A Comparative Overview of the Regulatory Landscapes Around Real-World Data/ Real-World Evidence in the USA and the EU, and the Wider Perspective

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List of abbreviations

AI	Artificial Intelligence
App	Application
ARIA	Active post-market Risk Identification and Analysis
ATMP	Advanced Therapies Medicinal Product
BDSG	Big Data Steering Group
BDTF	Big Data Task Force
BEST	Biologics Effectiveness and SafeTy Initiative
BloodSCAN	Blood Surveillance Continuous Active Network
CAR	Chimeric Antigen Receptor
CBER	Center of Biologics Evaluation and Research
CBOC	Sentinel Community Building and Outreach Center
CDE	Center for Drug Evaluation (China)
CDER	Center of Drug Evaluation and Research
CDM	Common Data Model
CERN	European Council for Nuclear Research
CeSHarP	Clinical electronic Structured Harmonized Protocol
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
Cures Act	21st Century Cures Act
DARWIN EU	Data Analysis and Real-World Interrogation Network EU
EC	European Commission
ECDC	European Centre for Disease prevention and Control
EEA	European Economic Area
EEHRxF	European Electronic Health Record Exchange Format
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDS	European Health Data Space
EHR	Electronic Health Record
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network

ENCePP	European Network for Centres of Pharmacoepidemiology and Pharmacovigilance
EPAR	European Public Assessment Report
EU PAS Register	European Union Post-Authorization Study Register
EU	European Union
EWG	Expert Working Group
FAIR	Findable, Accessible, Interoperable, Reusable
FARS	Focus Areas of Regulatory Science
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FDAAA	FDA Amendment Act
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GVP	Good pharmacoVigilance Practice
HC	Health Canada
HCP	HealthCare Professional
HMA	Heads of Medicines Agencies
HTA	Health Technology Assessment
IC	Sentinel Innovation Center
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IHI	Innovative Health Initiative
IMI	Innovative Medicines Initiative
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MAA	Marketing Authorization Application
MDED	Medical Device Evaluation Division (Japan)
MDIC	Medical Device Innovation Consortium
MFDS	Ministry of Food and Drug Safety (South Korea)

MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MINERVA	Metadata for data dIscoverability aNd study rEplicability in obseRVAtional studies
NCA	National Competent Authority
NEST	National Evaluation System for health Technology
NESTcc	NEST Coordinating Center
NMPA	National Medical Products Administration (China)
OECD	Organisation for Economic Cooperation and Development
OPTIMAL	OPerational, TechnIcal, and MethodologicAL framework
PAS	Post-Authorization Studies
PED	Pharmaceutical Evaluation Division (Japan)
PLD	Patient Level Data
PMDA	Pharmaceutical and Medical Devices Agency (Japan)
PRAC	Pharmacovigilance Risk Assessment Committee
PRISM	Post-licensure Rapid Immunization Safety Monitoring
PSEHB	Pharmaceutical Safety and Environmental Health Bureau (Japan)
RCT	Randomized Controlled Clinical Trial
RCT DUPLICATE	Randomized, Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology
RI	Regulatory Intelligence
RWD	Real-World Data
RWE	Real-World Evidence
SOC	Sentinel Operations Center
TEHDAS	Towards a European Health Data Space
TFDA	Taiwan Food and Drug Administration (Taiwan)
TGA	Therapeutic Goods Administration (Australia)
U.S.	United States
UK	United Kingdom
WHO	World Health Organization
WWW	World Wide Web

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1. Introduction and methods

1.1 Introduction

In 1989 the World Wide Web (WWW) was invented at the ‘European Council for Nuclear Research’ (CERN) in Geneva. (1, 2) It was the British scientist Tim Berners-Lee who developed the concept of an *“universal linked information system”* (3) to facilitate access to the information available on the CERN’s computer network and thus laid the foundation of the WWW as it is known today. (2, 4) In simplifying its use, and thus making information stored therein easily accessible to the wider public, Tim Berners-Lee’s invention became one of the main drivers of the success of the internet. (4) Since then the continuous development of new and advancement of existing digital technologies has fundamentally changed the way people across the globe communicate, consume and share information, interact and do business. A defining characteristic of today’s digital era is the creation, capture and replication of huge volumes of data. Until 2025, the amount of digital data created globally is projected to grow to more than 180 zettabytes, with one zettabyte being equivalent to 10^{21} bytes. (5, 6) Given these mind-boggling numbers, it is somewhat coherent for the term ‘big data’ to have gained currency and to now being ubiquitously used in the context of digitalization. (7) Many economic sectors have already taken advantage of digital technologies and successfully completed the digital transformation of their business models. (8) However, a report published by the ‘Organization for Economic Cooperation and Development’ (OECD) in 2019, and a more recently published OECD paper state that *“the health sector is a long way behind other industries”* (8, 9) when it comes to capitalizing on digital opportunities. (8, 9) The reasons for this are manifold – some of the challenges of deploying big data for public health purposes, for example, how to safeguard the protection of personal data, will be touched upon in chapter three of this master’s thesis.

But when speaking about big data, what exactly is meant by it at all? Big data is an umbrella term which covers a wide variety of data. (7) A formal, universally accepted definition for big data, however, is lacking. As per a definition of the ‘Joint Big Data Taskforce’ of the ‘Heads of Medicines Agencies’ (HMA) and the ‘European Medicines Agency’ (EMA) big data are

> *"extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analy[z]ed computationally to reveal patterns, trends, and associations"* (10).

Sources of big data, in a healthcare context, can be health monitoring devices, social media and online data, adverse drug reaction reports, consumption data, genomics, electronic health records (EHRs), insurance claims, registries, etc. (7, 11) The last three data sources listed are often grouped under the umbrella term 'Real-World Data' (RWD). (11–16) RWD are commonly regarded as belonging to big data, notwithstanding that RWD tend to be structured (i.e. adhering to a predefined data model) while the term big data is usually associated more closely with unstructured data. (11, 17, 18) To date, there is neither an internationally agreed guidance conclusively defining what kind of data should be classified as RWD, nor a harmonized definition of Real-World Evidence (RWE). (19) Instead, a wealth of varying definitions exists across regions and institutions (12, 20–22), leaving room for interpretation and accounting for inconsistent use of the terms RWD/ RWE. The term RWE, however, is generally understood as the evidence derived from the analysis of RWD. (20, 21, 23) As previously mentioned, the data sources most commonly named in conjunction with RWD are EHRs, insurance claims and registries. (11–16)

The use of evidence obtained through the analysis of RWD to answer research questions and inform decision-making is not new. The collection and analysis of RWD is well-established practice in disease epidemiology, RWE is used for observing comparative effectiveness of marketed products and regulatory authorities such as the United States (U.S.) Food and Drug Administration (FDA) and the EMA have a long history of using RWE to monitor and assess the safety of medicinal products in the post-authorization phase. (20, 24–27) When it comes to demonstrating efficacy of a drug, however, traditional randomized controlled clinical trials (RCTs) are still regarded as the gold standard for evidence generation. (24, 28) But as science and technology evolve, existing regulatory paradigms are being reassessed. The ongoing digital transformation and the accompanying advancements in the information technology brought along improved data accessibility and quality, enhanced data storage capabilities as well as access to increasingly sophisticated data analysis and data linkage tools and techniques. (29) These technological advancements coincide with a shift in the nature of products, from predominantly small molecules intended for the treatment of large numbers of patients back in the 20th century, towards a more heterogenous

mix of product types (chemicals, biologicals, Advanced Therapies Medicinal Products (ATMPs)), some of which targeted for very small patient populations or even being patient specific, today. (27) If, however, traditional RCTs are not feasible due to small patient populations or not ethical, new ways of knowledge generation need to be explored. (27) The above-mentioned developments have triggered increased interest in RWD/ RWE over the last couple of years (29), especially with regard to the potential of RWE to support regulatory decisions about efficacy. (20, 26) In the wake of the COVID-19 pandemic, the concepts around RWD/ RWE moved in the focus of a wider public and there is widespread consensus today to the effect that the pandemic has enhanced awareness and adoption of RWD/ RWE and spurred progress in the science of RWD/ RWE. (19, 30, 31) At present, a considerable number of RWD/ RWE-related initiatives are ongoing all over the world (29) which can be seen as indictive of the overall significance assigned to this topic. Against this backdrop, the objectives of this master’s thesis are to

- give a brief overview of the current role and evolving areas of use of RWD/ RWE in drug development and over the product lifecycle (with focus on the United States of America (USA) and the European Union (EU))
- and to provide a comprehensive overview of regulatory initiatives with relation to RWD/ RWE ongoing in the USA and the EU, followed by a comparison of the RWD/ RWE landscapes of these two regions.

Furthermore, this master’s thesis will have a look at the wider picture by providing

- a brief overview of RWD/ RWE-related regulatory guidance documents and/ or official statements published in other countries
- and a more in-depth insight into transnational harmonization efforts related to RWD/ RWE ongoing on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) level.

Finally, a summary, discussion and an outlook will be given.

To start with, some basic terminology and definitions in relation to RWD/ RWE will be covered in chapter two below.

1.2 Methods

1.2.1 Literature search for chapters two and three

The literature search for chapter two, ‘Basic terminology and definitions’, and chapter three, ‘RWD/ RWE landscapes in the USA and the EU’, of this thesis included the following steps: in a first step, a search of the public websites of the U.S. FDA and the EMA was performed, using the search terms ‘real-word evidence’, ‘real-world data’, ‘RWE’, ‘RWD’ and ‘big data’. Based on the results found, which mainly consisted of webpages and documents included therein, the search was deepened to include:

- reviews of sub-pages and websites referenced on the webpages or in the documents initially found,
- targeted searches for literature cited in the initial search results
- and targeted searches for additional information on topics deemed relevant based on the information found in the initial search results (e.g. targeted search for specific RWD/ RWE initiatives mentioned in the materials initially found).

