in a monograph by Jain in 1998. (1, 2) Its use has been increased rapidly since then. (3, 4) There is no official definition of “personalised medicine” and various expressions are used interchangeably to describe the concept thereof (4). Among these expressions the term “precision medicine” may be the most suitable as it has been defined as “the use of genomic, epigenomic, exposure and other data to define individual patterns of disease [...]” resulting in a “better individual treatment”. (5) The expression is described and the difference to the term “personalised medicine” is outlined in the appendix of the publication on “Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease” published by the US National Research Council in 2011. (6) The following tables give descriptions and an overview on various scopes of personalised medicine provided by different institutions.

TABLE 1-1: DESCRIPTIONS AND SCOPES OF PERSONALISED AND PRECISION MEDICINE BY DIFFERENT ORGANISATIONS

1. President’s Council of Advisors on Science and Technology. (USA)	
Personalised Medicine:	<i>“The tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment.”(7)</i>
Precision Medicine:	<i>“The term “precision medicine” is preferable to “personalized medicine”. It should be emphasized that in “precision medicine” the word “precision” is being used in a colloquial sense, to mean both “accurate” and “precise” (in the scientific method, the accuracy of a measurement system is the degree of closeness of measurements of a quantity to that quantity’s actual (true) value whereas the precision of a measurement system, also called reproducibility or repeatability, is the degree to which repeated measurements under unchanged conditions show the same results.” (6)</i>

1.

2.	National Cancer Institute (USA)	
Personalised Medicine:	<i>"A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease. In cancer, personalized medicine uses specific information about a person's tumor to help diagnose, plan treatment, find out how well treatment is working, or make a prognosis. Examples of personalized medicine include using targeted therapies to treat specific types of cancer cells, such as HER2-positive breast cancer cells, or using tumor marker testing to help diagnose cancer. Also called precision medicine."</i> (8)	
3.	European Commission (EC)	
Personalised Medicine:	<i>"Personalised medicine refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."</i> (9)	
4.	Wikipedia	
Personalised Medicine:	<i>"Personalised medicine is a medical procedure that separates patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease."</i> (10)	

The comparison of above presented descriptions of personalised medicine demonstrates the wide variety in definition of the term. While the first by the President's Council defines personalised medicine at a sub-population level (which may be described by a cure a patient is fit into), the second by the National Cancer Institute defines it more at an individual level (a patient a cure is fit to). The lack of one uniform definition and the "conceptual vagueness" which leaves room for multiple interpretations may be (one of) the reason(s) for misunderstandings in communication and discussions about PM. (11, 12) However, this discussion is not in scope of this thesis.

1.1.2 COMPANION DIAGNOSTICS

Advances in "-omic" sciences such as genomics, transcriptomics, proteomics, metabolomics, etc. as well as in information and communication technologies have strengthened the understanding of the molecular mechanisms of diseases and the human body. (13) The identification of more and more predictive biomarkers whose "[...] level of expression [...]" may be of value in predicting the effectiveness of a particular 'targeted' therapy "[...]" for a disease have boosted the development of assays detecting specific predictive biomarkers "[...] allowing classification of patients [...] into responders and non-responders, for the corresponding therapeutic agent." (14)

BIOMARKER

The term biomarker refers to an indicator of a biological state which is a characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. They are used in the pharmaceutical development and for diagnostic, prognostic, monitoring and screening purposes. (9)

Due to the “[...] lack of consensus when it comes to the terminology [...]” one might conclude that the concept of companion diagnostics “is still in its infancy.” (15) Similar to the situation personalised medicine, various expressions referring to the same concept can be found for a companion diagnostic in the literature and/or on the internet. Terms describing an *in-vitro* diagnostic associated with a therapeutic may be, for example:

- Pharmacodiagnostics
- *Theranostics* – mainly used in academic medical literature
- Pharmacogenomic biomarkers – this term is the preferred term by EMA (16)
- Companion diagnostics – most frequently used term, amended and defined by the FDA in (17)
- Predictive diagnostics
- Precision diagnostics
- Personalised diagnostics

The terms pharmacodiagnostics, theranostics or pharmacogenetics were employed until recently for predictive biomarker assays. However, in 2006 the term “companion diagnostic” was introduced by Papadopoulos *et al.* (18) for assays facilitating the drug discovery process, resulting in more efficient and informative clinical trials, and individualizing patients’ treatment. Regulatory authorities, mainly the U.S. Food and Drug Administration (FDA), have been designating predictive biomarker assays which are developed side by side with a therapeutic as companion diagnostics. (19)

Companion diagnostics had not been defined in the current EU legislation before Regulation (EU) 2017/746 on *in-vitro* diagnostic medical devices (IVDR) (20) recently came into force. The definition and regulatory framework of *in-vitro* diagnostics implemented with Directive 98/79/EC (21) have been applied to these tests and may be applied during the 5-years transition phase. As per article 1b) of Directive 98/79/EC (IVDD) an *in-vitro* diagnostic device is “any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination [...] to be used *in-vitro* for the examination of human 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 recipient or
- to monitor therapeutic measures.” (21)

With the adoption of the new Regulation on *in-vitro* diagnostic medical devices the term companion diagnostic has finally been laid down in European legislation. The definition presented in Table 1-2 refers to the definition of Art. 2, section 7, of the Regulation (EU) 2017/746 on *in-vitro* diagnostic medical devices which was officially published in the European Journal on May 5th, 2017. (20) The definition of companion diagnostics as provided in the recently adopted EU Regulation and therewith coupled changes to the regulatory framework for CDx are discussed in section 2.1.

TABLE 1-2: DEFINITION OF COMPANION DIAGNOSTICS BY FDA (US) AND THE EUROPEAN COMMISSION (EU)

EU	
	<i>Devices being essential for the safe and effective use of a corresponding medicinal product are “companion diagnostics”. Their use is intended to identify patients most likely to benefit from the treatment with the corresponding medicinal product before and/or during the treatment and/or to identify patients likely at a high risk for serious adverse reactions resulting from the treatment with the corresponding medicinal product. (20)</i>
US	
	<i>In-vitro diagnostic devices and/or imaging tools providing essential information with regard to the safe and effective use of a (corresponding) therapeutic product are called companion diagnostic devices. Its use in combination with a particular therapeutic product is specified in the instructions for use in the labelling of both the device and the corresponding therapeutic product, and in the labelling of any of its generic or biosimilar equivalents.(17)</i>

In 2014 the FDA published a guidance document on *In-vitro* Companion Diagnostics (17) which provided a definition for companion diagnostics (see Table 1-2) and clarified four characteristics of them regarded crucial for the safe and effective use of the corresponding therapeutic product by

- Identifying patients most likely benefitting from the therapeutic product;
- Identifying patients with an increased risk of serious adverse reactions when treated with the therapeutic product;
- Monitoring response to a treatment with the therapeutic product in order to continually adjust treatment to increase safety or effectiveness;

- Identifying patients for whom the therapeutic product has been defined safe and effective on the basis of adequate studies; identifying the part of the population for whom the therapeutic product may not be safe and effective. (17)

The definition of the FDA may best be summarised by companion diagnostics' use in outcome prediction with regard to safety and efficacy of a therapy and its monitoring. (19)

Table 1-3 summarises the different general types of companion diagnostics which "[...] provide critical information, but do not specify a corresponding therapeutic." (22) The assay types used in screening and detection, prognosis and recurrence do not match the FDA defined types theranostics and monitoring tests which are directly linked to a therapeutic. However, all five types presented may influence the CDx industry and regulatory framework in the future. (22)

TABLE 1-3: APPLICATIONS AND EXAMPLES OF CDx. Overview based and adapted from supplementary information provided in (22).

SCREENING AND DETECTION	CDx used for the screening for familial genetic patterns and detection of conditions difficult to diagnose. Examples are BRCA for aggressive breast cancer and CupPrint® for identification of cancers of unknown primary origin.
PROGNOSIS	CDx for the prediction of the future course of progression of a disease. One example is (eg, Genomic Health's Oncotype Dx® used for breast cancer).
THERANOSTICS	CDx used to stipulate a patient's response to a prescribed therapy. Example is (eg, HER2/Neu test for Herceptin®).
MONITORING	CDx used for the evaluation of the effectiveness and appropriate dosing of a prescribed therapy. Example (eg, CYP2C9 and VKORC1 for testing offor warfarin sensitivity).
RECURRENCE	CDx for the analysis the patient's risk for recurrence of the disease. An example is (eg, Agendia Mammaprint® to indicate the risk offor recurrence of breast cancer).

1.2 PM INITIATIVES IN THE USA AND EU

The currently applied approach in healthcare is best described by as a reactive “one-size-fits-all”. The majority of treatments are empirical and general, with patients being treated with broadly active pharmacotherapies without the application of highly sophisticated molecular diagnostic tests prior to therapy. However, “[...] as with personal training or even personal shopping tastes, there is now a move towards a system of predictive, preventive, and precision care based on an individual patient’s needs.” (23) The shift in healthcare concepts towards personalised / precision medicine has not only been promoted by industry, science and regulators, but also by politicians and governments. Initiatives such as the Precision Medicine Initiative launched by the former US president Barack Obama in 2015 or programmes for funding provided by the European Commission support the concept of personalised / precision medicine.

1.2.1 FUNDING OF PERSONALISED MEDICINE IN EUROPE

Between 2007 and 2011 funding for research in the field of personalised medicine was provided by the European Commission’s Health Theme of the Seventh EU Framework Programme for Research and Technological Development. A conference on “European Perspectives in Personalised Medicine” was arranged by the Personalised Medicine Unit within the European Commission’s Health Research Directorate in the spring of 2011 to provide a platform for the discussion on “key research needs for the development of personalised medicine approaches”. (24) One outcome was the publishing of the first European policy document on PM’s progress in 2013. This report emphasised the “Use of -omics’ technologies in the development of personalised medicine” (25).

In December 2015 personalised medicine was included in Council conclusions as one of its health priorities and a long list of notes, considerations and actions was published to promote this “[...] medical model using characterisation of individuals’ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention”. (26) The document covers actions laid down for the Member States to improve education, training and the professional development in healthcare, as well as for the EC and Member States to enhance common principles on data collection with regard to electronic health records. The prospect of continuing funding with more than € 2 billion in the Work Programs for 2014/15 and 2016/2017 of Horizon 2020 by the EC was presented. (27) Under the point “Personalising Health and Care” the objectives for research and innovations to support this goal are listed as

- Better understanding of causes and mechanisms for health, healthy ageing and diseases;
- Better monitoring of health, prevention, detection, treatment and management of diseases.

In total, an investment of €3.2 billion “[...] across the medical innovation cycle ‘from bench to bedside’ [...] from the research framework programs FP7 and Horizon 2020” has been made. (28)

In June 2016 a second conference on personalised medicine with “broader policy perspective” was organised by the EC to “[...] bring together research institutions, patients, healthcare practitioners and governments to use today’s vast data resources to foster the well-being of its citizens [...]” A “new paradigm” – the patient as “active partner” instead of “subject of research or treatment” was outlined which would require innovation in drug development and healthcare system structures. (29) The program of the conference was categorised by five key challenges which had been described in and analysed by the PerMed SRIA project report “Shaping Europe’s Vision for Personalised Medicine” published in June 2015. (30) Challenges mentioned are

- Development of awareness and empowerment;
- Integration of Big Data and ICT solutions;
- Translation of basic to clinical research (and beyond);
- Launch of innovations;
- Sustainable healthcare systems. (30)

The report identifies one major obstacle for the application of personalised medicine in Europe – the fragmentation of efforts by nationally and regionally restricted activities and a lack of concerted approaches due to different definitions and assessment approaches regarding PM. On one hand research policies and funding are required. On the other hand a common understanding of scientific evidence, professional context, experience, values, and quality standards is mandatory. To overcome these obstacles it is important to achieve strategic interactions between all key players. These are political decision makers, scientific bodies, patient interest groups, deputies of the healthcare systems, regulatory and governmental bodies as well as private enterprise. (30)

1.2.2 PERSONALISED MEDICINE IN THE USA - OBAMA'S PRECISION MEDICINE INITIATIVE

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine – one that delivers the right treatment at the right time. [...]to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and our families healthier." (31)

President Barack Obama, State of the Union Address, 20 January 2015, USA

As early as 2004 Francis Collins, Director of the US National Institute of Health, "[...] had already called for a large-scale prospective cohort study of genes and environment". (32) Barack Obama, at that time the Senator for Illinois, introduced the "Genomics and Personalized Medicine Act of 2006 [...]" to realize the promise of personalized medicine by expanding and accelerating genomics research, to improve the accuracy of disease diagnosis, and to increase the safety of drugs and to identify novel treatments." (33) As the 44th president of the USA, he announced in the 2015 State of the Union the *Precision Medicine Initiative* (PMI) – a \$215 million investment integrated in 2016's budget to "accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients." (34)

The objectives of the PM initiative as defined by the White House in its fact sheet published a few days after the State of the Union are the

- Increase and improvement of cancer treatments;
- Formation of a (voluntary) national research cohort;
- Protection of privacy;
- Regulatory modernisation
- Partnerships between the public and private sector. (35)

A summary of the objectives and milestones accomplished within the first year after the State of Union is provided in Table 1-4.

TABLE 1-4: OVERVIEW OF PMI'S OBJECTIVES FROM JANUARY 2015 (34) AND MILESTONES ACCOMPLISHED WITHIN THE FIRST YEAR. (35)

INVESTMENT	INSTITUTION	OBJECTIVES	MILESTONES
\$130 million	National Institutes of Health (NIH)	- Development of a voluntary national research cohort consisting of a million or more volunteers by 2019 - Starting point for innovative research based on engaged participants and open, responsible data sharing	<u>March 2015</u> - PMI Working Group organized <u>September 2015</u> - Report "The Precision Medicine's Initiative Cohort Program – Building a Research Program for 21st Century Medicine" providing direction on - o <i>Cohort Assembly</i> - o <i>Participant Engagement</i> - o <i>Data Considerations</i> - o <i>Security</i> - o <i>Biospecimens</i> - o <i>Policy considerations</i> - o <i>Governance</i>
\$70 million	National Cancer Institute (NCI) as part of the NIH	- Identification of genomic mechanisms in cancer - Development of more effective cancer treatment.	<u>August 2015</u> - Declaration of focus on four main areas - o <i>Expanding Precision Medicine Clinical Trials</i> - o <i>Overcoming Drug Resistance</i> - o <i>Developing New Laboratory Models for Research</i> - o <i>Developing a National Cancer Knowledge System</i>
\$10 million	Food and Drug Administration	- Further accomplishment of expertise - Development and establishment of high quality databases - Provision of the regulatory framework to promote precision medicine and protect public health.	<u>December 2015</u> - plan for online portal to collaboration and development the applications of next-generation sequencing - o <i>precision FDA platform</i>
\$5 million	Office of the National Coordinator for Health Information Technology (ONC)	- Support of the development of interoperability standards and requirements that address privacy and - Enablement of secure exchange of data across systems.	<u>Sept 2015</u> - Reporting letter on recommendations - o <i>Readily Applicable Standards for PMI</i> - o <i>Promising Standards for PMI</i> - o <i>Standards Gaps for PMI</i> - o <i>Accelerators</i>
\$ 215 million			

As announced by the White House at the beginning of 2016 aside from Federal investments and actions approximately 40 private sector organisations had already committed themselves to enhance precision medicine, “in alignment with the key principles of the Precision Medicine Initiative”. (36) These were defined to

- facilitate the access, understanding and sharing of personal digital health data with the option for donation;
- set up of user-centred ways for the engagement of participants in research;
- provide precision medicine to all patients
- set up data and technology tools for citizen participation for diverse collaboration and skill sharing. (36)

The precision medicine initiative is directly linked to the 44th president of the United States, Barack Obama. Especially the NIH dreamed big under his presidency by e.g. awarding \$55 million to start with the set-up of the million-person precision medicine study which was a cornerstone of the Precision Medicine Initiative. (37)

Nowadays, with the change in government, “the future of major projects to study the brain, personalise medical treatments and cure cancer is in flux” and leaves “the future of the Precision Medicine Initiative [...] uncertain.” (38) The budget blueprint “America First - Make America Great Again” published on 16th March, 2017 gives an insight in the President Trump’s 2018 budget plans and outlines cuts proposed in healthcare:

- \$69.0 billion for Human Health Service (HHS) resulting in a \$15.1 billion or 17.9 percent decrease from the 2017 annualized continuing resolution level
- Reduction of National Institutes of Health’s spending by \$5.8 billion to \$25.9 billion
- Increase of FDA’s medical product user fees by approximately \$1 billion over 2017 annualized CR level. (39)

Cuts of that size have outraged biomedical research groups and has drawn opposition from both Democrats and many Republicans in Congress.” (40) The 21st Century Cures Act, ratified in December 2016, is a bipartisan bill on NIH funding and speeding approvals of new drugs and medical devices. It earmarks a ten-year funding of more than \$1.4 billion for the PMI providing \$1 billion for the fiscal year 2018. Additionally, the law includes budget (\$4.8 billion) for the Cancer Moonshot and other NIH Innovation Projects. The Act has been sustained by both the Democrats and Republicans and there is still hope that the proposed cuts will not pass the House or Senate. The president of the Personalized Medicine Coalition, Edward Abrahams, may be right in stating “if Trump understood what personalised

or precision medicine was all about, he would be reluctant to move so forcefully against it, since it addresses so many of the things he cares about—mainly, how you persevere innovation and reduce overall systemic costs.” (41)

1.3 THE ROLE OF COMPANION DIAGNOSTICS FOR PERSONALISED MEDICINES

“It is far more important to know what person the disease has than what disease the person has.”

Hippocrates

Based on Hippocrates’ statement physicians have always considered not only the patients’ health conditions to decide on suitable treatments, but also personal factors such as the family history of diseases and / or the patient’s life style. (5) Nevertheless, the identification of the most effective and safest treatment has often been experienced as a long journey for many patients, resulting in the perception that the search for the right treatment is “trial and error”. Personalised medicine “[...] aims to better target intervention to the individual, maximise benefit and minimise harm” (42) and is an important part of recent developments in medicine which may be best described by “[...] from reactive to a proactive discipline [...] that is predictive, personalised, preventive and participatory (P4)”. (43)

The finalisation of the Human Genome Project in 2003 was not only “great feats of exploration in history” (44), but “set in motion the transformation of personalised medicine from an idea to practice” (45) by increasing the molecular understanding of diseases and its use in prediction of drug mechanisms of action. So far, more than 80 % of the proteins “predicted by the human genome have been identified [...]” by state of the art techniques and “[...] the remaining ‘missing proteins’ are being steadily accounted for.” (46) *Big Data* technologies have been applied in medical research resulting in an enormous number of biological and clinical data sets collected “[...] at an unprecedented speed and scale”. (47) This data is available for consolidation and allows to include clinical phenotypes into the decision making for (or against) a treatment. This development as well as recent progress in genomic based medicine “provide a unique framework for an individualised diagnostic and therapeutic approach” (42). Nowadays, pharmaceutical development is less driven by the “blockbuster principle” and “one size fits all” idea, but by the investigation of subgroups of patients sharing a “molecular make-up” identified by a valid biomarker considered as key to successful drug development. (9) For many treatments clinically relevant biomarkers have already been discovered and are investigated for their predictive feature for the development

of safe and effective therapeutic products and the stratification of the patient population in scope. For example, predictive biomarker-based assays have been developed in the last decades specifically “[...] to guide the use of targeted cancer drugs.” (19) These assays are considered and used as “companion diagnostics”. In many cases they “[...] are developed in parallel to the drug using the drug-diagnostic co-development model”,(48) since “[...] a thorough understanding of the underlying molecular pathology and the drug mechanisms of action [...]” enable a link of a “molecular characteristic to the treatment outcome.” (19, 48)

‘A high degree of correlation between response and positive estrogen-receptor assay suggests the value of the diagnostic test as a means to select patients for tamoxifen treatment’

Phase II study of tamoxifen: report of 74 patients with stage IV breast cancer (49)

Already in the 1970s the selective estrogen receptor modulator Nolvadex (tamoxifen) was developed for the treatment of advanced breast cancer and “[...] data on estrogen receptor status was correlated with the treatment outcome” as published in 1976. (19, 49) However, the success story of companion diagnostics really began with the monoclonal antibody trastuzumab, better known as Herceptin. It was developed as specific HER2 antagonist in the 1980s based on the “link between amplification of the HER2 gene and poor disease prognosis in breast cancer”. The simultaneously developed immunohistochemistry (IHC) assay to determine HER2 overexpression in tumour cells was used for the preselection of patients. The assay, HercepTest, is considered to be the first companion diagnostic linked to a specific therapeutic for which the US Food and Drug Administration granted co-approval in 1998. The history of the co-development “has served as an inspiration to a number of other pharmaceutical and biotech companies as well as regulatory agencies.” (19) Many more drug-diagnostic combinations have been approved by the FDA in the last two decades (refer to section 2.3 for a list of examples). Oncology is the main therapeutic field actively developing companion diagnostics and the “well-known examples of companion diagnostics have all come from the oncology segment”. (22) However, the interest in the development of CDx in other therapeutic areas is steadily increasing. Recently, therapeutics and their corresponding diagnostics were approved for the treatment of cystic fibrosis, human immunodeficiency virus and growth factor failure. (22)

Regulators worldwide have become aware of the relevance and importance of reliable companion diagnostic devices for the safety and efficacy of personalised medicines and that “[...] comparable regulatory standards and requirements [...]” for CDx and medicines are required. (15) As for the regulation of medicinal products, one would think that “[...] regulations for (...) diagnostics would not differ significantly among countries [...]” as the

same scientific data should be the basis of review by regulatory authorities. (50) This, however, is not the case.

The current regulatory framework for the registration of companion diagnostics in the European Union and United States of America follow different approaches. In the USA “[...] the most stringent requirements for safety and effectiveness documentation apply, [...]” and “countries including Australia, Canada, China and Japan have followed suit [...].” (48) In the EU, however, the term companion diagnostic had not been defined until recently and in most cases marketing of these devices is possible with only a conformity assessment rather than a full assessment and approval by a health authority. However, the regulatory framework in the EU is changing as a consequence of the implementation of the new legislation on *in-vitro* diagnostics.

In this thesis the regulatory framework in the European Union and US is summarised and differences are outlined. The current and future regulatory framework for the registration of companion diagnostics as applicable in the EU is presented. The (current) regulatory framework for CDx in the USA is described. Differences and the impact of the implementation of the new legislation on in-vitro diagnostic medical devices in the European Union are discussed and an overview on regulatory considerations for the registration of companion diagnostics in both regions is provided.

2. THE CURRENT REGULATORY FRAMEWORK FOR COMPANION DIAGNOSTICS IN THE EU AND THE US

In the EU and the USA medicinal products / drugs are highly regulated starting early in development, during the process of marketing authorisation application and throughout their lifecycle. Special procedures have been implemented for several types of drugs to support their development and authorisation as e.g. medicinal products intended for the treatment of rare diseases (orphan drugs). In several cases EMA and FDA have agreed on similar procedures and have been working together closely to establish parallel scientific advice on scientific issues during the development phase of new medicinal products / drugs. Especially in the field of innovative medicines, regulatory authorities aim to react to changes “[...] in scientific, economic and social demands [...] and alter content and format of their assessment procedures and their communication.” (51) An example is the adaptive licensing pathway adopted by the EMA or the break through program of the FDA to promote the authorisation of innovative medicines at an early time point. Novel diagnostic techniques, such as genotyping and biomarkers allow for innovative pharmaceuticals such as targeted and personalised medicines and “[...] are the scientific drivers of this development.” (51) “From a regulatory perspective, a CDx combines the pharmaceutical and medical device industries.” (52) But do the current regulatory frameworks in the EU and US reflect this reality sufficiently?

2.1 THE REGULATORY FRAMEWORK FOR COMPANION DIAGNOSTICS IN THE EUROPEAN UNION

The EU legislation on medicinal products is based on the consolidated Directive 2001/83/EC as the Community code relating to medicinal products for human use (53) and Regulation (EC) No 726/2004 laying down Community procedures supervised by the European Medicines Agency (EMA) (54). Its progression is in contrast to the development of the medical device legislation. As one of 17 industrial sectors affected by the “new approach” the “medical device regime” was introduced in 1985 and harmonised norms such as “conformity with the essential requirements” – the CE mark - were implemented. (52) These essential requirements have been stipulated by the directives 90/385/EEC (55) on implantable medical devices, 93/42/EEC (56) on medical devices and 98/79/EC on *in-vitro* diagnostics (21). Until the recent adaptation of (EU) 2017/746, the 98/79/EC has been the directive applicable to companion (*in-vitro*) diagnostics.

2.1.1 *IN-VITRO* DIAGNOSTIC DIRECTIVE 98/97 EC AND ITS IMPACT ON COMPANION DIAGNOSTICS

In contrast to the highly regulated marketing authorisation of medicinal products as laid down in Directive 2001/83/EC (53) and Regulation (EC) No 726/2004 (54), for a diagnostic device compliance with the essential requirements by performing “an appropriate conformity assessment” as per *in-vitro* diagnostic Directive 98/97/EC (IVDD) has been sufficient to “ensure a high standard of safety and performance when [...] placed on the market” (21).

Based on the IVDD definition an *in-vitro* diagnostic device is “any medical device [...] to be used *in-vitro* for the examination of human specimens, including blood and tissue donations, derived from the human body [...]. (21) The understanding of *in-vitro* diagnostic tests has long been that they are conventionally carried out by trained professionals and do therefore not offer immediate risk to the patients. This understanding, and the lack of an appropriate CDx definition have been the reasons why CDx have been treated as “general IVDs” for which the responsibility for conformity assessment has exclusively been with the manufacturer by allowing self-certification in the context of the IVDD. Independent third parties appointed by the European Commission, so called notified bodies, have only interfered in case of specific devices “where correct performance is essential to medical practice and failure can cause a serious risk to health” as stated in recital (22) of the IVDD. (21) The same principle has applied to devices intended for self-testing.

In contrast to the USA, where *in-vitro* diagnostics require a premarket approval (refer to section 2.2.2.2), in the European Union and European Economic Area medical devices have been marketed with the Conformité Européene (CE) mark.

The CE mark on a (IVD) medical device

- is the declaration of compliance with the essential requirements given by the manufacturer
- allows for placing on the market and free movement of the product in the EU and EEA
- permits the withdrawal of non-conforming products by customs and authorities.

A CE mark affixed to a device is either based on self-certification of the IVD manufacturers in case of general/“other” IVDs or on conformity assessment and certification by notified bodies, in case of specified IVDs (Annex II – list A and B), as laid down in the IVD Directive 98/79/EC. (21) Notified bodies are accredited to assess the conformity of an IVD medical device and confirm the legitimacy of the CE mark and/or declaration of conformity of the

manufacturer. (57) The types of IVDs as per IVDD 98/97 (EC) and the involvement of notified bodies are outlined in Table 2-1.

TABLE 2-1: CLASSIFICATION OF IVDs AND CONFORMITY ASSESSMENT AS PER IVDD 98/97(EC) (21)

IVDD CLASSIFICATION	INVOLVEMENT OF A NOTIFIED BODY & EXAMPLES
General/"other" IVDs	Declaration of Conformity by manufacturer without involvement of a notified body (see Annex III, section 2-5 of the IVDD) e.g. Hormone tests, hematology and clinical chemistry tests, cardiac marker
Self-testing	Review of Design/Labeling for lay user suitability by notified body (supplementary requirements, see Annex III, section 6 of the IVDD) e.g. Pregnancy, cholesterol (home) tests
Annex II – List B (critical IVDs)	Review of technical documentation and audit of quality management system of the manufacturer by notified body (see Annex IV or Annex V+VI or VII of the IVDD) e.g. Tests for infections, tumoral marker, hereditary diseases (, self-test for blood glucose
Annex II – List A (highly critical IVDs)	Review of design dossier, audit of quality management system, batch released by notified body (see Annex IV or Annex V+VII of the IVDD) e.g. Tests for HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D, ABO blood grouping

Annex III – EC Declaration of Conformity

Annex IV - EC Declaration of Conformity (Full Quality Assurance System)

Annex V – EC Type-Examination

Annex VI – EC Verification

Annex VII - EC Declaration of Conformity (Production Quality Assurance)

Figure 2-1 provides an overview of (regulatory) requirements of *in-vitro* diagnostics applicable to companion diagnostics (general/"other" IVDs) as per Directive 98/79/EC.