1.2.2 Literature search for chapter four

The initial literature search for chapter 4.1 was performed in the Clarivate™ ‘Cortellis Regulatory Intelligence’ (RI) database. The search term used was: ‘"real world data" or "RWD" or "RWE" or "real world evidence" or "real-world data" or "real-world evidence" or "big data"’. The results included ‘Regulatory Summaries’ on country-specific regulatory practices compiled by Cortellis experts as well as copies of relevant guidance documents and official statements in both the local language and/ or translated into English. Based on the information found, targeted searches for English versions of the original guidance documents and statements were performed on the official websites of the respective competent authorities/ governmental departments.

The literature cited in chapter 4.2 was predominantly obtained from the official ICH website. In terms of content, chapter 4.2 was informed by the results obtained via the searches described under 1.2.1 above.

1.3 Explanatory notes

1.3.1 Scope of the thesis

This master's thesis considers the regulatory landscapes around RWD/ RWE with focus on medicinal products for human use. Medical devices, in vitro diagnostics and veterinary medicines are not the focus of this work and are therefore, if at all, only touched upon briefly. The latter also applies to RWD/ RWE-related activities and/ or initiatives carried out by health technology assessment (HTA) bodies or organizations.

1.3.2 Use of the terms efficacy and effectiveness

Even though in epidemiology a difference is made between the terms efficacy and effectiveness, with efficacy referring to *"the extent to which a specific intervention […] produces a beneficial result under ideal conditions"* (32) and effectiveness of an invention referring to *"the extent to which [it] […] fulfills its objectives in [routine clinical] practice"* (32), the two terms are often used interchangeably. As a matter of fact, for reasons touched upon in the next chapter (e.g. the broad spectrum of possible study designs), drawing a clear line between the two definitions might not always be possible. In the context of this master's thesis, the two terms are generally used in accordance with the respective literature cited, i.e. the above-mentioned definitions are not strictly applied.

2. Basic terminology and definitions

To set the scene for the main part of this work, some basic definitions and terminology commonly used in the context of RWD/ RWE are addressed in the following sections.

2.1 Definitions of the terms epidemiology and pharmacoepidemiology

The thematic area of RWD/ RWE has overlaps with the field of epidemiology. The latest (6th) edition of *"A Dictionary of Epidemiology"* (32), a guidebook sponsored by the 'International Epidemiological Association', defines epidemiology as

> *"[t]he study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes, and the application of this knowledge to control relevant health problems"* (32).

Epidemiology aims at, inter alia, identifying the etiology of and risk factors for diseases, determining disease prevalence, studying the natural history of diseases, or assessing

preventive and therapeutic measures. (33) Thus, epidemiologic studies can be analytic, i.e. designed to evaluate possible cause-effect relationships (causal inference) between a treatment or exposure and a disease, or purely descriptive. (33)

Pharmacoepidemiology is a subdomain of epidemiology. (33) The *"European Network for Cent[ers] of Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology"* (19) defines pharmacoepidemiology as follows:

> *"Pharmacoepidemiology is the application of epidemiological methods to study the use and effects of medicines in specified populations"* (19).

2.2 Definitions of the terms RWD and RWE – the U.S. and the European perspective

As previously mentioned, there are currently no internationally harmonized definitions of the terms 'Real-World Data' and 'Real-World Evidence'. In the following, the definitions of RWD and RWE from an U.S. and European perspective are given.

2.2.1 The U.S. perspective

The *"21st Century Cures Act"* (34) (Cures Act), signed into law by the U.S. Congress in 2016 and subsequently amended in 2017, defines RWE as

> *"data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials"* (35). (34, 35)

In its *"Framework for FDA's Real-World Evidence Program"* (20) of 2018, developed in response to the RWD/ RWE related requirements of the Cures Act, the FDA introduced the below definitions which distinguish between RWD and RWE. (20)

> *"Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources"* (20).

> *"Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD"* (20).

Furthermore, it is specified in the above-mentioned framework that

> *"[u]nder FDA's RWE Program, evidence from traditional clinical trials will not be considered RWE. However, various hybrid or pragmatic trial designs and observational studies could generate RWE"* (20).

2.2.2 The European perspective

In 2019, the article *"Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe"* (21) was published in the scientific journal 'Clinical Pharmacology & Therapeutics'. (21) In this article, authored by three senior representatives of the EMA, it is stated that

> *"[f]rom the perspective of the European Medicines Agency (EMA), RWD are defined as 'routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials'"* (21).

The term RWE is defined by the authors as *"the information derived from analysis of RWD"* (21).

2.3 RWD/ RWE-related terminology

2.3.1 Terminology commonly used to describe study designs

Epidemiologic studies can be divided into two groups, experimental (i.e. interventional) and observational (i.e. non-interventional) studies. (33, 19)

- Observational studies do not involve any intervention, neither experimental nor otherwise, on the investigator's part. (32) Studies of this type can be descriptive or analytic. (33)
- Experimental studies are characterized by the fact that the study conditions are under the direct control of the investigator. (32, 33) These studies are designed to test hypotheses by intentionally modifying one or more factor/s while controlling the other study conditions. (32, 33)

Both in the USA and the EU, interventional clinical studies are referred to as clinical trials. (20, 36) The previously mentioned RCTs fall in the category of interventional studies. (33) In a RCT, the trial *"subjects are randomly allocated into groups, usually called test and control groups, to receive or not to receive a preventive or a therapeutic procedure or intervention"* (32). RCTs and observational studies do not represent the full spectrum of possible study designs, though. In interventional single-arm trials, for example, study participants are assigned an intervention by the investigator without randomization. (31) Also, there is not just one type of RCT. RCTs can incorporate different levels of 'pragmatism'. (37) Pragmatic trials,

> *"[i]n contrast to controlled explanatory clinical trials, which aim to maximize the internal validity by rigorous control of all variables except the intervention, [..] seek to maximize external validity and to achieve a large degree of generalizability of the results"* (38).

In other words, the more pragmatic a trial is, the better it reflects the real-world. Examples for pragmatic elements include *"wider inclusion and exclusion criteria and a less strict blinding of patients or physicians"* (38). A mere 'randomized trial' versus 'observational study' distinction is therefore not sufficient to delineate the full range of possible types of study designs. Nor is it suited to comprehensively characterize the architecture of a specific study. (39) Likewise, the inclusion of the terms RWD/ RWE in the description of a study does not allow definite conclusions to be drawn about the study design or the origin of the data used. This is because, as per the definitions cited in section 2.2 above, RWD can be collected from a variety of sources and because the field of application for RWD is not limited to observational study designs. From the U.S. FDA's perspective, RWE can be generated through various types of study designs, including observational studies, non-randomized trials (e.g. single-arm trials using an external RWD-based control group as comparator) and randomized trial designs (e.g. hybrid RCTs that include both traditional and pragmatic design elements). (20) The EMA's position on this subject matter is less clear. For the purpose of a recently published study, that used resources held by the EMA to examine the contribution of RWE to marketing authorization and extension of indication applications submitted to the EMA in 2018 and 2019, not only non-interventional studies were classified as generating RWE but also interventional trials that involved the use of RWD sources, such as single-arm trials using a RWD-based external control. (24) However, the inclusion and exclusion criteria used in this study were defined by the investigators and their views cannot be construed to represent the position of the EMA.

In view of the fact that the spectrum of possible study designs is broad, clarity in terminology is demanded when describing the design of a specific study. (21, 39) Important aspects to be considered include whether a study is interventional or non-interventional, whether it involves primary data collection or secondary analysis of data originally collected for other purposes, what the characteristics of the comparison groups are and an assessment of the causal determinism for the corresponding exposure-outcome association. (39)

2.3.2 Traditional clinical trials

In the context of the above-mentioned U.S. and European definitions of RWD, the term 'traditional clinical trial' is mentioned. (20, 21) To the knowledge of the author, there is no single definition of this term. The ICH reflection paper on *"GCP [Good Clinical Practice] Renovation"* (40), endorsed in 2017 and revised in 2021, speaks of 'traditional interventional trials' and specifies for these to

> *"encompass trials of unapproved drugs or of approved drugs for a new indication or use in a controlled setting with prospective collection of trial data"* (40).

The framework for the U.S. FDA's RWE program provides a very detailed description of what the FDA considers to be a traditional clinical trial:

> *"FDA generally considers a traditional clinical trial to be one that is usually supported by a research infrastructure that is largely separate from routine clinical practice and is designed to control variability and maximize data quality. A traditional clinical trial is [.] likely to have restrictive eligibility criteria […]. Traditional clinical trials are usually randomized, double-blind trials in which both the investigator and patient are unaware of which treatment is being administered. These trials typically use separate procedures […] to collect specified data using standardized procedures and detailed case report forms […]. Personnel follow specified protocol directives to conduct scheduled monitoring and encourage precise adherence to study procedures"* (20).

In brief, from the FDA's perspective, the term traditional clinical trial refers to a protocol-based, interventional, randomized, controlled trial, usually double-blind and with narrow eligibility criteria, conducted in a setting largely separate from routine clinical practice, which involves primary data collection. In relevant EMA-affiliated publications, the term 'traditional' is often used in association with RCTs, however, without further specification. (21, 24, 41) Hence, if the term traditional clinical trial is used in an U.S. or EU context, the lowest common denominator seems to be that reference is made to a RCT.