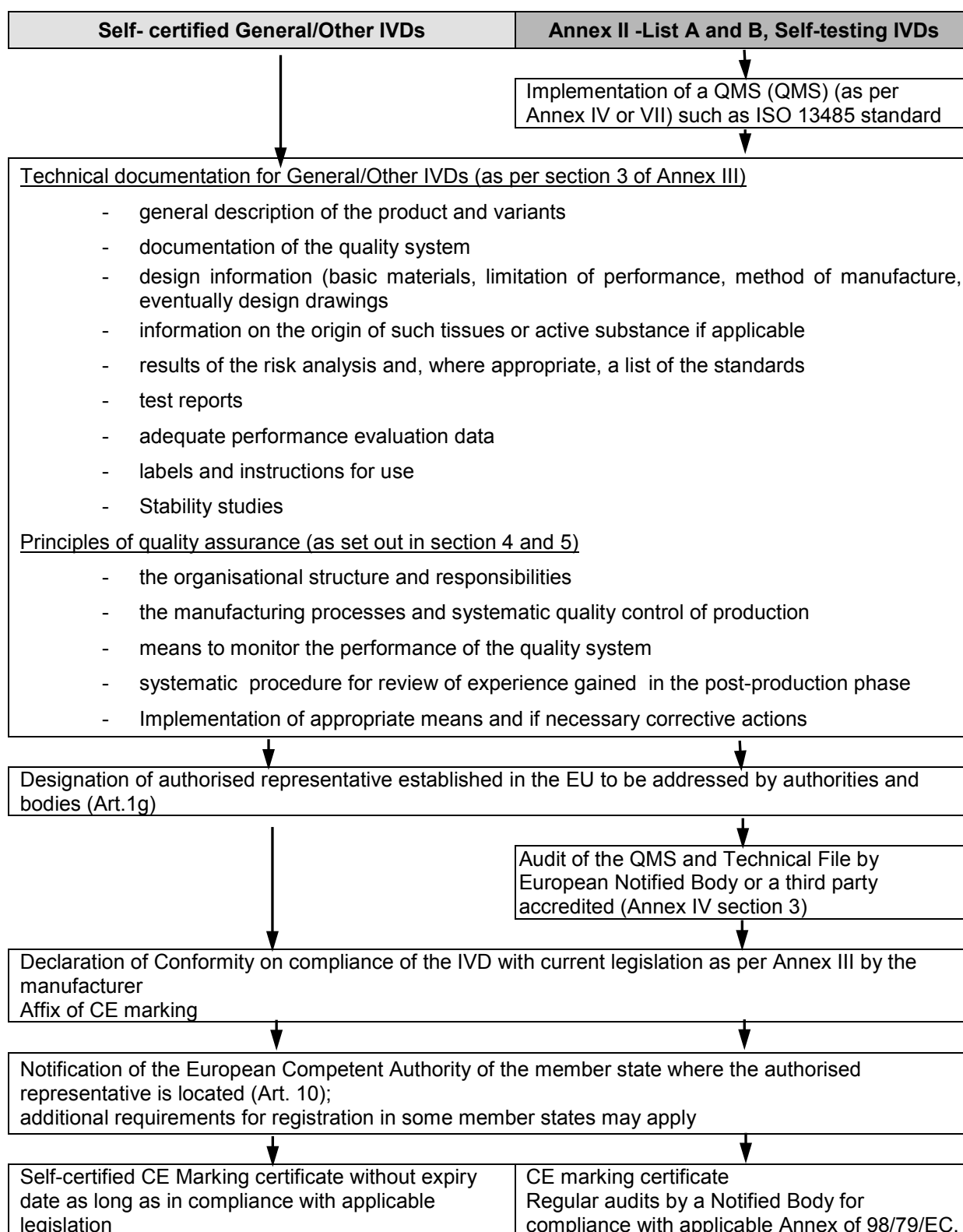


FIGURE 2-1: CONFORMITY ASSESSMENT FOR SELF-CERTIFIED GENERAL/OTHER IVDs AS PER ANNEX III OF DIRECTIVE 98/79/EC. Further requirements for List A and B and Self-testing IVDs are outlined, but are not complete. Figure prepared and adapted from (21, 58)

As outlined above the assessment and evaluation of medical devices and medicinal products is the responsibility of different parties. The manufacturer of a CDx performs a self-

certification and affixes the CE mark while notified bodies are rarely involved in the conformity assessment (see Table 2-1). Meanwhile, the national health authorities or the Agency (EMA) are responsible for determination of the benefit-risk ratio of a medicinal product. The separation of responsibilities with regard to the regulation of medical devices and medicinal products had been favoured in the European Union for many years and is in contrast to the more integrated approach pursued by the FDA, where the responsible functions for are located within the same authority (refer to Table 2-7).

Lately, however, the European Union has been urged from different parties to involve medicinal product regulators in the assessment and approval of medical devices, particularly for *in-vitro* diagnostics used as companion diagnostics to “provide more effective pharmaceutical treatments”. (59) The on-going discussion on appropriate regulation of (*in-vitro*) medical devices between politicians, regulators, professionals and healthcare sectors has resulted in “a fundamental revision [...] to establish a robust, transparent, predictable and sustainable regulatory framework for *in-vitro* diagnostic medical devices which ensures a high level of safety and health whilst supporting innovation. (20)

The adoption of Regulation (EU) 2017/746 on *in-vitro* diagnostics is one of the major results of this discussion and its impact with regard to companion diagnostics is outlined in the following sections.

2.1.2 INSIGHTS INTO REGULATION (EU) 2017/746 ON *IN-VITRO* DIAGNOSTICS AND ITS IMPACT ON COMPANION DIAGNOSTICS

*“It should be made clear that all tests that provide information on the predisposition to a medical condition or a disease (e.g. genetic tests) and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are *in-vitro* diagnostic medical devices.”*

Recital (10) of the IVD Regulation of the European Parliament and the council on *in-vitro* diagnostic (20)

The revision of the medical device legislation started in September 2012 and draft regulations for medical devices and *in-vitro* diagnostics were released in May 2016 that “[...] expected to achieve a twofold aim: making sure that medical devices and *in-vitro* diagnostics medical devices are safe while allowing patients to benefit of innovative health care solutions in a timely manner.” (60) The Regulation (EU) 2017/746 on *in-vitro* diagnostic medical devices was adopted by the European Council on March 7th (61) and was passed by the EU parliament on April 5th, 2017. The text was published in the Official Journal of the European Union and came into force one month later on May 5th, 2017. (20) A fact sheet published by

the European Commission in April 2017 summarises the changes from the “old” to the “new” rules for medical devices (62). Table 2-2 provides an overview on the measures for improvements.

TABLE 2-2: OVERVIEW ON MEASURES TO IMPROVE THE REGULATION OF MEDICAL DEVICES. Overview created and adapted from (62). All citations are taken from this reference.

Safety and market surveillance – European regulatory management
The regulatory management of medical devices is introduced to enable better and more frequent exchange of information to grant regulatory decisions by either Member States or Commission on a basis of consent. Appropriate reaction to safety issues should be facilitated. The European governance is strengthened by - Introduction of a Medical Device Coordination Group (MDCG), composed of Member States experts and chaired by the Commission; - Increase of cooperation between Member States with regard to vigilance and market surveillance; - Mandatory coordinated assessment of multi-national clinical studies on devices
High-risk devices - control by a pre-market scrutiny mechanisms
Notified Bodies are required to consult with an expert panel on high risk devices to obtain a scientific opinion on the assessment of clinical file provided by the manufacturer. The opinion is not binding but a justification not to follow it is necessary. All documents relevant for the opinion and decision of the notified body on a high risk device will be available in the database EUDAMED.
Notified Bodies – reinforcement of designation and oversight
Medium and high-risk devices require a conformity assessment procedure, involving a notified body designated and monitored by the Member States and acting under the control of the national authorities. The joint assessments of Notified Bodies introduced in 2013, are reinforced. Independent experts could be required to provide an opinion to the Notified Body on certain high-risk products before the final decision on the certification of the product is taken to support “[...] more informed decisions and stimulate a process of continuous learning [...] while preserving a high level of safety and performance of products.”
<i>in-vitro</i> diagnostics – new risk classification system
In line with international guidance four risk classes for <i>in-vitro</i> diagnostic medical devices are introduced. Different conformity assessment procedures are applicable and involvement of Notified Bodies depends on the risk class of the device.
Administrative procedures – simplification of registration
A single registration of medical devices and operators is introduced in the EU instead of registration in each member state the device is intended to be placed on the market.
Legal certainty – stable set of requirements
With the regulation a stable set of legal requirements is introduced in all member states to and provides “precise and detailed clarifications, [...]”.
Credibility and Reputation – increase of confidence
“[...] the confidence of patients and healthcare professionals in the safety of the devices [...]” has suffered from incidents demonstrating “an alleged “uneven approach” among the bodies responsible for certification and approval of medical devices” and have confirmed “some weaknesses in today’s legislation.” The new Regulations “aim to increase the overall confidence in the medical device market.”

The extent of the revision is illustrated by the fact that the new IVD Regulation is composed of 113 articles - compared to 46 articles of the directive– and is advancing the legislative procedures applicable for *in-vitro* diagnostics by repealing Directive 98/79/EC and Commission Decision 2010/227/EU. The regulation is directly binding for all member states and after the five years transition phase, meaning from 2022 on, a “harmonised application of the rules throughout the EU” will be ensured. (63)

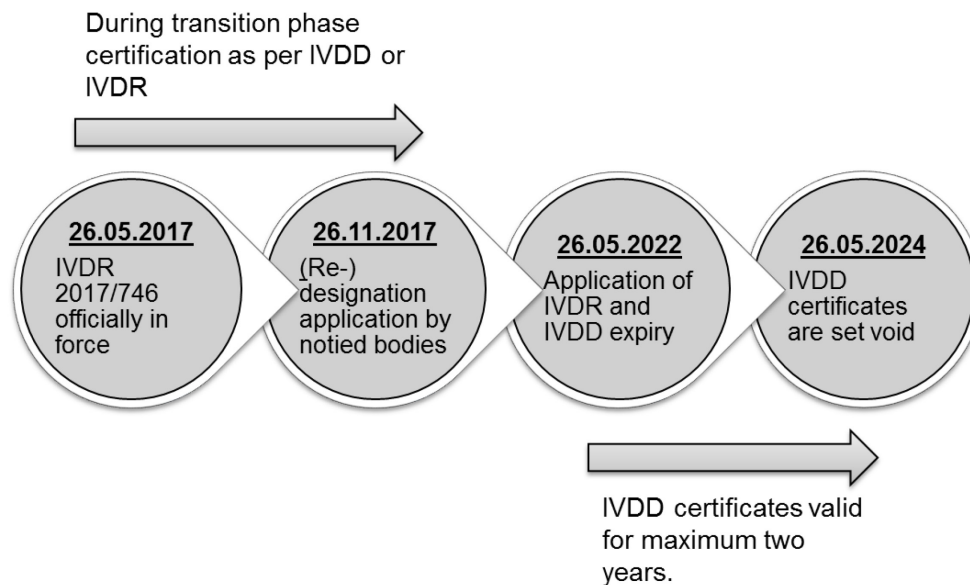


FIGURE 2-2: IMPORTANT TIME POINTS FOR THE TRANSITION PHASE FROM IVDD TO IVDR.

Companion diagnostics specifically addressed as IVDs are now subject to EU legislation as outlined in recital (11) of the IVDR. (20, 64) However, at this time, only the legislative text is available, and no specific guidance documents to facilitate the transition from one to the other regulatory framework yet exists.

2.1.2.1 DEFINITION OF COMPANION DIAGNOSTICS

The Regulation (EU) 2017/746 provides a definition for companion diagnostics in chapter I, Article 2, section (7). Compared to the 2016 draft version of the IVDR (65) where the definition of a CDx included monitoring as intended use, the adopted regulation provides a broader definition of a CDx as being “essential for the safe and effective use of a corresponding medicinal product”. (66) This reflects partially the FDA’s definition (see section 1.1.2) and demonstrates the Council’s attempt to harmonise the regulation of companion diagnostics between the EU and USA. (67). However, the section of the definition on “monitoring of responses to treatment with a medicinal product” has been deleted from

the European definition, marking a major difference to the US guidance document on *In-vitro* Companion Diagnostics published by the FDA in 2014. (17) The modifications made to recital 12 presented in Table 2-3, emphasise even more that *in-vitro* diagnostics “used with a view to monitoring a treatment” are not considered as companion diagnostics.

TABLE 2-3: DEFINITION AND DESCRIPTION OF COMPANION DIAGNOSTICS AS PER IVDR. (20, 65)

DEFINITION AS PER ART. 2 (7)	
'companion diagnostic' means a device <i>which is essential for the safe and effective use of a corresponding medicinal product to:</i>	
a) <i>Identify, <u>before and/or during treatment</u>, patients who are most likely to benefit from the <u>corresponding medicinal product</u>; or</i> b) <i>Identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product.</i> c) <i>Monitor response to treatment by the medicinal product for the purpose of adjusting treatment to achieve improved safety or effectiveness specifically intended to select patients with a previously diagnosed condition or predispositions as eligible for a targeted therapy;</i>	
RECITALS ON COMPANION DIAGNOSTICS	
(11)	<i>Companion diagnostics are essential to define patients' eligibility to specific treatment with a medicinal product through the quantitative or qualitative determination of specific markers identifying subjects at higher risk of developing adverse reaction to the specific medicinal product or identifying patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective. Such biomarker(s) may be present in healthy subjects and/or in patients.</i>
(12)	<i>It should be clarified that devices monitoring the response to treatment by the corresponding medicinal product for the purpose of adjusting treatment to achieve improved safety or effectiveness of that corresponding medicinal product are considered companion diagnostics. Devices that are used <u>with a view to monitoring in treatment drug monitoring with a medicinal product in order to ensure that the drug concentration of relevant substances in the human body is within the therapeutic window of the drug</u> are not considered companion diagnostics.</i>

Note:

The text of the regulation is presented with changes made to the Commission proposal indicated. New text is presented in *italics*, deletions by strikethrough. Changes to the General Approach are marked by underlining.

As a consequence of this broad definition many IVDs may be considered a companion diagnostic. Tests performed to detect patient-specific characteristics which are important for treatment decisions but are not directly related to a specific disease or a specific therapeutic (or active compound) fall under this definition, as explained by following example.

Since “knowledge regarding genetic factors that affect drug effectiveness and adverse drug reactions is continuously increasing [...]” pharmacogenetic tests as for common cytochrome polymorphisms are relevant for a variety of medicinal products and are included in their label. (68) Cytochromes affect the metabolism of drugs in the body and are therefore non-specific for a disease or treatment, but still relevant for the effective use of many. Any test is regarded a CDx as per IVDR’s definition if the determination of a patients’ characteristic - such as the lack of cytochrome CYP2D6- is included in the indication of a (corresponding) medicinal

product. (66) Devices used for the monitoring of the medicinal product itself during treatment are not defined as companion diagnostics. This is despite the fact that both the monitoring of the medicinal product and the determination of cytochrome polymorphism have the same intention - the prevention of sub-optimal plasma concentrations of the active compound and/or its metabolites. This is relevant for the safe and effective use of the corresponding medicinal products and therefore further discussion on this issue may be needed.