2.3.3 Spectrum of study designs and use of RWD

To illustrate the range of study design types and possibilities to use RWD, an exemplary overview of representative study designs and their reliance on RWD is given in Figure 1 below. The illustration is adapted from a diagram by Concato (FDA) and Corrigan-Curay

(Yale University) (31) and information from the FDA's RWE framework. Although the original diagram is included in the latest version of the 'ENCePP Guide on Methodological Standards in Pharmacoepidemiology', not all the information provided therein may be in line with the views of the EMA, especially when it comes to the potential of RWE to be generated in the context of RCTs.

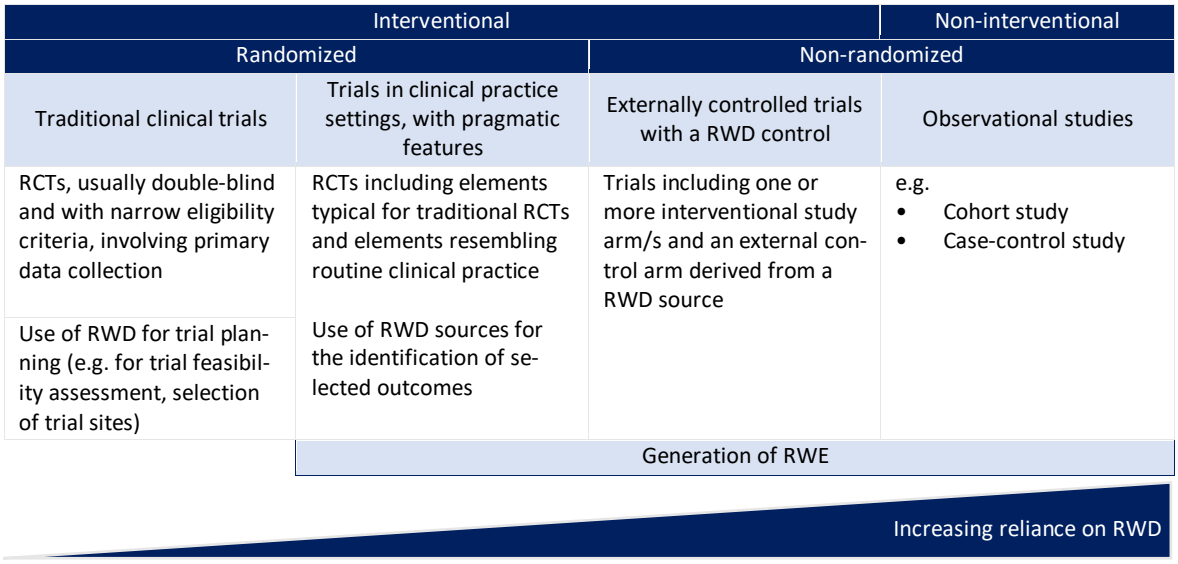

Figure 1: Overview of representative study designs and reliance on RWD (adapted from (31) & (20))

3. RWD/ RWE landscapes in the USA and the EU

3.1 Current use of RWE

3.1.1 Established and emerging RWE use cases

As pointed out in the introductory section, the use of what is called RWD today is not a new phenomenon but has a long history in the fields of disease epidemiology, drug utilization and post-authorization safety surveillance of medicines. (19, 20) Both in the USA and the EU, regulatory guidance is available on non-/ interventional post-authorization safety studies, for example, Module VIII of the European *"Guideline on good pharmacovigilance practices (GVP)"* (42) which was first adopted in 2012, the FDA guideline *"Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets"* (43) (Pharmacoepidemiologic Guidance) of 2013 or the FDA guidance for industry on *"Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act"* (44) which was first adopted in 2011. (42–44)

Against the backdrop of digitalization, accompanying technological advancements, emerging trends such as the shift in the nature of medicinal products towards more individualized treatments and the COVID-19 pandemic, there has been increasing interest in recent years in expanding the use of RWD/ RWE beyond the established fields of application. Not only in the USA and the EU, but also in other countries, efforts have been made, and are still ongoing, to build up new and adapt existing technology infrastructures as well as legal and regulatory frameworks to help enable the utilization of RWD/ RWE to its full potential. (20, 45, 46) One example is the establishment/ expansion of distributed RWD networks and analysis platforms such as the U.S. ‘Sentinel System’ and the European ‘Data Analysis and Real-World Interrogation Network’, DARWIN EU® (which is currently under development). These systems are designed to provide regulators, and eventually other stakeholders such as HTA bodies, policy makers, payers and the industry, timely access to reliable RWE on the use, safety and effectiveness of medicines with the goal to enable better, evidence-based regulatory and public health decision-making. (46, 47) The spectrum of possible use cases includes the provision of RWE to

- inform drug development and assessment (e.g. RWE may help regulators to evaluate the design and feasibility of planned or the representativeness and validity of completed studies),
- support possible repurposing of existing drugs,
- inform impact assessments of regulatory actions/ public health interventions (e.g. RWE may inform on the effectiveness of risk minimization measures),
- inform crisis management (e.g. RWE on drug utilization may help predict demand and possible shortages, RWE on the natural history of diseases may support vaccine/ drug development),
- actively monitor the performance (safety and effectiveness) of medicines in the post-authorization phase. (45–47)

RWD networks, like the above-mentioned, are considered central pillars to support a learning healthcare system, *“in which evidence is generated and applied as part of real-world clinical care”* (48) in order to improve healthcare delivery. (45, 46, 48)

A question of high interest, which has been subject to intensive debate in the last years, is whether RWE is suited to serve as substantial evidence to support regulatory decisions

about marketing authorization or extension of indication applications. (28, 27) Although there is widespread consensus for traditional RCTs still to be the most scientifically rigorous method to establish the initial risk-benefit profile of a drug, some regulatory authorities accept high-quality RWE submitted to support decisions about efficacy in certain circumstances, for instance, to support decisions about extensions of indications, or if the conduct of a RCT is not ethical or feasible. (20, 15, 24, 49, 50) A recent example is the U.S. FDA's approval of the expansion of indication for tacrolimus (Prograf®) for use in combination with other immunosuppressant drugs to prevent organ rejection in patients receiving a lung transplantation. The approval, granted in 2021, was based on a non-interventional study that compared data from a registry with data from historical controls. (31)

3.1.2 Current prevalence of RWE in regulatory decision-making

In recent years, some research has been conducted aimed at assessing the role of RWD/ RWE in regulatory submissions made to the EMA and the U.S. FDA, respectively. In a recently published study by Purpura et al., a systematic review of publicly available FDA approval documents was conducted, covering the period from January 2019 to June 2021. Only marketing authorization applications (MAAs) for new molecules were considered for the review. The authors found that 85% of the approvals considered for the study incorporated RWE in any form. (51) A European study by Flynn et al., which used resources held by the EMA to evaluate the characteristics of RWE submitted as part of new MAAs and extension of indication applications to the EMA in the period from January 2018 to December 2019, found that 39.9% of the MAAs and 18.3% of the extension of indication applications contained references to RWE/ RWD. (24) In a study by Eskola et al., a review of the European Public Assessment Reports (EPARs) of medicinal products, except generics and biosimilars, centrally authorized between January 2018 and December 2019 was conducted, with the aim to identify and quantify the role of potential use of RWD/ RWE during the pre-authorization phase. The authors found that nearly all EPARs included reference to potential use of RWE in the discovery (98.2%) and lifecycle management phase (100%). For the early development phase, 35.1% of the EPARs included RWE signatures, while for the full development and the registration phase it was 48.6% and 46.8%, respectively. (52) Given the fact that the data sources, study designs and methodologies as well as the definitions of what was classified as RWD/ RWE differed across these studies, the findings cited above

are not comparable. However, the results of these studies, even if not comparable, indicate that RWD/ RWE already play a considerable part in drug development and regulatory decision-making both in the USA and the EU.

3.2 RWD/ RWE-related initiatives in the USA

3.2.1 The 21st Century Cures Act – the legal basis for the FDA’s RWE Program

In 2016, the Cures Act was signed into law with the objective of expediting drug development and improving patient access to innovations. (34) Among other provisions, the Cures Act mandates for a new section 505F on *“Utilizing real world evidence”* (34) to be included in the ‘Federal Food, Drug, and Cosmetic Act’ (FD&C Act). (34) Section 505F directs the FDA to

> *“establish a program to evaluate the potential use of real-world evidence -*
>
> *(1) to help to support the approval of a new indication for a drug […]; and*
>
> (2) *to help to support or satisfy postapproval study requirements”* (34).

Besides giving a definition of RWE, section 505F of the Cures Act demands for certain milestones to be achieved by the FDA within specified timeframes. These milestones include the development of a framework for the FDA’s RWE program in consultation with external stakeholders and the creation of guidance on RWD/ RWE for the industry. (34) Furthermore, section 505F includes a statement clarifying that the existing standards of ‘substantial evidence’ for the demonstration of effectiveness of a medicinal product, as defined in subsection (d) of section 505 of the FD&C Act, are not altered by this new section. (34)
In the following section, a comprehensive overview is given of the initiatives launched and activities performed by the FDA to fulfill the legislative mandates under section 505F of the Cures Act.

3.2.2 Framework for the FDA’s Real-World Evidence Program

In accordance with the provisions of the Cures Act, the *“Framework for FDA’s Real-Word Evidence Program”* (20) was published in December 2018. (20) The framework is divided into several sections. The three main sections are:

- an introductory part covering the scope of the FDA’s RWE Program and the FDA’s definitions of RWD and RWE,
- a section on *“Current Use of RWD for Evidence Generation”* (20)

- and the actual *"Framework for Evaluating RWD/RWE for Use in Regulatory Decisions"* (20).

Furthermore, the framework includes a section on 'stakeholder engagement' and an overview of 'demonstration projects' ongoing at the time the RWE framework was issued, designed to inform the FDA about potential uses of RWD and RWE. (20) The framework also includes definitions of basic terminology used in the context of the framework and a references section.

In the following, an overview of the main points of the framework is provided, except for the aspects 'current use of RWD' and 'terminology and definitions', since these have already been addressed in previous sections of this thesis.

Scope and priorities of the FDA's RWE Program

The framework for the FDA's RWE Program is applicable to both drugs and biological products. Medical devices are out of scope. (20) With regard to studies and trial designs covered by the FDA's RWE Program, the framework distinguishes between:

- traditional clinical trials,
- trial designs that can potentially generate RWE, for example, trial designs with pragmatic elements
- and observational studies. (20)

Traditional clinical trials are out of scope of the FDA's RWE Program as the evidence derived from these trials is not considered RWE. However, 'non-traditional' "*clinical trials that generate RWE in some capacity*" (20) are covered by the program, together with observational studies. (20)

As mandated by section 505F of the Cures Act, the focus of the framework is on exploring the suitability of RWD-derived evidence to inform regulatory decisions about the effectiveness of medicinal products, specifically in post-authorization settings, i.e. to support decisions about extension of indication applications or to support or fulfill post-approval study requirements. (20) RWD-derived knowledge used to enhance the efficiency of clinical trials (e.g. if used for biomarker identification or hypotheses generation), rather than to support decisions about drug effectiveness, is not an area of focus of the RWE framework. (20)

Key aspects of the RWE framework

The RWE framework defines a three-part approach to guide the FDA's RWE Program or, more specifically, the FDA's decision-making when being provided with RWE to demonstrate product effectiveness:

1. the assessment of the fitness of the RWD to be used in regulatory decision-making,
2. the assessment of the suitability of the study design used to generate satisfactory evidence to answer the research question
3. and the assessment whether or not FDA requirements are met in regard to study conduct. (20)

Furthermore, the framework covers data standards and strategies for their implementation, an aspect which underlies all the three above-mentioned parts. (20, 53)

In the following, each of the above-listed aspects is looked at in more detail. The corresponding 'Program Items', i.e. the respective action items to be executed by the FDA under its RWE Program, are presented at the end of each subsection.

RWD fitness for use

According to the RWE framework, the FDA's evaluation of whether or not RWD are fit for use includes an assessment of data relevance and data reliability, the latter including data accrual and data assurance (quality control). (20) This approach is based on the FDA's previous experience with assessing RWD in the context of drug safety, particularly through experience with the Sentinel System. (20) Aspects to be considered when assessing data reliability include, for instance, data completeness, consistency, accuracy and trends over time. (20) The data relevance assessment considers the suitability of the data and analysis methods used to address the questions of interest and includes an assessment of the capability of the selected data source to capture relevant elements such as exposure, outcomes and covariates. (20) The FDA does not generally endorse one type of RWD or RWD source over another. The RWE framework acknowledges that different sources of RWD have different strengths and limitations and recommends for RWD sources to be selected based on their suitability to answer the questions of interest. (20)

The RWE framework also considers challenges to be addressed by the FDA to improve the reliability and relevance of RWD sources. Gaps in RWD sources are named as one of these challenges. (20) Traditional RWD sources, such as EHRs and medical claims data, are

generated for purposes other than supporting regulatory decision-making. As a consequence, these data sources do not necessarily capture all the data elements required to answer a specific regulatory question or, if they do, the relevant data elements may not be captured consistently, the level of data granularity may be insufficient or certain relevant data elements may not be readily accessible and usable, for example, if recorded in an unstructured format and/ or without the use of standardized terminology. (20) Capturing missing data elements by means of integration of multiple RWD sources bears further challenges, such as how to safeguard patient privacy when linking data about individual patients across various data sources and how to manage possible duplication of data. (20) To address the above-mentioned challenges, the FDA's RWE Program aims at exploring ways to fill gaps in existing RWD sources and at developing strategies to integrate data sources and to address duplication. (20)

For each of the above-discussed aspects, the RWE framework defines action items to be executed by the FDA under its RWE Program. An overview of these 'Program Items' is provided below:

- Guidance development on how to assess the relevance and reliability of RWD obtained from different sources when used to generate RWE to support product effectiveness (20)
- Review of potential gaps in RWD sources and development of guidance on strategies to address the gaps identified (20)
- Exploration of the potential of digital tools and technologies, for example, wearables, biosensors, mobile technologies to fill gaps in RWD sources (20, 53)

Suitability of RWD-using study designs to generate RWE to support effectiveness decisions

According to the FDA's RWE framework, RWE can be generated through a range of study designs, i.e. not only through observational studies but also in the context of RCTs, if those include elements relying on RWD, or in the course of non-randomized single-arm trials with an external RWD control. (20) The RWE framework does not provide detailed guidance as to regulatory circumstances in which certain study designs or design attributes using RWD would be considered appropriate to support valid cause-effect inference. However, the framework addresses factors to be considered when assessing the suitability of different study designs using RWD to answer or help answer various regulatory questions and to be

further explored by the FDA under its RWE program. With regard to randomized clinical trial designs including pragmatic elements, questions to be considered are:

- For what therapeutic areas and types of interventions might routine clinical care environments be well-suited? (20)
- What data quality levels can be reached in such settings? (20)
- How to bridge between regulatory and clinical practice endpoints if they are not the same? (20, 53)

Non-randomized, externally controlled clinical trials are considered acceptable by the FDA to support regulatory decisions about effectiveness if the conduct of a randomized clinical trial would be unethical or not feasible. (20, 53) While bearing challenges, the use of robust contemporary RWD as a basis for external controls, instead of historical control data, may be beneficial from the FDA's perspective, provided that relevant covariates are captured and adequate statistical methods are used to adjust for confounding. (20, 53)

Evaluating the potential of observational, i.e. non-interventional, studies to contribute valid evidence of drug product effectiveness is another objective of the FDA under its RWE Program. (20) As briefly touched upon in the previous section on 'RWD fitness for use', the FDA has extensive experience in evaluating non-interventional safety studies. (20) The FDA's perspective on the conduct of, and reporting requirements for, such observational safety studies using electronic healthcare data is represented in the 'Pharmacoepidemiologic Guidance' for industry and FDA staff. (43) Two core demands of this guidance are for the sponsor to submit a protocol to the FDA before initiation of a study and a final report upon study completion. (20) As per the framework, the FDA's evaluation of observational studies for determination of drug effectiveness will be guided by its previous experience with the assessment of non-interventional safety studies and the principles outlined in the 'Pharmacoepidemiologic Guidance'. (20) Critical questions the FDA will focus on in the context of retrospective observational studies include whether the depth and breadth of the data captured is adequate to generate satisfactory evidence to answer the research question and what study design and analysis characteristics hold promise to enhance the probability of a valid result (e.g. an active comparator design, pre-specification of certain statistical analyses to provide confidence for the causal inference not to be changed by the effect of unmeasured cofounders). (20, 53)

Another question to be considered by the FDA under its RWE Program, especially with regard to retrospective observational studies, is how to establish up-front transparency about the study design and analysis to prevent practices such as the reanalysis of datasets until the desired result is obtained and subsequent submission of the thus derived result as if it was the outcome of a single study with a pre-specified protocol. (20, 53)

In regard to study designs with the potential to generate RWE, the FDA’s RWE framework lists the following program items:

- Development of guidance for designing randomized clinical trials including pragmatic design elements that are aimed at generating evidence of drug product effectiveness (20)
- Guidance development on the use of RWD as a basis for control arms in externally controlled clinical trials (20)
- Development of further guidance, building on the existing ‘Pharmacoepidemiologic Guidance’, on observational study designs, including whether and how such studies might provide RWE to support decisions about effectiveness (20)
- Consideration of reporting requirements for observational studies aimed at supporting decisions about effectiveness (20)

Regulatory requirements

The third part of the FDA’s RWE framework addresses the need for the FDA to consider whether the existing sets of regulatory guidance documents and regulations, for example, in relation to GCP, inspections, electronic records and signatures, adequately cover study designs that use RWD for the generation of RWE to inform regulatory decisions about drug effectiveness. (20) Program items in regard to the topic ‘regulatory considerations for RWD-using study designs’ include an assessment whether available guidance on the above-mentioned aspects is sufficient as well as the development of additional guidance as needed. (20)

Data standards and implementation strategies

The fourth, cross-cutting theme sought to be addressed under the FDA’s RWE Program involves the identification, assessment, adaptation or development of suitable data standards for RWD and of strategies for their implementation to enable or improve data

interoperability. The framework stipulates for the FDA to collaborate with internal and external stakeholders to accomplish this goal. (20)

According to the RWE framework, the FDA's efforts towards an effective utilization of RWD/ RWE for regulatory decision-making will be multifaceted, including stakeholder engagement, shared learning, development of guidance documents and funding of demonstration projects to further the understanding of potential RWD use cases. (20)

The next section addresses the FDA's Sentinel Initiative which represents an important engine for the advancement of the science of RWE. (46)