2.1.2.2 CLASSIFICATION AND CONFORMITY ASSESSMENT OF COMPANION DIAGNOSTICS

The classification of IVD medical devices into classes A, B, C and D as per Chapter V, section 1, article 47 and Annex VIII of the IVDR is based on “[...] the intended purpose of the devices and their inherent risks.” (20) The procedure of conformity assessment is directly linked to the risk class as laid down in section 2, article 48 of the IVDR. This risk-based classification system is comparable to the classification of medical devices applied by the FDA (refer to section 2.2.1).

Table 2-4 provides an overview on the conformity assessment procedure linked to the four risk classes with reference to the Annexes of the IVDR where the procedure is described in more detail.

TABLE 2-4: RISK CLASS AND CONFORMITY ASSESSMENT PROCEDURES LINKED TO IT. Table based on and prepared from (69)

RISK CLASS	CONFORMITY ASSEMENT PROCEDURE
<u>Class A</u>	Self-certification of conformity based on technical documentation (incl. risk/benefit analysis, product verification and validation)
<u>Class A sterile IVDs</u>	The notified body is involved in the assessment of issues with regard to the sterility of the device (Annex IX, except Chapter II – QMS and Annex XI - Product quality assurance)
<u>Class B</u>	The notified body is involved in - the assessment of the QMS (Annex IX, except Chapter II), or - the review of the technical documentation of not less than one device per generic device group <i>(Self-testing and near-patient testing require assessment of technical documentation)</i>
<u>Class C</u>	The notified body is involved in - the assessment of the QMS (Annex IX, except Chapter II), or - the review of technical documentation of not less than one device per generic device group, or - the EU type-examination (as per Annex X), and - the Production quality assurance (Annex XI) <i>(Self-testing and near-patient testing require assessment of technical documentation)</i>

<u>Class D</u>	The notified body is involved in • the full QMS audit IX) and assessment of technical documentation, and Batch verification, • the EU type-examination (Annex X), and Production quality assurance (Annex XI) and Batch verification • organisation of reference laboratory to verify performance • (Self-testing and near-patient testing require assessment of technical documentation)
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Whereas the certification of class A and B IVDs under the IVDR is based on technical features and the quality is assessed by the manufacturer (in case of class A devices) and / or a notified body, for *in-vitro* diagnostic devices of higher risks, e.g. class C and D devices, the conformity assessment has a stronger focus on clinical evidence and performance. Conformity assessment procedures are laid down in Article 48 of the IVDR.

For class C devices (other than those for performance study), Section 8 declares the conformity assessment to be performed as described in Annex X “Conformity assessment based on type examination” in conjunction with conformity assessment as per Annex XI “Conformity assessment based on quality production assurance” (section 5 excluded). Both annexes define the procedure “whereby a notified body ascertains and certifies that a device including its technical documentation and relevant life cycle processes [...] fulfils the relevant provisions of this Regulation”. (20). For Class C companion diagnostics notified bodies shall consult with a competent authority for each device, as designated in accordance with Directive 2001/83/EC or with the European Medicines Agency. The consultation procedure is defined in point (k) of paragraph 3 in Annex X.

Therefore, the classification of IVDs “[...] is completely changed from a list- based to a decision tree- based system.” (70) The determination of the risk class of an *in-vitro* diagnostic device, based on seven rules laid down in Annex VIII of the Regulation, is outlined in Figure 2-3. The principles of Annex X on “Conformity assessment Based on Type Examination” are summarised in Table 2-5.

RULE		CLASS
1.	- Transmissible agents in substances, cells, tissues, organs, etc. intended for donation - Transmissible life-threatening agent with high risk of propagation - Monitoring infectious load of life-threatening disease	Class D
2a	- Blood grouping - Tissue typing as part of transfusion, transplantation or administration	Class C
2b	High risk blood groups and tissue types	Class D
3	- Infectious diseases, incl. sexually transmitted agents - Pre-natal screening, congenital disorders in embryo/fetus/new-born Companion Diagnostics - Disease staging - Genetic testing - Screening, diagnostics, staging of cancer	Class C
4a	Self-testing Except uses noted in rules 4b	Class C
4b	Self-testing for - detection of pregnancy - fertility - cholesterol level - glucose - erythrocytes - bacteria in urine	Class B
5	- General laboratory use, accessories with no critical characteristics, buffer solutions etc - Instruments for IVD procedure - Specimen receptacles	Class A
6	Devices not covered by rules 1-5	Class B
7.	Controls without quantitative or qualitative assigned value	Class B

FIGURE 2-3: CLASSIFICATION OF IVDs AS PER ANNEX VIII OF THE REGULATION ON *IN-VITRO* DIAGNOSTICS. Overview prepared and adapted from (69) and (70)

TABLE 2-5: SUMMARY OF THE IVDR - ANNEX X ON “CONFORMITY ASSESSMENT BASED ON TYPE EXAMINATION” (20)

Application
(Section 2)

Application for assessment at a notified body including

- Administrative information (name, address, place of business)
- Technical documentation (as per Annexes II and III) together with a representative sample of the device (“type”)
- If applicable, test reports and study results on handling suitability in relation to its intended purpose (self-testing or near-patient testing)
- Information on intended label and instructions for use
- Confirmation that no other application for the device has been lodged with any other notified body; information on previous applications for the same type of device (refused or withdrawn before final assessment of notified body)

Section 3 –
Assessment

The assessment by the notified body includes

(a)	• Examination of application by “staff with proven knowledge and experience in the evaluation of the technology and the devices concerned and the evaluation of clinical evidence”. Further tests or evidence may be requested. The notified body shall perform “adequate physical or laboratory tests” or request those.
(b)	• Examination and assessment of technical documentation for conformity to “verify that the type has been manufactured in conformity with the documentation”
(c)	• Review of documentation with regard to clinical evidence provided in the performance evaluation report (section 1.3.2 of Annex XIII) by “device reviewers with sufficient clinical expertise”. External experts may be employed.
(d)	• Evaluation of suitability/adequacy of data on clinical evidence in case it is based on data from “devices which are claimed to be similar or equivalent”.
(e)	• Documentation of assessment outcome in performance evaluation assessment report (Section 4.8 of Annex IX)
(f)	• Arrangement of “appropriate assessments” to verify if solution by the manufacturer presented in case “standards referred to in Article 8” have not been applied.
(g)	• Arrangement of “appropriate assessments” if manufacturer “has chosen to apply the relevant harmonized standards”
(h)	• Agreement on the “place where the necessary assessments and test carried (as per (a) to (g)).
(i)	• EU type-examination report on assessment results and tests carried out (as per (a) to (g)).
(j)	• <i>Class D devices only:</i> Request EU reference laboratory to verify the performance claimed – scientific opinion within 60 days; Consultation with relevant experts
(k)	• <i>Specific for CDx</i> Seek the opinion, on the basis of the draft summary of safety and performance and the draft instructions for use” of a competent authority or EMA (“the medicinal products authority consulted”) on the “suitability of the device in relation to the medicinal product concerned.” An opinion shall be available within 60 days of receipt of all necessary documentation. An extension by another 60 days may be justified. The opinion of the medicinal products authority consulted shall be included in the documentation of the notified body; this opinion should be considered in the decision of the notified body.
(l)	• EU type-examination report on the results of the assessments and tests carried out, an scientific opinions provided under points (a) to (k) including a performance evaluation assessment reports for class C or D devices

**Section 4 –
Certificate**

- Issue of an EU type-examination certificate if type conforms to the Regulation drawn in accordance with Annex XII.
- The relevant parts of the documentation are attached to the certificate; the notified body keeps a copy.

**Section 5 –
Changes to
the type**

- | | |
|-------|---|
| 5.1 – | <ul style="list-style-type: none"> • The notified body responsible for EU type-examination is to be informed of “any planned changes to the approved type or of its intended purpose and conditions of use”. • Where the Changes impacting the performance or the intended use of a companion diagnostic or its suitability in relation to a medicinal product, the notified body shall consult the medicinal products competent authority that was involved in the initial consultation or the EMA. Its opinion, if any, shall be given within 30 days after receipt of the valid documentation regarding the changes. The approval of any change to the approved type shall take the form of a supplement to the initial EU type-examination certificate. |
| 5.4 | |
| 5.5 | |

**Section 6 –
Administrative
provisions**

- The manufacturer or authorised representative shall “for a period ending no sooner than 10 years, after the last device has been placed on the market, [...]” be able to provide to the competent authorities
- Documentation as referred to in Section 2
- Information on changes as referred to in Section 5
- Copies of EU type-examination certificates, scientific opinions and reports as well as additions/supplements

The notified body performs the assessment in accordance with Annex X, which includes the review of the technical file, clinical evidence of the companion diagnostic and the audit of the Quality Management system of the manufacturer. In parallel, a scientific opinion is requested from the consulted authority which is provided based on the draft summary of safety and performance and instructions on use of the device.

Section k) specifically describes the procedure for consulting with the relevant health authority on the “suitability of the device in relation to the medicinal product concerned”. No official guideline on this consultation procedure has yet been issued.

However, Figure 2-4 illustrates the procedure as proposed by the EMA at the stakeholder platform meeting in April 2017 where an anticipated timeline for a concept paper on the co-development of biomarker-based companion diagnostics and medicinal products in the context of drug development was presented. (71)

The timeline suggested by EMA for the review of the documentation on a companion diagnostic provided by a notified body is based on the 60 / 120 days assessment of a type II variation and may include a clock stop in case of a request for supplementary information

(RSI). Once the Committee for Medicinal Products for Human Use (CHMP) has issued its opinion, the notified body finalises the procedure, draws up the final report and announces its final decision. The CE mark is affixed to the CDx and the public assessment report of the medicinal product is updated by EMA. (71)

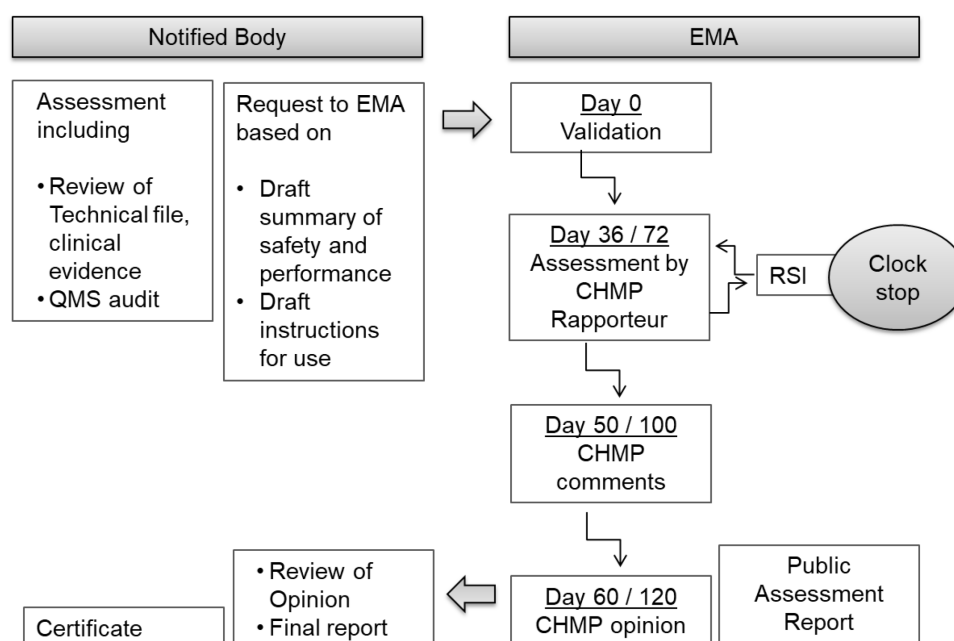


FIGURE 2-4: ROUGH SCHEME OF CONFORMITY ASSESSMENT OF A CDx BY A NOTIFIED BODY AND NOT YET DEFINED CONSULTATION PROCESS WITH EMA. The presented timeline is based on the Type II variation review timeline. Illustration prepared and adapted from (71).

As mentioned before, no adopted guideline exists yet in the EU. The draft reflection paper *Co-development of pharmacogenomic biomarkers and assays in the context of drug development* (EMA/CHMP/641298/2008) from 2011 has focused on co-development of genomic biomarkers and assays. Unfortunately, companion diagnostics are described only marginally as pharmacogenomics biomarker used in the patient selection for confirmatory clinical trials as part of a MAA and of Risk Management Plans. (16)

In the context of the revision of the IVD legislation, on July 28th, 2017, the draft concept paper *on predictive biomarker-based assay development in the context of drug development* was published for public consultation with the intention to lead into a guideline replacing -above mentioned reflection paper. (16, 72)

The scope of the concept for a guideline includes “[...] recommendations relating to the interface between predictive biomarker-based assays including CDx, and the development and lifecycle of medicinal products”. Following three “problems” are stated. (72)

-
1. Clinical development phase – guidance on the co-development of medicinal products and biomarker-based assays

In case no CE-marked IVD is available for the measurement of a predictive biomarker in the drug development phase, an “[...] assay used in clinical development may itself be co-developed as an eventual CDx.” The alignment of technical and clinical performance requirements (as per IVDR) for CE marking and approval of the medicinal product and general timing of co-development will be discussed.

2. Post-approval phase – guidance on the development and use of biomarker-based assays during the marketing phase of medicinal products

In case a predictive biomarker-based assay “[...] is recommended for the safe and effective use on an approved drug” the development of suitable assays for the clinic will be discussed with regard to concordance testing and bridging studies and the storage of samples. Considerations on information provided in the Summary of Product Characteristics and European public assessment reports (EPARs) as well as in the risk management plans (RMPs) will be included in the guideline. Guidance on labelling aspects will furthermore be included.

3. Glossary of terms used in EMA guidelines and in the IVDR

A glossary will be compiled with the intention to “define and explain regulator’s understanding of specific terms [...]” as analytical / clinical validation / performance, clinical utility, concordance studies, training and validation sets.

2.1.2.3 NOTIFIED BODIES DESIGNATED TO PERFORM CONFORMITY ASSESSMENT OF COMPANION DIAGNOSTICS

The IVDR will change the principles of the oversight of (*in-vitro*) medical devices in the member states of the EU. Notified bodies are currently facing the challenge to apply for their (re-)designation within six months of the regulation coming into effect – that is by November 2017. However the criteria applicable to the application and the re-designation process have not yet been defined well. As per chapter IV, article 31 of the Regulation, the bodies designated to perform conformity assessment activities shall be appointed by an “authority responsible for notified bodies” within the member states. (20) This authority will be responsible for the assessment, designation and notification as well for the monitoring of notified bodies and subcontractors. Article 34 and 35 outline the application and assessment process for the designation of conformity assessment bodies by the authority responsible for

notified bodies. Only designated notified bodies will be listed with an identification number on the list of notified bodies (Art. 39). (20) A joint-assessment of the re-designation application is planned to be performed by representatives of two member states and the EU Commission. Even though additional inspectors have been trained, capacity constraints and delays in the assessment timelines are very likely.