3.2.3 The Sentinel Initiative and the NEST program

The Sentinel Initiative

The Sentinel Initiative was launched by the FDA in 2008 (54), in response to a legislative mandate to *"establish a post-market risk identification and analysis system to link and analyze safety data from multiple sources"* (46). To meet this requirement of the 'FDA Amendment Act' (FDAAA), signed into law in 2007, a pilot program, the Mini-Sentinel, was launched in 2009. Mini-Sentinel transitioned to the full-scale Sentinel System in 2016. (55) Today, the Sentinel Initiative comprises three chief components,

- the Sentinel System,
- FDA-Catalyst
- and the 'Biologics Effectiveness and SafeTy' (BEST) Program

and includes three coordinating centers, the Sentinel Operations Center (SOC), the Sentinel Innovation Center (IC) and the Sentinel Community Building and Outreach Center (CBOC). (46, 54, 56) While the focus of the SOC is on operational aspects, the IC and the CBOC, both established in 2019, focus on the development of innovative methods, and on communication and collaboration, respectively. (56, 54)

The Sentinel System

The FDA Sentinel System was initially set up, and still serves, as an active surveillance system that uses medical claims data and EHR information held in a distributed database and a set of customizable querying tools to detect and assess potential safety concerns of approved medicinal products. (46, 18, 57) The Sentinel System is formally embedded in the regulatory decision-making process through the *"Active Post-market Risk Identification and*

Analysis (ARIA)" (46) process, which *"determines whether the Sentinel System or ARIA data coverage and analyses are sufficient for evaluating a potential safety concern"* (46) or if there is a need for the safety concern in question to be evaluated through other approaches, for example, sponsor-led post-market requirement studies. (46) ARIA represents a subset of the Sentinel System's full capabilities. Due to the nature of the product sets they regulate, the use of ARIA tools is more relevant for the 'Center of Drug Evaluation and Research' (CDER) than for the 'Center of Biologics Evaluation and Research' (CBER). (55) While routinely using ARIA for initial analysis, the CBER often relies on other Sentinel programs such as the 'Post-Licensure Rapid Immunization Safety Monitoring' (PRISM) program or the 'Blood Surveillance Continuous Active Network' (BloodSCAN) to help answer their regulatory questions. (55, 54)

The aforementioned distributed database, which represents a key component of the Sentinel System, is a collection of distinct datasets of routinely collected RWD held by different healthcare organizations, referred to as 'Sentinel Data Partners', in a standardized Sentinel 'Common Data Model' (CDM) format. (57) The distributed approach of the Sentinel System preserves patient privacy and data security in that the analysis of the source data is performed by the Sentinel Data Partner who owns the respective dataset and de-identified results being returned to the Sentinel Operations Center. The SOC then provides aggregated results, devoid of individual identifiers, to the FDA. (57)

FDA-Catalyst

The Sentinel infrastructure supports not only the Sentinel System but also FDA-Catalyst. (54) While leveraging its infrastructure, FDA-Catalyst supplements the Sentinel System in that its activities may involve the use of data from interventions and interactions with patients and/ or providers in addition to using the data held in the Sentinel System. (46, 54) This allows for a wider range of questions to be answered than could be addressed by relying on the data included in the Sentinel System alone. (20) The development of FDA-Catalyst paved the way for an expanded use of the Sentinel System beyond safety into efficacy. (46)

In its five-year strategy for the Sentinel System, published in 2019, the FDA envisions for the Sentinel System to evolve by 2023 into *"a transformative, multi-purpose national data and scientific resource center for evidence-generation that a wide array of stakeholders use*

to inform all aspects of healthcare decision-making" (46). The strategy focuses on the two components of the Sentinel Initiative that share the Sentinel infrastructure: the Sentinel System and FDA-Catalyst. (46) To achieve its vision for the Sentinel System, the FDA has defined five strategic aims:

1. The first aim is to *"[e]nhance the foundation of the Sentinel System"* (46). Measures to realize this aim include adding new and improving existing data sources, expanding data linkages, improvement of data infrastructure, development of methods to enhance the utility of existing data sources and the improvement of operational efficiency (e.g. through incorporation of innovative technologies such as machine learning and natural language processing). (46)
2. The second aim, which is to *"[f]urther enhance [the] safety analysis capabilities"* (46) of the Sentinel System, is closely related to the first one since improving the Sentinel System's foundation can be expected to benefit its safety analysis capabilities. (46)
3. *"Accelerate access to and broader use of real-world data to evaluate effectiveness"* (46) is the third strategic aim. The Sentinel System five-year strategy roadmap foresees FDA-Catalyst as a key enabler to realize this aim in serving as a platform for demonstration projects to inform the development of expertise in the application of RWD/ RWE across the spectrum of possible use cases and as a testbed for the development and advancement of relevant methods, standards and data infrastructure. (46)
4. The fourth aim defined by the FDA is to *"[c]reate a national resource by broadening the Sentinel System user base"* (46). Measures to realize this aim include streamlining user access to increase utilization of Sentinel tools, methods and infrastructure, refinement of the Sentinel System operation model as well as direct engagement with potential Sentinel System users. (46)
5. *"Disseminate knowledge, and advance regulatory science"* (46) represents the fifth strategic aim. It focuses on stakeholder engagement and knowledge sharing across the healthcare community. (46)

Several of the initiatives in support of the Sentinel System strategic aims tie in with the FDA's broader mandate regarding the exploration of the utility of RWE, as outlined in section 505F of the Cures Act. (46)

The Biologics Effectiveness and SafeTy (BEST) Initiative

The BEST System is an active surveillance system for biologics, including vaccines and blood products, under the aegis of the CBER, established in 2017 to fulfill the mandate of the FDAAA of 2007. (58) BEST is designed to meet specific needs of the CBER regarding safety and effectiveness surveillance of biologics that are not covered by the Sentinel System. (46, 58) While being part of the Sentinel Initiative, BEST operates outside of the Sentinel infrastructure. (54) Analogous to the Sentinel System, BEST uses a distributed data network and a common data model. (59) It leverages RWD from EHRs, administrative claims and linked claims-EHR data sources as well as sophisticated analysis tools to interrogate the data sources and generate evidence to inform regulatory decisions. (58) In its Sentinel System five-year strategy of 2019, the FDA foresees for new capabilities established through BEST to *"contribute to the evolution of the Sentinel Initiative, informing best practices for utilization of RWD effectiveness studies, including causal inference methodologies, and the application of innovative technologies"* (46).

The National Evaluation System for Health Technology (NEST)

The NEST is a national data network leveraging RWD/ RWE to inform the evaluation of medical devices and to support regulatory decision-making. (60, 61) NEST is aimed at generating evidence across the whole lifecycle of medicinal devices by linking and analyzing data from different RWD sources, including EHRs, medical claims databases, clinical registries and patient-mediated data. (60, 61) NEST is not part of the FDA's Sentinel Initiative but operates under the aegis of the 'Medical Device Innovation Consortium' (MDIC), which is a public-private partnership. (62) In 2016, the MDIC was awarded a grant by the FDA to establish the 'Coordinating Center for NEST' (NESTcc). (62) Today, NESTcc serves a dual role as coordinating center, providing the organizational framework to operationalize NEST, and as a collaborative community with participation of stakeholders across the medical device ecosystem, including the FDA. (63)

3.2.4 Demonstration projects

As touched upon previously, the FDA is involved in various initiatives and demonstration projects aimed at advancing the utilization of RWD/ RWE. This chapter provides a brief overview of three selected RWE projects with FDA participation in support of the RWE provisions of the Cures Act.

RCT DUPLICATE Initiative

In 2018, the FDA launched a partnership with the 'Brigham and Women's Hospital/ Harvard Medical School' aimed at calibrating non-randomized RWE against evidence derived from RCTs through large-scale replication of RCTs. The objective of the project is to better understand under what circumstances RWE studies can reach the same conclusions as RCTs and reliably support causal inference. (20, 64, 65) The results of the first ten, of thirty planned, trial emulations conducted as part of a FDA demonstration project under the umbrella of the so-called 'Randomized, Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology' (RCT DUPLICATE) initiative were published in December 2020. (64, 65, 66) According to the authors of the publication, the *"initial findings of the RCT DUPLICATE program indicate circumstances when RWE may offer causal insights where RCT data are either not available or cannot be quickly or feasibly generated"* (64). However, the authors also emphasize the need of further research to be conducted to gain deeper insights about the *"circumstances that determine whether RWE findings can predictably match those of RCTs across different therapeutic areas"* (64).

While the above-mentioned RWE demonstration project focuses on the replication of completed phase 3/ 4 RCTs, other projects conducted under the umbrella of the RCT DUPLICATE Initiative aim at emulating ongoing RCTs to determine the predictive power of the corresponding RWD studies. (66)

OneSource Project

The OneSource Project is a collaboration between the FDA and the 'University of California San Francisco'. (67) The project was

> *"established with the goal of developing methods and tools to automate the flow of structured EHR data into external systems [namely electronic data capture systems for the collection of clinical trials data] and thereby reduce operating costs, save time, and improve data quality for clinical trials"* (67).

One of the main benefits of electronic source data capture, i.e. the retrieval of research data directly from EHRs, is that it may eliminate the need for source data verification, a process representing one of the key cost drivers of clinical trials. (67) Phase I of the OneSource Project has been completed and the research outcomes and results made

publicly available in 2019. (67, 68) The phase I project report also includes a roadmap for phase II of the project. (67)

FDA MyStudies App

The FDA 'MyStudies App' is a customizable mobile device application (app), specifically designed for the use in clinical research, that allows for data to be collected from patients in real time and linked to existing electronic health data sources. (69) The app and a secure storage environment for the patient data collected was developed as part of a project under the FDA-Catalyst program. (69) A follow-on project aimed at developing advanced app features, under the umbrella of FDA-Catalyst, is ongoing. (70) The source code for the MyStudies App and the technical documentation are publicly available for use by researchers and software developers. (69, 70) During the COVID-19 pandemic, the FDA MyStudies App was made available free of charge to investigators of eligible clinical trials that needed a digital platform to securely obtain electronic informed consent from patients. (71) Funding for the use of this so-called COVID MyStudies App was provided by the FDA. (72)

3.2.5 Guidance documents

Section 505F of the Cures Act of 2016 requires the FDA to develop and issue draft guidance on RWD/ RWE for the industry within a period of five years after the date of enactment of the Cures Act. (34) A list of the guidance documents issued by the FDA as part of its RWE Program to satisfy the aforementioned mandate is provided below. For the sake of comprehensiveness, the list includes the guidance on the use of RWE to support regulatory decision-making on medical devices, even though medical devices fall not within the scope of section 505F of the Cures Act and are not the focus of this thesis.

- *"Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Guidance for Industry and Food and Drug Administration Staff"* (73) – issued August 2017 (73)
- *"Use of Electronic Health Record Data in Clinical Investigations, Guidance for Industry"* (74) – issued July 2018 (74)
- *"Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics, Guidance for Industry, Draft Guidance"* (13) – issued May 2019 (13)

- *“Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Guidance for Industry, Draft Guidance”* (75) – issued September 2021 (75)
- *“Data Standards for Drug and Biological Product Submissions Containing Real-World Data, Guidance for Industry, Draft Guidance”* (76) – issued October 2021 (76)
- *“Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products, Guidance for Industry, Draft Guidance”* (77) – issued November 2021 (77)
- *“Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products, Guidance for Industry, Draft Guidance”* (78) – issued December 2021 (78)

3.2.6 FDA strategic initiatives and 2021 Focus Areas of Regulatory Science

To fulfill its *“mission to protect, promote, and advance public health”* (18) the FDA needs to keep pace with and adapt to the rapid and continuous evolution of science and technology. In 2021, the report *“Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS)”* (18) was published by the FDA. This report identifies and communicates priority areas of regulatory science where continued targeted investments in research capacity are considered necessary to support the regulatory and public health mission of the FDA. (18) The FARS identified in the report are organized across the four below-listed strategic initiatives, three of which defined by former FDA Commissioner Stephen Hahn in 2020 and one, the initiative “Public Health Emergency Preparedness and Response” (18), added by the committee tasked with the development of the FARS:

- *“Public Health Emergency Preparedness and Response”* (18)
- *“Increasing Choice and Competition through Innovation”* (18)
- *“Unleashing the Power of Data”* (18)
- *“Empowering Patients and Consumers”* (18)

The strategic initiative *“Unleashing the Power of Data”* (18) refers to big data and how fit for purpose big data, new computational tools and advanced analysis techniques can be harnessed to improve regulatory decision-making and benefit public health and innovation. (18) One of the FARS associated with this strategic initiative is *“Use of Real-World Evidence to Support Medical Product Development and Regulatory Decision-Making”* (18). This, for

one thing, highlights the importance ascribed to this research field and, for another thing, places RWD/ RWE in the wider context of big data.

3.3 RWD/ RWE-related initiatives in the EU

3.3.1 Key players in the field of RWD/ RWE in the EU

The European Medicines Regulatory Network (EMRN)

The regulatory ecosystem in the EU is unique, in that there is not one main regulatory body, such as in the USA, but a closely coordinated network of regulatory bodies including the ‘European Commission’ (EC). (79) Besides the EC, the ‘European Medicines Regulatory Network’ (EMRN) is comprised of the ‘National Competent Authorities’ (NCAs) in the member states of the ‘European Economic Area’ (EEA), their representative forum, i.e. the HMA, and the EMA. (80) The European regulatory system largely relies on the scientific expertise available in the NCAs. Collaboration and regulatory decision-making on European level takes place in scientific committees, working parties and advisory groups, mostly staffed with experts from the NCAs and coordinated by the EMA or the HMA. (80) The EC’s principal role in the system for regulating medicines in Europe is to adopt binding decisions based on the recommendations provided by the EMA’s scientific committees. (79) Furthermore, the EC is an important sponsor of scientific research projects and initiatives, for example, via its research and innovation program ‘Horizon Europe’.

The European Network for Centres of Pharmacoepidemiology and Pharmacovigilance

The ‘European Network for Centres of Pharmacoepidemiology and Pharmacovigilance’ (ENCePP) is a voluntary network of public institutions and contract research organizations with a focus on pharmacoepidemiology and pharmacovigilance research. (81) The network was established and is coordinated by the EMA. (81, 82) The ENCePP Steering Committee, which is the highest authority and final decision-making body of ENCePP, consists of representatives from the ENCePP network and one or more representative/s from the following organizations: the EMA, the HMA, the International Society for Pharmacoepidemiology (ISPE), the International Society of Pharmacovigilance, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the U.S. FDA, Health Canada (HC) and the ‘European Federation of Pharmaceutical Industries and Associations’ (EFPIA), with the last three having observer status. (83, 84) The four major accomplishments of the ENCePP

in support of its aim to *"build capacity in the delivery of post-authori[z]ation studies"* (82) and *"strengthen the monitoring of the risk-benefit-balance of medicinal products in Europe"* (81) are:

- the establishment of a publicly accessible and searchable electronic index of research resources available in Europe, the *"ENCePP Database of Research Resources"* (85),
- the creation of the *"ENCePP Code of Conduct"* (85) which is *"a set of rules and principles for pharmacoepidemiology and pharmacovigilance studies to promote transparency and scientific independence throughout the research process"* (81) that all ENCePP members are committed to adhere to,
- the development and regular update of the *"ENCePP Guide on Methodological Standards in Pharmacoepidemiology"* (85) which offers methodological guidance in pharmacoepidemiology
- and the creation of the *"ENCePP Checklist for Study Protocols"* (85), a tool aimed at enhancing the quality of studies and promoting transparency. (81, 85)

Innovative Health Initiative

The 'Innovative Medicines Initiative' (IMI), a long-lasting public-private partnership between the EU, represented by the EC, and the European pharmaceutical industry, represented by the EFPIA, has been an important sponsor of RWD/ RWE related research projects in recent years. (19, 86) In 2021, a new public-private partnership to replace the IMI was launched: the 'Innovative Health Initiative' (IHI). (86) The IHI *"Strategic Research and Innovation Agenda"* (87), published in 2022, specifies *"strengthening [..] ongoing developments to harness opportunities of big data in healthcare"* (87) as one of its goals.

3.3.2 OPTIMAL framework for RWE

In 2019, a scientific article authored by three senior representatives of the EMA was published, outlining the European perspective on the use of RWD for regulatory decision-making. (21) The authors provided definitions of RWD and RWE and proposed a framework, based on three pillars, to address the operational, technological and methodological challenges posed by the utilization of RWD: the *"OPerational, TechnIcal, and MethodologicAL framework (OPTIMAL) for regulatory use of real-world evidence (RWE)"* (21). The objective underlying the framework is an *"appropriate use of valid RWE"* (21) for regulatory use cases

such as safety, efficacy and benefit-risk monitoring. (21) To meet this objective, the framework request for RWE, and the RWD it is based on, to satisfy the following acceptance criteria:

- the data source/s the RWE is derived from should be of proven good quality,
- internal and external validity of the RWE should be given,
- consistency of the RWE across the data sources used/ countries covered should be given
- and the RWD/ RWE should be adequate in terms of depth and breadth (including adequate precision, time period and range of elements covered). (21)

In the following section, an overview is given of the operational, technological and methodological challenges identified by the authors as well as of the solutions they proposed for Europe.

Operational challenges and possible solutions for Europe

The operational challenges identified by the authors relate to feasibility, governance and sustainability. (21) Feasibility considerations include the aspects data availability and accessibility, costs, data privacy and patient consent. Governance relates to aspects such as funding, transparency requirements and legal regulation of data sharing. Sustainability is about continuity with regard to data collection and analysis. (21) The solutions proposed by the authors to address these challenges include:

- *“[l]andscaping of potential data sources”* (21),
- establishment of long-term solutions for the funding of data infrastructures,
- access management in line with existing legislation, for example, the EU ‘General Data Protection Regulation’ (GDPR),
- development of data sharing legislation,
- development and implementation of anonymization processes where required,
- public disclosure of data source characteristics
- and observance of the ENCePP Code of Conduct. (21)

Technical challenges and possible solutions for Europe

The technical challenges outlined by the authors cover aspects such as missing data, challenges related to data linkage, inadequate coverage of the full range of relevant data

elements (e.g. exposure, outcomes, population characteristics, time elements), heterogeneity in content of datasets (impeding data pooling), inconsistencies in terms of the use of data formats and terminologies as well as challenges associated with the collection, recording and management of data in a consistent, accurate and timely manner. (21) Possible solutions proposed by the authors include:

- usage of common data elements, formats and terminologies,
- mapping of data to a CDM, including mapping validation,
- implementation of quality assurance and control processes
- and introduction of a data source qualification procedure by the EMA. (21)

Methodological challenges and possible solutions for Europe

According to the authors, the methodological challenges inherent to the generation of acceptable RWE are mainly attributable to the fact that RWD are often not collected for the principal purpose of supporting research to inform regulatory decision-making. (21) Therefore, a good understanding of the data source environment, as well as sound data analysis and interpretation, is required to identify and manage possible challenges, such as inadequate capture of potential confounders and effect modifiers, potential biases, missing data and, in case of multi-database studies, potential heterogeneity in content. (21) The authors propose the following solutions to address these challenges and help dispel concerns around the reliability and validity of RWE:

- obtaining EMA scientific advice for study protocols,
- exercising transparency by providing detailed descriptions of the study design and the data collected as well as by documenting feasibility analyses,
- study registration in a public database (e.g. the EU 'Post-Authorization Study' (PAS) Register) as well as publication of the study protocol and final study report
- and application of the highest methodological and statistical standards (e.g. by adhering to the respective standards defined by ENCePP). (21)

3.3.3 HMA-EMA Joint Big Data Task Force and Joint Big Data Steering Group

The HMA-EMA 'Big Data Task Force' (BDTF), which operated from 2017 until end of 2019, was established to explore and assess the big data landscape from a regulatory perspective, identify and report on challenges and opportunities associated with big data utilization for

evidence generation as well as make recommendations on how to enable the European regulatory system to guide the use of, analyze and interpret big data to improve regulatory decision-making and benefit innovation and public health. (10, 11, 45) With the launch of this ‘big data initiative’, RWD/ RWE were incorporated into the wider context of the EU’s big data approach, which is guided by the recommendations of the BDTF.