The requirements to be met by notified bodies are laid down in details in Annex VII of the regulation and are divided into four sections further divided into subsections starting with “general” remarks. Table 2-6 lists the major points of these requirements. For further details, refer to Annex VII of Regulation (EU) 2017/746. (20)

TABLE 2-6: OVERVIEW ON REQUIREMENTS TO BE MET BY NOTIFIED BODIES AS PER ANNEX VII OF THE IVDR. (20)

1. Organisational and General Requirements
• Legal status and organisational structure • Independence and impartiality • Confidentiality • Confidentiality • Financial requirements • Participation in coordination activities
2. Quality Management Requirements
• Establishment, documentation, implementation, maintenance and operation of an QMS appropriate to the nature, area and scale of its conformity assessment activities • Capable of demonstrating consistent fulfilment of the regulation’s requirements
3. Resource Requirements
• Capability of carrying out all the tasks as per IVD Regulation with the highest degree of professional integrity and the requisite competence in the specific field • Qualification criteria in relation to personnel • Documentation of qualification, training and authorisation of personnel • Subcontractors and external experts • Monitoring of competences, training and exchange of experience
4. Process Requirements
• Documented processes and sufficiently detailed procedures are in place for the conduct of each conformity assessment activity the notified body is designated for • Notified body quotations and pre-application activities • Application review and contract • Allocation of resources • Conformity assessment activities, Quality management system auditing, Product verification, Performance evaluation assessment and Specific Procedures

- Documented procedure fulfilling the requirement of the Regulation in the case of companion diagnostics for consultation of the EMA or a medicinal products competent authority during its assessment of such
- Reporting
- Final review
- Decisions and certifications
- Changes and modifications
- Surveillance activities and post-certification monitoring
- Re-certification

Due to increasingly complex procedures and tightened legal requirements the number of notified bodies has already decreased and it is unclear whether all currently designated notified bodies will apply for their re-designation and which ones will be re-designated for the same scopes as before. As a consequence manufacturers of *in-vitro* medical devices may not be further supported by their previous responsible notified body and may need to find new partners in the future. (64, 70)

2.2 THE REGULATORY FRAMEWORK FOR COMPANION DIAGNOSTICS IN THE UNITED STATES OF AMERICA

“[...] We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices.”

CDRH’s mission as stated in “2016-2017 Strategic Priorities” (73)

The Food and Drug Administration (FDA) is the responsible body in the USA for ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices. (74) Different Centers within the FDA provide product specific expertise and assess the different product types for which the FDA is responsible. The Centers involved in the assessment and review of applications for therapeutics and companion diagnostics are outlined in Table 2-7.

The Center for Devices and Radiological Health (CDRH) is the FDA department in charge of the regulation of medical devices and radiation-emitting electronic products (medical and non-medical). (75) The CDRH is responsible for the oversight of a wide range of devices “from simple tongue depressors and bed pans to [...] *in-vitro* diagnostic products, [...], which may include monoclonal antibody technology.” (76)

TABLE 2-7: RESPONSIBILITIES OF FDA CENTERS WITH REGARD TO APPLICATION REVIEWS.

FDA CENTER	RESPONSIBLE FOR
<u>Center for Drug Evaluation and Research</u>	
CDER	assesses and reviews the NDA of a therapeutic which is not a biotechnological product.
<u>Center for Biologics Evaluation and Research</u>	
CBER	assesses and reviews a therapeutic handled as a biological license application (BLA) and regulates a small number of diagnostic devices such as tests used for blood donor screening, blood collection and processing, cellular therapies and HIV diagnostics. (77)
<u>Center for Devices and Radiological Health</u>	
CDRH	assesses and reviews of all other companion diagnostic devices not in scope of the CBER.

The FDA has issued guidance documents on regulatory procedures addressed to the industry on the classification of medical devices (section 2.2.1) and on how to apply for premarket clearance (section 2.2.2.1) or premarket approval (section 2.2.2.2). The procedures applicable to *in-vitro* companion diagnostic devices as well as available guidance are introduced and discussed in the following sections.

2.2.1 CLASSIFICATION OF MEDICAL DEVICES

On May 28, 1976 the Federal Food, Drug, and Cosmetic (FD&C) Act was amended by the Medical Device Amendments (MDA) introducing a classification system for medical devices. Three regulatory control categories were established, namely Class I, II and III.

The device classification regulation defines the regulatory requirements for a general device type. The regulatory control increases from Class I to Class III. Class I and II devices not being exempt are to be filed under a Premarket Notification 510(k) while Class III devices require a Premarket Approval (PMA). The procedures are outlined in section 2.2.2.

Table 2-8 summarises the definitions of the three classes as laid down in section 513(a)(1) of the FD&C Act -21 U.S.C. § 360c(a)(1) (78) and provides an overview of associated risks and measures.

TABLE 2-8: CLASSES OF MEDICAL DEVICES AS PER FD&C ACT AND ASSOCIATED RISK AND MEASURES.

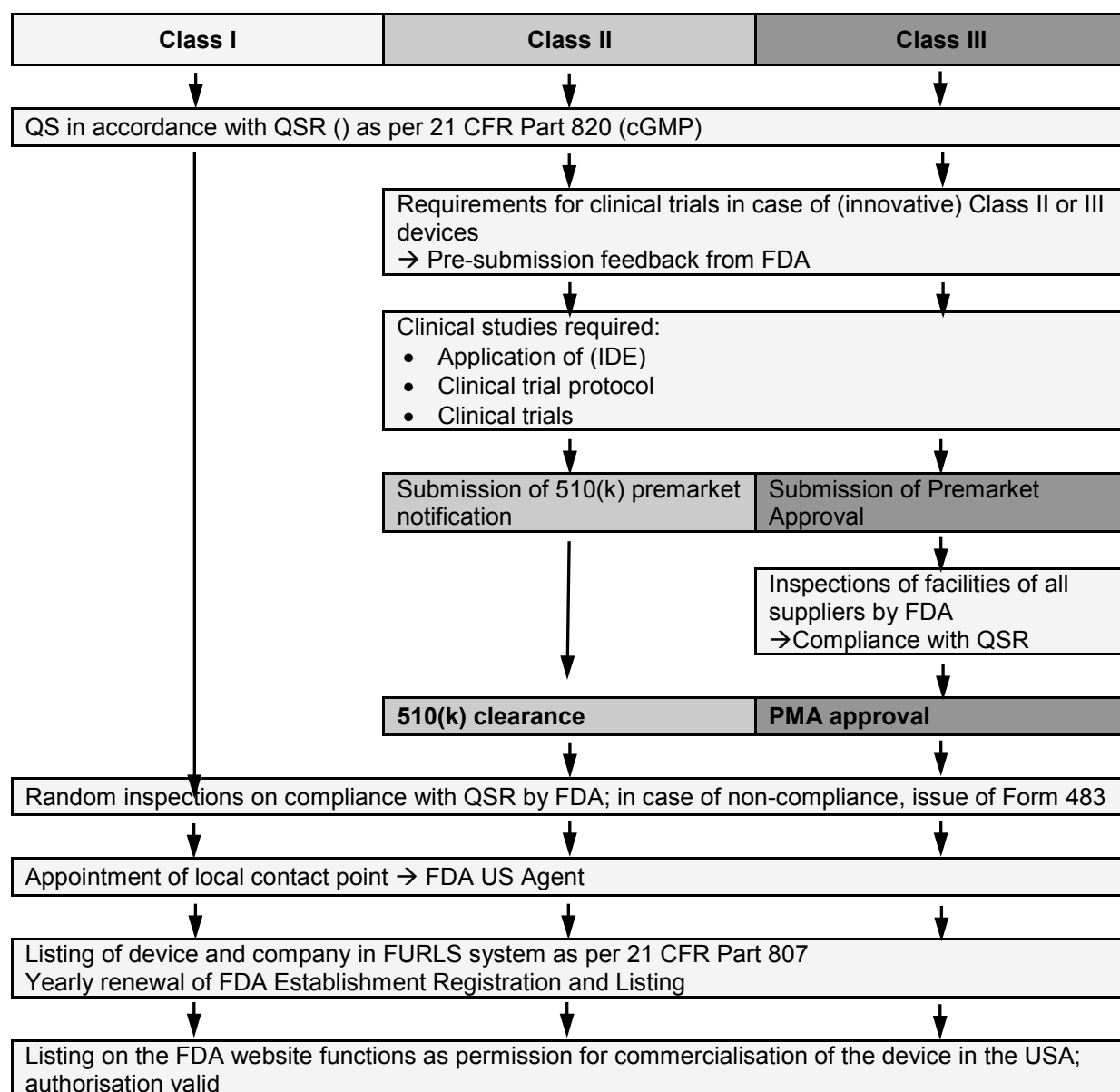
CLASS	DEFINITION AS PER 21 U.S.C. § 360c(A)(1)	ASSOCIATED RISK AND MEASURES
I	Devices are subject to a comprehensive set of regulatory authorities called general controls that are applicable to all classes of devices. ^a	low to moderate risk → general controls
II	Devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. ^b → Premarket Notification 510(k)	moderate to high risk → general controls and special controls
III	Devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device. Class III devices typically require premarket approval. ^c → Premarket approval	High risk

^a General controls are controls authorized by or under section 351, 352, 360, 360f, 360h, 360i, or 360j of Section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A)) or any combination of such sections are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

^b Special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 360(k) of Section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A))

^c In addition FD&C Act section 513 and section 515, 21CFR Part 814, Device Advice on PMA to be considered

The classification of a medical device is based on the intended indication and use of the device. Companion diagnostics and the corresponding therapeutics are generally applied in serious therapeutic indications such as oncology or HIV. Therefore, these devices are commonly classified as Class III devices. The regulatory requirements associated with the different medical device classes are outlined in Figure 2-5.



QSR – Quality System Regulation
cGMP – current Good Manufacturing Practice

IDE – Investigational Device Exemption
FURLS – FDA Unified Registration and Listing System

FIGURE 2-5: HIGH LEVEL OVERVIEW ON REGULATORY REQUIREMENTS FOR MEDICAL DEVICE CLASSES I, II AND III. Flowchart adapted from (79)

As outlined, companion diagnostics are generally classified as Class III medical devices due to their intended use and indication and the associated risk level. However, there are a few examples of companion diagnostics classified as Class II devices, and therefore the two applicable regulatory procedures – Premarket Notification 510(K) and Premarket approval - are described in following sections 2.2.2.1 and 2.2.2.2, respectively.

2.2.2 REGULATORY PROCEDURES APPLICABLE TO COMPANION DIAGNOSTICS

In this context the terminology and difference of *cleared* and *approved* is shortly outlined as described on the FDA homepage. (80)

CLEARED MEDICAL DEVICES	
	are medical devices determined as substantially equivalent to an already marketed device by the FDA. A premarket notification 510(k), is to be submitted to obtain clearance.
APPROVED MEDICAL DEVICES	
	are high-risk medical devices approved by a premarket approval (PMA) application by the FDA. A rigorous premarket review is performed than for a 510(k) procedure.
510(k) EXEMPT MEDICAL DEVICES	
	are low-risk medical devices determined to not require a 510(k) to provide a reasonable assurance of safety and effectiveness.

2.2.2.1 PREMARKET NOTIFICATION 510(k)

For distribution and marketing of Class II medical devices in the USA a premarket notification 510(k) submission is required in case the type of device is not exempt. As per 21 CFR part 807 subpart E, §807.81 (81) an 510(k) application is required for a new device which “[...] is not of the same type as, or is not substantially equivalent to

- (i) a device in commercial distribution before May 28, 1976, or
- (ii) a device (...) reclassified into class I or II. (81)

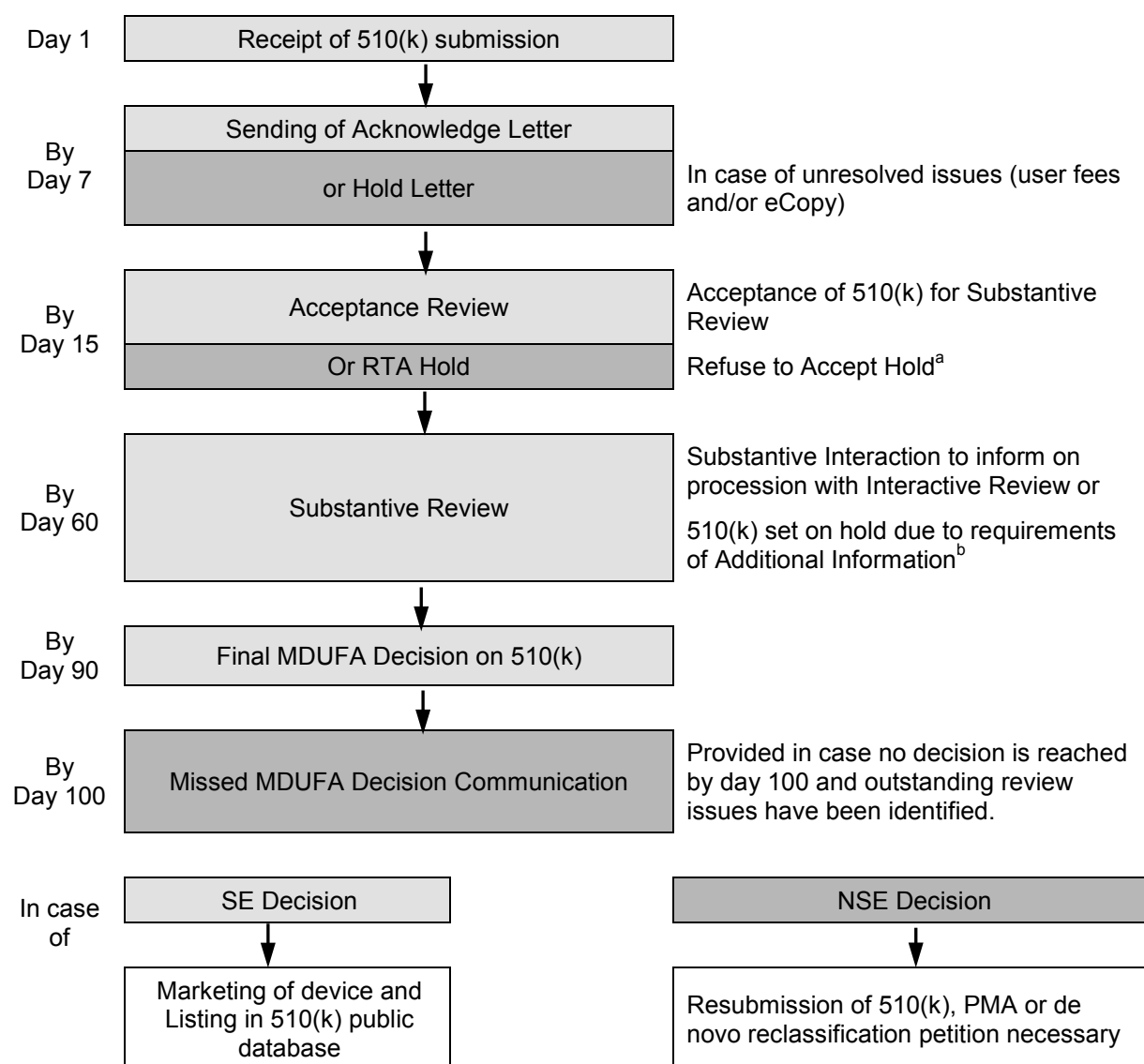
Such devices can be placed on the US market with a FDA letter of substantial equivalence after review of the 510(k) application and final determination by the CDRH at the FDA. A 510(k) premarket notification is considered a marketing clearance application. Hence, a 510(k) medical device is cleared and not approved. The submission of a 510(k) does therefore not result in a premarket approval as mentioned above. A clearance of a medical device is required in case of