The work of the BDTF was carried out in two phases. Phase I resulted in 47 core recommendations and more than 100 associated reinforcing actions. (45) In phase II, the recommendations from phase I were prioritized, practical steps for their implementation worked out and a resource estimation conducted to inform and guide decisions on implementation. (45) The final report of the BDTF, published in January 2020, includes ten priority recommendations along with a recommendation to establish a steering group to oversee implementation of the phase II recommendations and define and measure success factors. (11, 45) The subsequently created HMA-EMA ‘Big Data Steering Group’ (BDSG) initiated its work in May 2020 and recently published its third workplan which covers 2022 to 2025. (11) The ten BDTF priority recommendations are line with the current legal framework for the regulation of medicinal products in the EU. (45) A core demand of the BDTF was to establish a secure platform and infrastructure to access, share and analyze healthcare data (including EHRs, insurance claims, registry data, laboratory results, medical images and genomics data), similar to the U.S. Sentinel System. Taken together, the recommendations of the BDTF are suited to address the operational, technical and methodological challenges associated with the utilization of RWD that were presented in the previous chapter.

In the following, each priority recommendation is introduced, and an overview given of key deliverables, activities currently ongoing and milestones already achieved under the current and previous BDSG workplans. The overviews are aimed at highlighting key activities and outputs and do not raise claims to completeness.

Recommendation I: “Deliver a sustainable platform to access and analy[z]e healthcare data from across the EU (Data Analysis and Real-World Interrogation Network - DARWIN)” (45)

In its final report of 2020, the BDTF expressed its view for the EMRN to be at risk of falling behind other leading industry nations, namely the USA, Canada and Japan, when it comes to secondary use of health data to support the development, authorization and supervision of medicines. (45) Accordingly, the BDTF recommended to secure funding for, establish and

maintain a secure EU data platform allowing access to and analysis of health data to support a better, evidence-based decision-making on medicines. (45) The platform, named DARWIN EU®, is sought to be set up as a distributed network of real-world datasets from across the EU. (88) DARWIN EU® is aimed at being a resource of validated, high-quality RWD on medicines that can be used for generating reliable RWE on diseases, patient populations as well as the use, safety and effectiveness of medicines. (88) Principal users of DARWIN EU® are foreseen to be regulators, mainly from the EMA. However, an expansion to include other actors in the European health sector (e.g. HTA bodies, payers, the European Centre for Disease Prevention and Control (ECDC)) in the longer term is considered. (88, 89) DARWIN EU® is intended to support regulators in their decision-making by:

- providing a catalogue of RWD sources that are suitable for the use in a regulatory context and their metadata
- and by conducting tailored non-interventional studies to inform scientific evaluations. (88)

A recently established DARWIN EU® coordination center is responsible for building the DARWIN EU® network and for managing its day-to-day operations. (88) The DARWIN EU® project is closely intertwined with the ‘European Health Data Space’ (EHDS) initiative of the EC. (88) This initiative aims at creating a common space for EU citizens to access and control their electronic personal health data. (90) Furthermore, it is intended for the EHDS to enable *“researchers, innovators, [regulators,] and policy makers to [make] use [of] this electronic health data [for the public good] in a trusted and secure way that preserves privacy”* (90). (91) The EHDS is governed by a wealth of data protection laws (e.g. the GDPR, the recently adopted ‘Data Governance Act’ (92), the Directive (EU) 2016/1148 on security of network and information systems) and other laws and regulations. (91) DARWIN EU® is deemed to be a key user of the future EHDS and is supposed to contribute to its creation by acting as a pilot and pathfinder for a secure exchange and secondary use of healthcare data. (88)

Milestones achieved

- In 2021, a DARWIN EU® advisory board was established to provide strategic advice on the establishment of DARWIN EU® and its use of the EHDS, ensure *“coordination and alignment with relevant European and EU Member State initiatives and policies, and support communication on DARWIN EU”* (93).

- In February 2022, the ‘Erasmus University Medical Center Rotterdam’ was appointed as service provider for the DARWIN EU® coordination center. (93)

Activities currently ongoing

- Development and definition of operational processes and governance structures for DARWIN EU® by the DARWIN EU® coordination center (88)
- Collaboration between the EMA and the EC to ensure sustainable funding for DARWIN EU® (93)

Deliverables

- Stepwise increase of the number of DARWIN EU® data partners (target: 10 additional data partners p.a.) and studies initiated (starting with four, targeted for 2022, to 100, targeted for 2025) (89)
- Phased provision of routine access to RWE for EMA’s scientific committees, starting with the ‘Pharmacovigilance Risk Assessment Committee’ (PRAC) in 2022 (2022 – 2024) (89)
- Launch of DARWIN EU® website (planned for 2023) (88)
- Support of a pilot on RWD analysis through the EHDS (2023) (89)
- Pilots with HTA bodies and payers (starting Q4 2022 until 2024) (89)
- Pilot with ECDC on the use of RWD in a health crisis (starting 2023 until 2024) (89)

Recommendation II: “Establish an EU framework for data quality and representativeness” (45)

The scientific value of evidence is determined, inter alia, by the quality and representativeness of the underlying data. The question whether the data used to generate RWE is representative for the population of interest is key, not only for investigators and regulators but also for other stakeholders such as HTA bodies and payers. (45) However, for RWD to be utilizable at all, they must be accessible in the first place. Hence, fostering accessibility of existing RWD-sets is considered a priority. (45) Furthermore, transparency regarding the characteristics of available data sources is key to inform the choice of data, the interpretation of study results and the assessment of their evidentiary value. (93) The BDTF’s priority recommendation II proposes the following practical steps to help address the aforementioned challenges:

- promotion of *"the uptake of electronic health records, registries, genomics data, and secure data availability"* (45) across the European member states,
- development of guidelines
- and strengthening the process for data qualification through scientific advice. (45)

Milestones achieved

In 2021, a consortium to deliver a draft EU data quality framework was appointed by the EMA. (93)

Activities ongoing

Continuous collaboration with the joint action 'Towards A European Health Data Space' (TEHDAS), a project carried out by 25 European countries, aimed at advancing the cross-border secondary use of health data and thus supporting the EC and the EU member states in establishing the EHDS. (94, 89)

Deliverables

- Publication of a first version of a data quality framework (planned for Q4 2022) (89)
- Development of recommendations on data qualification (planned for Q2 2023) (89)
- Development of *"good practices on regulatory data science, management and software"* (89) (Q2 2023 - 2025) (89)

Recommendation III: "Enable data discoverability" (45)

Discovering suitable RWD sources for research purposes represents a challenge for the scientific community. (45) Not only that data sets are often siloed (e.g. by country, language, institution) but also heterogenous in terms of the data elements captured and the data formats and terminologies used (the latter impeding data pooling and/ or linkage across multiple data sets). (45) Making available comprehensive and accurate metadata information can help researchers in identifying suitable data sources for their observational studies and regulators in assessing the evidentiary value of the study results. (95) To improve discoverability and interoperability of RWD, the BDTF recommended the following actions:

- strengthening of the ENCePP resource database to lead researchers to the most suitable data sets,
- promotion of the use of the so-called FAIR, i.e. 'Findable, Accessible, Interoperable, Reusable' principles

- and identification of metadata that are essential for regulatory decision-making on the choice of data source. (45)

Milestones achieved

- A list of metadata to describe RWD sources and studies for regulatory purposes is publicly available on the EMA website since June 2022. (11) The list serves as basis for the development of an electronic catalogue of metadata of existing RWD sources. (11, 93)
- In September 2022, draft guidance on the use of the proposed metadata catalogue of RWD sources was made available for public consultation on the EMA website. (11)

Activities ongoing

In 2021, the work to construct the public interface to access the aforementioned metadata catalogue via the EMA website has been initiated and populating of the catalogue has started. (93)

Deliverables

- Launch of the metadata catalogue of RWD data sources (to replace the ENCePP database) and of a catalogue containing information on studies performed using these data sources (to replace the EU PAS Register) (planned for Q4 2023) (11, 93, 89)
- Implementation of standardized study protocols (89)
- Evaluation of the usability of eHealth and social media data to augment existing RWD data sources (anticipated by Q4 2023 and Q4 2024, respectively) (89)