- a new device not yet marketed,
- change in indication for a previously cleared device or
- modifications to a cleared device

Demonstration of substantial equivalence compared to a predicated device is part of the notification process. Substantial equivalence is demonstrated when the 510(k) device and the predicate device share an intended use and have the same technology characteristics, or

if the differences in the technology characteristics do not result in a different safety and/or effectiveness profile as per 21 CFR 807.92(a)(3). (81)

A simplified timeline applicable to traditional or abbreviated 510(k) submissions as proposed by the performance goals included in the Medical Device User Fee Amendments to the FDA Safety and Innovation Act (MDUFA III) is presented in Figure 2-6. (82)



^a clock at FDA starts with date of receipt when 510(k) is accepted for review

^b clock stop up to 180 days for complete response submission

SE substantial equivalent

NSE non-substantial equivalent

PMA Premarket approval

FIGURE 2-6: SIMPLIFIED TIMELINE OF THE 510(k) CLEARANCE PROCESS (TRADITIONAL/ABBREVIATED).
Figure prepared and adapted from (82)

A 510(k) submission is filed as a “traditional” 510(k) in case all 21 CFR 807.87 requirements to prove substantial equivalence to an already cleared device are met under any circumstance. A 510(k) may be filed as “abbreviated” under certain circumstances and special controls and recognised standards apply. Submission of a complete set of test data may not be needed for an abbreviated 510(k). The third 510(k) type refers to “special” 510(k) in which device modifications to a legally marketed device are filed. These modifications/changes must not affect the intended use or the fundamental technology and do therefore not require an evaluation of data by a FDA Center. The timeline of review by the FDA for traditional and abbreviated 510(k) submissions is 90 days. A 30 days review timeline is followed in case of special 510(k) submissions. (83)

Companion diagnostics are by default classified as Class III medical devices and require a pre-market approval. However, the company Resonance Health Analysis Services Pty Ltd had requested a de novo classification for its diagnostic FerriScan R2-MRI Analysis System which measures the liver iron concentration and is used for the identification and monitoring of non-transfusion-dependant thalassemia patients treated with the therapeutic Deferasirox. The de novo classification was granted and the device was cleared as Class II device by a 510(k) as “Liver Iron Concentration Imaging Companion Diagnostic” for Deferasirox as per regulation 21 CFR 892.1001. (84)

2.2.2.2 (MODULAR) PREMARKET APPROVAL

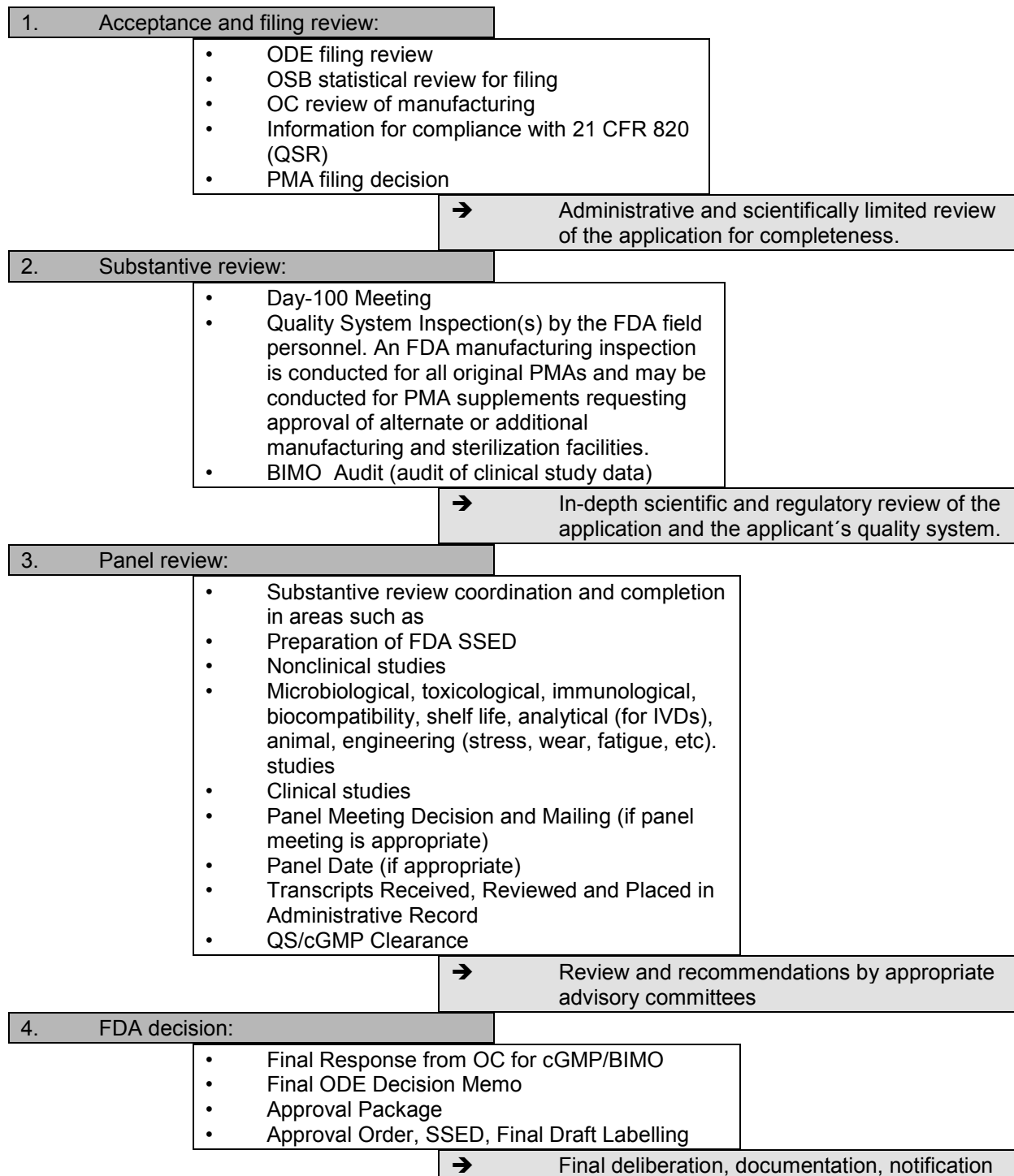
As per section 515 of the FD&C Act (85) a premarketing approval is mandatory for the marketing of Class III devices. The scientific and regulatory assessment during the PMA procedure is performed to assure the safety and effectiveness of their intended use. For IVDs, and especially for companion diagnostics, safety of the device is directly linked to their performance and the impact of false negative/positive results to patient health. All IVD companion diagnostics on the List of Cleared or Approved Companion Diagnostic Devices (*In-vitro* and Imaging Tools) (86), except for the example presented above cleared by a 510(k) and two devices cleared by a so called Humanitarian Device Exemption (HDE) (see below), have been granted a Premarket Approval (PMA).

The review of PMA submissions follows a timeline of 180 days. Like the review of a New Drug Applications after approval (NDA) or Biological License Application (BLA) submission for a therapeutic product, the PMA review may be set on hold for instance in the case of missing data. The assessment by the responsible Center of the FDA includes the review of premarket data, of the manufacturing process, inspections of the manufacturing site and clinical study centers as well as a bioresearch monitoring audit of the latter. The PMA

process is finalised by granting an official approval order in case the product has been found to be safe and effective. In case it is not considered safe and effective the approval is denied. Once a Premarket Approval is granted for a medical device regulatory actions during its life cycle are mandatory to maintain the license as it is mandatory for a NDA or BLA. PMA supplements are to be submitted for review and approval for changes affecting the safety or effectiveness of a device. (87)

The PMA process, as it is applicable for a companion diagnostic, consists of four major steps which are divided in sub-steps. (87) These are outlined in Figure 2-7.

Review of a PMA filing for a companion diagnostic in parallel to a NDA or BLA for the associated therapeutic is performed within “an intercenter collaborative process that is structured to provide appropriate review expertise to each product”. (88) As outlined in Table 2-7 the NDA or BLA of the therapeutic is evaluated by the CDER or CBER. Review of the PMA application of the companion diagnostic is performed by the CDRH or by the CBER in case of tests used for blood donor screening, blood collection and processing. Cellular therapies and HIV diagnostics are also regulated by CBER. (77) Review by the responsible Center is followed by “a collective review between centers”. The same principles apply to the review of post-approval modifications impacting the labelling of the diagnostic and the therapeutic. (88)



ODE → Office of Device Evaluation

OSB → Office of Surveillance and Biometrics

OC → Office of Compliance

QSR → Quality System Regulation

BIMO → Bioresearch Monitoring

SSED → Summary of Safety and Effectiveness Data

FIGURE 2-7: OVERVIEW ON THE FOUR PARTS OF FDA'S PREMARKET APPROVAL PROCESS. Figure prepared from and based on (87).

Delays in the co-approval of a therapeutic product and companion diagnostic are in most cases the result of data not being available at the time of PMA filing. Even though a CDx is often granted expedited review, the PMA may set the approval timeline of the therapeutic at risk. As per 21 CFR 814.20 (85) submission of all components of a PMA at once is required. However, an alternative regulatory approach has been implemented – the modular PMA of which an overview is provided in Figure 2-8.

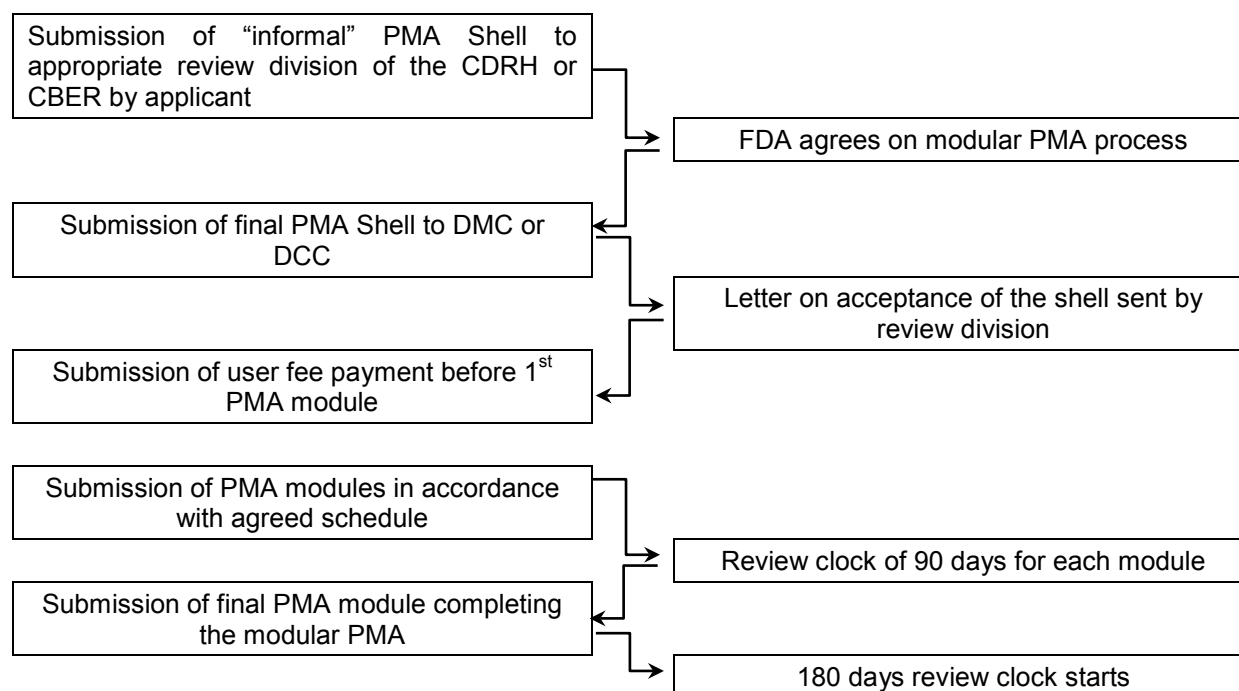


FIGURE 2-8: OVERVIEW ON THE PRINCIPLE OF A MODULAR PREMARKET APPROVAL SUBMISSION. Figure prepared and adapted from (89)

Filing of an application under the modular PMA allows the submission of modules such as analytical data, manufacturing information and/or other requirements at different time points. The requirements on data and content of the submission are the same for a traditional and modular PMA. (89) However, this approach offers a higher flexibility in timing and allows for better coordination of NDA/BLA submission for the therapeutic with the PMA submission for the companion diagnostic and may therefore enable a shorter approval process. (90)

In 1990 an alternative pathway for the development and approval of medical devices intended for the use in rare diseases or conditions was established. As per 21 CFR 814.3(n): "A Humanitarian Use Device (HUD) is a medical device intended to benefit patients in treatment or diagnosis of a disease or condition that affects or is manifested in fewer than

4,000^a individuals per year in the United States". (85) For a this type of device, demonstration of its safety and probable benefit is mandatory whereas evidence on its effectiveness is not required since it may not be possible to obtain relevant clinical data due to a small number of patients.

This regulatory pathway is a two-step process as per 21 CFR 814.100(c):

1. Submission of a HUD designation request by the applicant to the Office of Orphan Products Development (OOPD); the request is evaluated and reviewed by the OOPD within 45 days. A decision letter informing about approval, disapproval or request of additional information is sent to the applicant.
2. After granted HUD designation: a HDE application is submitted to the CDRH or the CBER. (85)

Two examples of companion diagnostics with a HUD and approved under a HDE can be found in the *List of Cleared or Approved Companion Diagnostic Devices (In-vitro and Imaging Tools)* (86), namely the diagnostics "PDGFRB FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)" and "KIT D816V Mutation Detection by PCR for Gleevec Eligibility in Aggressive Systemic Mastocytosis (ASM)". These diagnostics are indicated for the selection of ASM patients for whom Gleevec® (imatinib mesylate) treatment is being considered. The label of both tests refer to Humanitarian Use Devices - HUD approved by the U.S. Food and Drug Administration under the HDE or Humanitarian Device Exemption procedure, which means the effectiveness of this device for this has not been demonstrated. (91, 92)

2.3 (US) CO-APPROVED COMPANION DIAGNOSTICS AND RESPECTIVE THERAPEUTIC PRODUCTS AND DIFFERENCES TO THE EU

In the USA, the first steps towards regulation and guidance on co-development of therapeutics and diagnostics were initiated early, such as the organisation of several public meetings between 2002 and 2005 which resulted in a draft concept paper published by the FDA. (93) This paper described a first regulatory approach for companion diagnostics and "has become a landmark for the formalization of the drug-diagnostic co-development strategy." (48) The concept paper was later transferred into draft guidance on *in-vitro* companion diagnostics published in its final version in 2014. (17) This document has not been a "how to" guidance and "[...] pharma and diagnostic companies have seldom found

^a On December 13, 2016, the 21st Century Cures Act (Pub.L. No. 114-255) changed the population estimate required to qualify for HUD designation from "fewer than 4,000" to "not more than 8,000."

the co-development model [...] feasible, [...]”. (48) Nonetheless, one might say that since 2005 the FDA has “set the standard for the CDx regulatory pathway.” (48).

In July 2016, FDA released its three Center (CBER, CDER and CDHR) draft guidance “*Principles for Co-development of an In-vitro Companion Diagnostic Device with a Therapeutic Product*” which “[...] is intended to be a practical guide to assist therapeutic product and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic.” (94) This “how to” guidance provides “[...] general principles to guide codevelopment to support obtaining contemporaneous marketing authorization for a therapeutic product and its corresponding IVD companion diagnostic [...]” and relates to “[...] regulatory requirements [...], considerations [...] for a therapeutic product clinical trial that includes the investigation of an IVD companion diagnostic, and administrative issues [...]” for the filing of the BLA/NDA for the therapeutic and the PMA for the CDx. (94, 95)

Companion diagnostics have a “gatekeeper role” in gaining regulatory approval for a therapeutic (15) as they are “[...] a prerequisite for therapeutic approval if the therapy is targeted for a specific population [...]”. (96) To broaden the concept of companion diagnostics and their application, the term and concept of complementary diagnostics has been introduced recently.

COMPLEMENTARY DIAGNOSTIC

<i>“A test that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre requisites for receiving the drug.”(97)</i>

Complementary diagnostics are described as “[...] an alternative tool to develop successful therapies [...]”.(96) Unlike companion diagnostics, complementary diagnostics are not approved for the use of a corresponding therapeutic, but for a group of therapeutics.

The first complementary diagnostic was approved by the FDA in 2015 and underlines FDA’s intention to provide more patients access to (cancer) immune therapies by not being used “[...] with a specific drug but rather with a class of drugs, [...]” in contrast to companion diagnostics which “[...] are typically linked to a specific drug within its approved label.” (98) Complementary diagnostics will likely impact economic, regulatory and strategic considerations in the term of personalised medicine. (98)

The FDA has been increasing its “practical experience in the review and approval of molecular companion diagnostics” (90) and has granted approval for approximately 30 companion diagnostics as of December 2016 (96).

In the USA, the use of an IVD companion diagnostic device in combination with a particular therapeutic product is stated in the instructions for use in the labelling of both the diagnostic device and the corresponding therapeutic product. The same holds true for any generic or biosimilar equivalents of the therapeutic product. In the EU, however, the requirement of a test prior to the use of a medicinal product is indicated in the product information, but in contrast to the US labelling requirements, does not name a specific companion diagnostic device.

As outlined above the FDA has started to promote complementary diagnostics which are not specifically approved for one therapeutic, but rather for a class of therapeutics. The intention of this new approach is to enable a broader application of *in-vitro* devices and provide more patients access to (cancer) immune therapies. So far two IVDs have recently been approved as complementary diagnostic devices, namely PD-L1 IHC 28-8 pharmDx (P150025) and VENTANA PD-L1(SP142) CDX ASSAY (P160002).(96). The first measures PD-L1 protein in non-squamous non-small cell lung cancer (NSCLC) tissue samples and a positive result for the protein may indicate a prolonged life of the patient when treated with OPDIVO® (nivolumab). The latter identifies PD-L1 expression levels in NSCLC and urothelial carcinoma tissues of patients considered for treatment with TECENTRIQ® (atezolizumab).

Table 2-9 provides a selection of companion diagnostics and corresponding therapeutics the approvals of (supplements to) the NDA or BLA and PMA were granted by the responsible Centers of the FDA on the same day. Information on the first companion diagnostic, the HER2 test to identify HER2 protein overexpression in tumour tissue of patients suffering from breast cancer, which was approved together with the therapeutic Herceptin (trastuzumab) in 1998, is presented for completeness. As a consequence of advanced technologies and commercial opportunities additional HER2 assays have been developed. As of today, almost half of all approved companion diagnostics are assays for the identification and/or measurement of HER2. These tests were not co-developed with trastuzumab in the classical way since their PMA was granted after the initial BLA approval of the therapeutic.

Table 2-9 is based on the “List of Cleared or Approved Companion Diagnostic Devices (*In-vitro* and Imaging Tools)” publically accessible on the FDA homepage (86) and was adapted from (96, 99).

THE CURRENT REGULATORY FRAMEWORK FOR COMPANION DIAGNOSTICS IN THE EU AND THE US

TABLE 2-9: LIST OF THERAPEUTICS AND RESPECTIVE COMPANION DIAGNOSTICS (CO-)APPROVED RECENTLY (2010-2017) BY THE FDA. Table created and adapted from (86, 96, 99)

COMPANION DIAGNOSTIC SUBMISSION No.	COMPANY	THERAPEUTIC BLA/NDA	INDICATION	REMARK ON CO-APPROVAL	APPROVAL DATE
Dako HercepTest P980018	Dako Denmark A/S	Herceptin (trastuzumab) BLA 103792	Determination of HER2 overexpression in breast cancer tissues	Co-approval granted for PMA and BLA Dako HercepTest and Herceptin are the first co-approved drug-device combination in the history of FDA.	Sept 1998
Dako HercepTest P980018 - S010		Herceptin (trastuzumab) BLA 103792 – S 5250	Determination of HER2 overexpression in metastatic gastric or gastroesophageal junction adenocarcinoma tissues	Co-approval granted for supplements to PMA/BLA	Oct 2010
HER2 FISH pharmDx Kits P040005 - S005					
COBAS 4800 BRAF V600 Mutation Test P110020	Roche Molecular Systems, Inc.	Zelboraf (vemurafenib) NDA 202429	Detection of BRAF V600E mutation in unresectable or metastatic melanoma	Co-approval granted for PMA and NDA	Aug 2011
Vysis ALK Break Apart FISH Probe Kit P110012	Abbott Molecular Inc.	Xalkori (crizotinib) NDA 202570	Determination of ALK in locally advanced or metastatic NSCLC tissue	Co-approval granted for PMA and NDA	Aug 2011
Therascreen® EGFR RGQ PCR Kit P110030 (withdrawn) P110027 (new)	Qiagen Manchester, Ltd.	Erbix (cetuximab) BLA 125084 – S 225	Detection of K-Ras mutation-negative EGFR expression in metastatic colorectal cancer	Co-approval granted for PMA and supplement to BLA	July 2012
Dako HercepTest P980018 - S015	Dako Denmark A/S	Perjeta (pertuzumab) BLA 125409 – S32	Determination of HER2 overexpression in (metastatic) breast cancer tissues	Co-approval granted for supplements to BLA and PMA; device had already been approved for the target population in conjunction with herceptin	Aug 2012
Her2 FISH PharmDx Kits P040005 - S006					
Dako HercepTest P980018 - S016	Dako Denmark A/S	Kadcyla (ado-trastuzumab emtansine) BLA 125427	Determination of HER2 overexpression in (metastatic) breast cancer tissues	Co-approval granted for BLA and supplements to PMA; device had already been approved for the target population in conjunction with herceptin	Feb 2013
Her2 FISH PharmDx Kits P040005 - S009					

COMPANION DIAGNOSTIC SUBMISSION No.	COMPANY	THERAPEUTIC BLA/NDA	INDICATION	REMARK ON Co-APPROVAL	APPROVAL DATE
THxID™ BRAF Kit P120014	bioMérieux Inc.	Tafinlar (dabrafenib) NDA 202806 Mekinist (trametinib) NDA 204114	Detection of BRAF V600E mutation in unresectable or metastatic melanoma	Co-approval granted for PMA and NDA	May 2013
cobas EGFR Mutation Test P120019	Roche Molecular Systems, Inc.	Tarceva® (erlotinib) NDA 021743 – S18	Qualitative detection of exon 19 and 21 deletions substitutional mutations of epidermal growth factor receptor NSCLC tumour tissues.	Co-approval granted for PMA and supplement to NDA	May 2013
Therascreen EGFR RGQ PCR Kit P120022	Qiagen Manchester, Ltd.	Gilotrif (afatinib) NDA 201292	Detection of EGFR mutation in locally advanced or metastatic NSCLC tissues	Co-approval granted for PMA and NDA	July 2013
Therascreen KRAS RGQ PCR Kit P110027 (new)	Qiagen Manchester, Ltd.	Vectibix (panitumumab) BLA 125147 – S186	Identification of K-Ras mutation-negative EGFR expression in metastatic colorectal cancer tissues	Co-approval granted for PMA and supplement to BLA	May 2014
BRAC Analysis CDx P140020	Myriad Genetic Laboratories, Inc.	Lynparza™ (olaparib) NDA 206162	Detection of deleterious or suspected deleterious germline BRCA mutated in advanced ovarian cancer tissues	Co-approval granted for PMA and NDA	Dec 2014
PD-L1 IHC 22C3 pharmDx P150013	Dako, North America, Inc.	KEYTRUDA® (pembrolizumab) BLA 125514 - S5	Detection of PD-L1 protein in NSCLC tissue	Co-approval granted for PMA and supplement to BLA	Oct 2015
cobas® EGFR Mutation Test v2 P120019 – S007	Roche Molecular Systems, Inc.	Tagrisso® (osimertinib) NDA 208065	Identification of EGFR mutation T790M in NSCLC tissues	Co-approval granted for NDA and supplement PMA	Nov 2015
VYSIS CLL FISH PROBE KIT P150041	ABBOTT MOLECULAR, INC	VENCLEXTA® (venetoclax) NDA 208573	Detection of deletion of the LSI TP53 probe target (17p-) for identification of B-cell chronic lymphocytic leukemia.	Co-approval granted for PMA and NDA	April 2016
cobas® EGFR Mutation Test v2 P150047	Roche Molecular Systems, Inc.	Tarceva® (erlotinib) NDA 021743 – S26	(Qualitative) detection of defined EGFR mutations NSCLC tissues	Co-approval granted for PMA and supplement to NDA	June 2016
cobas® EGFR Mutation Test v2 P150044	Roche Molecular Systems, Inc.	TAGRISSO™ (osimertinib) NDA 208065 –S26	(Qualitative) detection of defined EGFR mutations NSCLC tissues	Co-approval granted for PMA and supplement to NDA	Sept 2016
FoundationFocus CDxBRCA P160018	Foundation Medicine, Inc.	Rubraca (rucaparib) NDA 209115	(Qualitative) detection of BRCA1 and BRCA2 alterations in ovarian tumour tissues	Co-approval granted for PMA and NDA	Dec 2016

COMPANION DIAGNOSTIC	COMPANY	THERAPEUTIC	INDICATION	REMARK ON Co-APPROVAL	APPROVAL DATE
SUBMISSION No.		BLA/NDA			
LeukoStrat® CDx FLT3 Mutation Assay P160040	Invivoscribe Technologies, Inc.	Rydapt (midostaurin) NDA 207997	Detection of ITC mutations and tyrosine kinase domain mutations D835 and I836 in the FLT3 gene from blood or bone marrow of patients with acute myelogenous leukaemia	Co-approval granted for PMA and NDA	April 2017
Praxis Extended RAS Panel P160038	Illumina, Inc.	Vectibix (panitumumab) BLA 125147 – S207	Detection of 56 specific mutations in RAS genes and NRAS in DNA extracted colorectal cancer tissues	Co-approval granted for PMA and supplement to BLA	June 2017
Oncomine Dx Target Test P160045	Thermo Fisher Scientific (Life Technologies)	Tafinlar® (dabrafenib) NDA 202806 - S006 Mekinist® (trametinib) NDA 204114 - S005 Xalkori® (crizotinib) NDA 202570 - S021 Iressa® (gefitinib) NDA 206995	Detection of single nucleotide variants and deletions in 23 genes from DNA and fusions in ROS1 from RNA in NSCLC tumour tissues	Co-approval granted for PMA and supplement to NDA Approval granted for PMA at a later time point than for NDA	June 2017

Submission numbers: P → PMA
S → (BLA/NDA/PMA) Supplement(s)

NDA → New Drug Application
BLA → Biological License Application

3. DISCUSSION AND CONCLUSION

3.1 COMMONALITIES AND DIFFERENCES IN THE REGULATORY FRAMEWORK FOR COMPANION DIAGNOSTICS IN THE EU AND USA

3.1.1 DEFINITION OF COMPANION DIAGNOSTICS

As per FDA guidance, companion diagnostics are *in-vitro* diagnostic devices providing information essential for the safe and effective use of corresponding therapeutics. (17) So far the definition included in the recently adopted Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in-vitro* diagnostic medical devices follows the US one by defining CDx as devices which are essential for the safe and effective use of a corresponding medicinal product to a) Identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or b) Identify, before and/or during treatment, patients likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding medicinal product. (20)

A profound basis for a harmonised regulatory framework for companion diagnostics in the European Union and the United States would be a streamlined definition. (67) However, the FDA specifies four areas, where a companion diagnostic assay could be essential: (I) to identify patients who are most likely to benefit from the therapeutic product; (II) to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with the therapeutic product; (III) to monitor response to treatment with the therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness; and (IV) to identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population. (17) The FDA's definition may be described best as outcome predictive with regard to efficacy and safety. (19) With the fourth role of CDx, the FDA has drawn a connection to the enrichment or targeted study design, which is a common study design used in the clinical validation of companion diagnostics. (19)

A major difference in the US and EU definition is the monitoring of responses to the therapeutic - the third identifying characteristic of a CDx according to the US definition provided in FDA guidance. (17, 19) The Council's draft (65) included this aspect, but has not been included in the IVDR resulting in a broader definition of CDx leaving "[...] room for interpretation of the exact meaning of 'essential'" and its "gatekeeper role" (15, 66, 67).

During the transition phase manufacturers of *in-vitro* (companion) medical devices should carefully assess whether their marketed devices or devices planned to be placed on the European market are in scope of the definition of companion diagnostics as laid down in Article 2 of the Regulation. In case they are, analysis of the status quo should be performed to take all measures for the implementation of the new Essential Requirements as introduced in the legislation on *in-vitro* (companion) diagnostic devices.

3.1.2 CLASSIFICATION OF COMPANION DIAGNOSTICS

In the USA, companion diagnostics are generally classified as devices with a high-risk associated. As Class III devices, companion diagnostics require a premarket approval based on a scientific and regulatory assessment. There is only one exempt CDx which was cleared as Class II device on basis of a 510(k) notification after a de novo classification was granted.

A new classification system is laid down in the IVDR, fundamentally different to the “[...] classification system for devices set out in Directive 98/79/EC”. It defines four risk-based classes linked to corresponding risk-based conformity assessment procedures. (20) The “robust risk-based classification rules” classify companion diagnostics as “high individual risk or moderate public risk” devices which is in contrast to the classification of general/“other” IVDs as per IVDD. (20, 66) As Class C devices, companion diagnostics require conformity assessment by the manufacturer and a notified body. The assessment is based on clinical performance and evidence. The risk-based classification approach introduced by the European Commission and Parliament is comparable to the FDA approach, but does not result in comparable regulatory pathways.

The IVDR provides now a decision tree- like classification system facilitating the classification of IVDs. In future, discussions may arise in case an IVD is not clearly in scope of the definition of a companion diagnostic device. The classification as Class C devices correlates to the Class III classification in the USA. The harmonisation of device classes is reasonable and was overdue.

During the transition phase manufacturers should reclassify their *in-vitro* (companion) diagnostic medical devices currently marketed or planned to be marketed in the EU in accordance with the seven rules outlined in the IVDR to determine if the conformity assessment is applicable during and after the transition phase. Currently approx. 85 % of marketed IVDs are self-certified. Re-certification of these products under the supervision of a notified body before Directive 98/79/EC becomes void in 2022 is a big challenge for both, the notified bodies and manufacturers alike. Compliance with the new Essential Requirements

does and will require additional capacities and able personnel. Especially the lack of experienced personnel may be a critical factor for both parties in the near future.

3.1.3 REGULATORY PATHWAYS FOR COMPANION DIAGNOSTICS AND RESPONSIBLE INSTITUTIONS

Whereas the responsibility of the review and assessment of therapeutics and companion diagnostics is with different Centers (refer to Table 2-7 in section 2.2) but within one authority in the USA, in the European Union different authorities are involved in the conformity assessment of the diagnostic and benefit-risk assessment of the therapeutic. The IVDR “maintains the separation between medicine’s marketing authorisation [...] by the EMA and certification of CDx by any of numerous notified bodies.” (66) At least, medicines regulators and notified bodies will have to cooperate during the certification of a companion diagnostic as outlined in the IVDR. However, medicine regulators will not be responsible for the approval of “[...] one or more specific CDx for use in conjunction with a given drug.”(72) Designated notified bodies are to be involved in the conformity declaration and certification process dependant on the classification of the *in-vitro* diagnostic as per new Regulation. The conformity assessment applicable for companion diagnostics as outlined in section 2.1.2.2 includes a consultation step with a national competent authority or the Agency. The notified body requests the scientific opinion of the competent authority responsible for the assessment of the medicinal product the CDx is intended for. No guidance or detailed schemes of the complete process is available. Only a superficial timeframe but no detailed timeline or flowchart of this consultation procedure has been established. So far only a proposal presented at the EMA platform meeting (refer to Figure 2-4) is available and highlights further the current lack of guidance.

Regarding the role and responsibilities assigned to notified bodies the re-designation by the European Commission is on-going. Notified bodies have to apply for their re-designation six months after the regulation came into force. Since the requirements for NBs assessing companion diagnostics are not defined well, the number of notified bodies may decrease significantly. Simultaneously, the number of IVD manufacturers requiring interaction with a NB will certainly increase. Consequently, many IVD manufacturers may face the loss of their current partner, while many others may need one for the first time. In both cases a reliable partnership with a body of the (not yet available) list of designated notified bodies is to be started early enough to fulfil the new Essential Requirements once the transition phase has terminated. (64, 70)

As outlined in section 2.2.2.2, in the USA a premarket approval application needs to be filed for a companion diagnostic with the FDA. In many cases simultaneous approvals for a therapeutic and its corresponding companion diagnostic have been granted, highlighting the integrative approach of the US regulatory framework for companion diagnostics. Comparable to the regulatory pathway for the filing of orphan drugs, a special pathway has been established for devices used in the context of rare diseases. A similar approach might further enhance the development of (personalised) treatments of rare diseases in the EU. A conformity assessment procedure for companion diagnostics of a corresponding orphan drug may be feasible to overcome issues in the demonstration of clinical evidence and performance. The introduction of “special procedures” for companion diagnostics will certainly not be discussed before the new legislation has been implemented successfully.

As per Article 15 of Regulation (EU) 2017/746 “manufacturers shall have available within their organisation at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of *in-vitro* diagnostic medical devices.” Recital 33 outlines this person’s responsibility to ensure the “[...] supervision and control of the manufacture of devices, as well as post-market surveillance and vigilance activities [...]” (20) The expertise and qualifications are described include “professional experience in regulatory affairs or in quality management systems [...]”. With the notified bodies being obliged to perform the conformity assessments by personnel with specific expertise, the implementation of the Essential Requirements as laid down in the Regulation will definitely offer new and interesting perspectives for professionals in regulatory affairs and related fields.

The first companion diagnostic devices to be certified by the first re-designated notified bodies will mark test cases and may be the basis for currently missing guidance. Manufacturers and notified bodies may already have a profound idea of the theory since associations of the *in-vitro* diagnostic industry try to prepare their members for the acid test in seminars and workshops. It will be interesting to see if theory and practice match once the first products are being certified.

3.1.4 LABELLING REQUIREMENTS OF COMPANION DIAGNOSTICS

Current practice of the EMA is to describe “[...] findings rather than naming specific products in the [...]” Summary of Product Characteristics (SmPC), whereas “the US approach is focused on the product rather than the finding.” (66) Contrary to the USA, the product information for the medicinal product does not mention a specific test and the label of the diagnostic does not refer to the specific medicinal product. This means that a certification as Class C device is mandatory for each diagnostic able to detect a finding specified in a label

of a medicinal product. Consequently, more than one CDx can be related to a medicinal product. (66) Dependent on the wording on a required test in the SmPC, the certification of additional companion diagnostics for a medicinal product may not result in a label change to the marketing authorisation of the medicinal product. It may be feasible to introduce a kind of simplified procedure for diagnostics intended to use for medicinal products for which a companion diagnostic has been certified before and the finding to be detected by it is already included in the SmPC since a consultation has already occurred.

On July 28th, 2017, the draft concept paper on predictive biomarker-based assay development in the context of drug development was published for public consultation with the intention to lead into a guideline. (72) This concept indicates that further details on the labelling may be available in the near future. The description of the finding a companion diagnostic should detect is critical, especially with regard to mandatory and optional testing. Reimbursement issues are not in scope of this thesis, but are an interesting topic to be discussed.

The term complementary diagnostic has been introduced to allow the broader use of an assay not being assigned to one specific therapeutic but rather to a therapeutic class. (96, 98) The mandatory application of a (companion) diagnostic device and the optional application of a (complementary) diagnostic device will for sure trigger further discussions. A clear definition of complementary diagnostics will be needed with regard to regulatory aspects and may alter the regulatory framework for companion and complementary diagnostics in both regions in the future.

3.2 REGULATORY CONSIDERATIONS SUMMARISED

(Regulatory) considerations for the registration of a companion diagnostic device are summarised and outlined as per EU Directive and Regulation on *in-vitro* medical devices and the US legislation on medical devices for companion diagnostics in Table 3-1. Steps in the (co-) development process are not considered and the summary is limited to aspects with regard to the definition and classification of companion diagnostics, the quality management system required, the regulatory review performed and labelling requirements. Reference to the sections of this thesis where the topic is described is made where applicable.

TABLE 3-1: REGULATORY CONSIDERATIONS FOR THE REGISTRATION OF A COMPANION DIAGNOSTIC IN THE EU AND USA.

EU		US	
DEFINITION (refer to sections 1.1.2 and 2.1.2.1)			
CDx are not defined in the IVDD.		The US definition for CDx includes in addition the monitoring of responses to the treatment with the corresponding therapeutic.	
The IVDR defines CDx as “essential for the safe and effective use” of a corresponding medicinal product for the identification of patients to benefit or being at increased risk.			
CLASSIFICATION (refer to sections 2.1.2.2 and 2.2.1)			
List-based classification in the IVDD resulting in most CDx being classified as “general/other” IVDs.		CDx are classified in the highest risk class - Class III if no predicate for equivalent or De novo process apply. ^a	
The IVDR classifies CDx as Class C devices due to their high individual risk or moderate public risk.			
QUALITY MANAGEMENT SYSTEM			
A QMS for self-certified “general” IVDs is formally not required as per IVDD.		A QMS in compliance with FDA Quality System Regulation - 21 CFR Part 820 (100) (cGMP) is required. GMP inspections are performed by the FDA.	
Article 10(8) of the IVDR outlines the QMS required which is assessed by a notified body as described in Annex IX, chapter 1.2. ^b			
REGULATORY REVIEW (refer to sections 2.1.2.2, 2.1.2.3 and 2.2.2)			
IVDD allows the affixing of the CE mark via self-certification by the manufacturer for general/”other IVDs most CDx are classified as.		Review of the application and Premarket approval of Class III CDx or clearance by a 510 (k) in the rare case of a Class II CDx - is performed by the corresponding FDA CentersCDRH or CBER . The FDA Centers exchange during co-registration of the therapeutic and CDx. (modular) PMA procedure with defined timeline of 180 days	
As per IVDR notified bodies are designated to be involved in the conformity assessment of CDx. A consultation procedure to seek the opinion of the competent authority responsible for the assessment of the medicinal product is part of it.			
Conformity Assessment Based on Type-Examination (Annex X) is outlined without defined timeline except for competent authority consultation procedure - section 3, paragraph (k) and should follow a 60 day timeline.			
LABELLING			
A CDx may be mentioned in the description of results within the product information.		The labelling of the therapeutic includes information on approved/cleared CDx. The therapeutic the CDx is intended to be used for is indicated in the device information.	
A guideline on how a CDx is to be included in the labelling, EPARs and RMPs of the corresponding medicinal product is currently under preparation. Findings rather than specific (mandatory/optional) tests may be included in the SmPC.			

^a Classification by research of “predicate devices” as listed in the FDA classification database, if no predicate a De Novo process may apply

^b The implementation of a QMS in accordance with the requirements of the IVDR is an important step towards well controlled *in-vitro* diagnostic devices. In the USA pharmaceuticals and medical devices are regulated by the main standards of Good Manufacturing Practice. The description of an essential QMS in the IVDR does not explicitly say GMP but uses its principles.

3.3 OVERALL CONCLUSION AND OUTLOOK

So far, no process for coordinated assessment of “[...] drug-diagnostic companion products [...]” has been established in Europe due to differences in legislation and regulatory guidelines for medicines and diagnostics “[...] which lead to inconsistent decision making at the EU level, hence hindering market access.” (57) Significant technological as well as scientific progress, have been the driving forces for the recent revision of the EU legislation on medical devices. The IVDR does not elaborate a parallel registration process comparable to the FDA approach nor shift the responsibility for companion diagnostics to the institution(s) responsible for therapeutics. Questions not yet answered are:

Which measures are to be taken by the authorities in case a therapeutic including a mandatory test prior its application in its product information is authorised by the EMA (or other national competent authorities) and the certification process has not been finalised for any potential companion diagnostic?

How will the assessment of a diagnostic be finalised in case the therapeutic the test has been developed for is not authorised?

At this time point, the EU concept seems rather complicated, decentralised and poorly defined when compared to the US pathway(s) where one authority is responsible for the assessment of the therapeutic and the device. The FDA started discussions on the role of companion diagnostics early. Therefore many companies feel more confident by relying on the FDA guidance on co-development. A European guideline specifically addressing the development of (companion diagnostic) assays in parallel to the development of a medicinal product and/or later in its lifecycle resulting in a contemporary approval of the medicinal product and certification of the diagnostic is urgently needed, even though the simultaneous development of CDx and medicines from beginning to end is not stressed in the current regulatory framework. The draft concept outlines that contemporaneous marketing authorisation of the medicinal product and certification of the companion diagnostic is not a requirement, but mentions co-development as a tool to facilitate it. (72) Hopefully, the concept for *predictive biomarker-based assay development in the context of drug development* does not undergo the same fate as the draft reflection paper *Co-development of pharmacogenomic biomarkers and assays in the context of drug development* (EMA/CHMP/641298/2008) from 2011 and is adopted as guideline in a feasible timeframe.

Only if the cooperation between notified bodies and the authorities / Agency is successfully implemented, the new European legislation on *in-vitro* diagnostic medical devices and especially for companion diagnostics will improve and “[...] assure the safe use of CDx [...]”

and “[...] support the development of more and better CDx [...] and the corresponding medicine.” (66)

Manufacturers of IVDs in general and of CDx in particular face challenges with regard to the implementation of the IVDR since all devices being conform as per IVDD need to comply with the requirements laid down in the IVDR from May 2022. For a smooth transition better guidance is desirable – especially, for the first CDx receiving its CE mark through the IVDR certification process becoming the exemplary case for all following.

Even though in the European Union a convergence to the US system can be observed, the frameworks remain region specific. The framework as laid down by the Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in-vitro* diagnostic medical devices is definitely shaping new regulatory perspectives.

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EIDESSTATTLICHE ERKLÄRUNG

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Ort, Datum

Sandra E. Hennig