Recommendation IV: “Develop EU Network skills in Big Data” (45)

The BDTF identified the need to enhance the expertise and skills of the EMRN in big data and recommended for the following measures to be taken to develop the EMRN’s capabilities to interpret and advise on big data:

- development of a *“big data training curriculum and strategy based on a skills analysis across the Network”* (45),
- collaboration with external experts
- and targeted recruitment of data scientist and experts in the fields of statistics, omics, epidemiology, advanced analytics and artificial intelligence (AI) to enhance the EMRN’s capability to receive, manage and analyze big data. (45)

Milestones achieved

In 2020 and 2021, three training curricula on big data were adopted by the BDSG: a curriculum on data science, a curriculum on pharmacoepidemiology and RWE as well as a curriculum on biostatistics and clinical trial methodology. (93) In April 2022, the EMA launched a call for tender to select external training providers to deliver the content for these three curricula. (96)

Deliverables

- Delivery of big data curricula trainings (planned for 2022 – 2025) (89)
- Training modules to be offered to the wider public (planned for Q4 2023) (89)

Recommendation V: "Strengthen EU Network processes for Big Data submissions" (45)

Besides consideration of data quality and representativeness, the acceptability of evidence is determined by factors such as the methods used for evidence generation, the measures taken to manage potential confounding and bias, and, ultimately, by the research context (i.e. the nature of the disease under study, the scientific questions to be answered, the level of risk involved, available treatment options, unmet medical need, etc.). (45) This is true regardless of the study type the evidence is obtained from. However, acceptability evaluation might hold additional challenges for regulators if the evidence is derived from less highly controlled observational studies, as compared to RCTs. (45) To strengthen the EMRN's processes for submissions including big data, the BDTF recommended the following approaches:

- initiation of a big data learnings initiative, in such a way that submissions including big data are tracked, outcomes reviewed and the learnings used to inform the development of guidance
- and enhancement of the EU PAS Register to promote transparency on study methods. (45)

Milestones achieved

- In 2021, routine processes were established for the PRAC to access RWD to support its decision-making. (93)
- A 'learnings initiative' workshop was held in November 2021, the results of which will inform follow-on activities (such as guidance development) in 2022-2023. (93)

Activities ongoing

Pilots on the use of EMRN-generated RWE to support regulatory decision-making are ongoing with a number of the EMA's scientific committees. (89, 93) The RWE use cases explored during these pilots include various safety use cases (e.g. RWE used to inform effectiveness assessments of risk minimization measures or to support safety signal evaluation) as well as orphan and pediatric procedures (e.g. RWD used to inform about disease prevalence in general or in selected populations). (97)

Deliverables

- Incremental publication of the reports on the above-mentioned RWE pilot studies; final report to be published after completion of all pilots (by Q1 2025) (89)
- Development of a portfolio of EMRN RWE use cases and publication of these use cases (2023 – 2025) (89)

Recommendation VI: "Build EU Network capability to analy[z]e Big Data" (45)

The current European regulatory system does not provide for raw data, i.e. patient level data (PLD), from clinical studies to be routinely included into marketing authorization or variation applications. (45, 98) The regulatory assessment mainly relies on data provided in aggregated form, not allowing for data re-analysis. (98) As a consequence, the EMRN does not currently have sufficient computational capacities and no routine processes in place to analyze large data sets. (45) In view of the fact that the data landscape has significantly changed over the last decade and science and technology are rapidly evolving, the BDTF recommended to build the EMRN's capability to analyze big data by:

- building the EMRN's computing capacity *"to receive, manage and analy[z]e Big Data including PLD from clinical trials, [to enable] regulators [to] validate analyses performed by the industry and test assumptions"* (45),
- establishing a network of data analytics centers
- and strengthening the EMRN's expertise in AI. (45)

Milestones achieved

- A workshop on AI and machine learning in medicines regulation was held in 2021, resulting in two top priorities being identified: the development of a framework to access and validate AI and of a framework in support of the development of AI guidelines. (93)

- Work on a discussion paper on ‘Clusters of Excellence’, i.e. data analytics centers of excellence at member state level, has been initiated in 2021. (93)

Activities ongoing

In July 2022, the EMA launched a two-year proof-of-concept pilot with the ‘Committee for Medicinal Products for Human Use’ (CHMP) to evaluate benefits and practicality of an integration of clinical raw data analyses in the scientific assessment of medicines and to inform the EMRN on the future role of raw data analysis in regulatory decision-making. (89, 11, 98) Applicant participation in the pilot is voluntary. (98)

Deliverables

- Publication of a reflection paper on AI use in regulatory processes (planned for Q3 2022) and subsequent development of AI guidelines (planned for 2024) (89)
- Review of the EMRN’s computing capacities and capabilities to analyze big data and subsequent delivery of recommendations (2023 – 2024) (89)
- Delivery of enhanced EudraVigilance data analytics (planned for 2024) (89)
- Launch of a new EudraVigilance system website (planned for Q4 2024) (89)

Recommendation VII: “Moderni[z]e the delivery of expert advice” (45)

This BDTF recommendation is aimed at strengthening the EMRN’s ability to provide expert advice in the field of big data by consolidating and re-organizing the EMA’s working party structure and establishing a ‘Methodologies Working Party’ to encompass biostatistics, advanced analytics, modelling and simulation, extrapolation, pharmacokinetics, RWD as well as epidemiology and an ‘Omics Working Party’ building on and reinforcing the existing pharmacogenomics working party. (45)

Milestones achieved

- EMA management board adoption of the establishment of the aforementioned ‘Methodologies Working Party’ in 2021 (93)
- Publication of a new guideline on registry-based studies in October 2021 (93)
- Publication of the tenth revision of the ‘ENCePP Guide on Methodological Standards in Pharmacoepidemiology’ in June 2022, including a new chapter on AI in pharmacoepidemiology and a new chapter on RWE and pharmacoepidemiology (19, 41)

Deliverables

- Formation of the new ‘Methodology Working Party’ (planned for Q4 2022 – 2023) (89)
- Publication of a data and methods guidance roadmap (planned for Q1 2023) (89)
- Strengthening of expert advice on AI and RWE through the establishment of dedicated *“European Specialized Expert Communities”* (89) in these fields (2023 – 2025) (89)
- Establishment of a clinical trial raw data cluster of excellence (2023 – 2025) (89)

Recommendation VIII: “Ensure data are managed and analy[z]ed within a secure and ethical governance framework” (45)

Data sharing and secondary use of data bears challenges in terms of data protection (how to share data while maintaining both, patient privacy and the scientific value of the data) and data ethics. The latter includes considerations about data privacy, ownership, trust and measures of accountability. (45) The BDTF recommended the following activities and measures to ensure for big data to be managed and analyzed within a secure and ethical data governance framework:

- engaging with relevant stakeholders regarding EU data protection requirements (45)
- and stakeholder engagement (patients and healthcare professionals (HCPs)) on data governance as well as establishment of an ethics advisory committee. (45)

Activities ongoing

The EMA, in consultation with the EC and the European Data Protection Supervisor, is working on finalizing guidance on the application of the EU data protection legislation within the context of secondary use of health data in support of drug development, evaluation and post-authorization surveillance. (11)

Deliverables

- Delivery of training on data protection (planned for Q4 2022 – 2025) (89)
- Continuous support of TEHDAS in its preparations for the future EHDS and conduct of a preliminary assessment of the impact of the EHDS on medicines regulation (2023 – 2024) (89)

- Strengthening the BDSG's ethics expertise (by Q3 2023) and review of options for an ethics framework (planned for Q4 2023) (89)

Recommendation IX: "Collaborate with international initiatives on Big Data" (45)

The BDTF identified the need for international collaboration to unleash the full potential of big data. (45) Measures recommended by the BDTF to address this need are:

- engagement in the development of internationally harmonized guidelines,
- development and implementation of a data standardization strategy
- as well as best practice sharing and bilateral collaboration with international partners. (45)

Milestones achieved

- The EMRN 'Data Standardization Strategy', aimed at guiding and supporting the creation and implementation of internationally applicable data standards, was published in December 2021. (11, 89)
- In June 2022, the EMA, the U.S. FDA and HC co-chaired an workshop on RWE under the umbrella of the 'International Coalition of Medicines Regulatory Authorities' (ICMRA). (99) One of the workshop outputs was a call for international collaboration to enable RWE for regulatory decision-making, published in July 2022. (99)

Ongoing activities

- International collaboration on a framework for RWE is ongoing (89)
- Active involvement of the EMRN in the development of the new ICH M11 guideline (89)

Recommendation X: "Create an EU Big Data 'stakeholder implementation forum'" (45)

Besides international collaboration and coordination, the BDTF identified active engagement with stakeholders on European level, including patients, HCPs, industry, HTA bodies, payers and notified bodies as a key priority and means to leverage synergies and foster the transformation to a data-driven regulation of medicines. (93, 45) In accordance with the recommendations of the BDTF, the BDSG has established dedicated fora to facilitate the exchange of information and promote stakeholder collaboration, for example, an annual big data stakeholder forum, a biannual industry meeting, topic-specific workshops, etc. (45, 89)

The activities and approaches described above tie in with various other strategic initiatives of the EMRN including:

- the *“European medicines agencies network strategy to 2025”* (16), in particular, with the strategic focus area *“Data analytics, digital tools and digital transformation”* (16),
- the *“EMA Regulatory Science Strategy to 2025”* (100), in particular, with the core recommendations *“Exploit digital technology and artificial intelligence in decision making”* (100), *“Promote use of high-quality real-world data (RWD) in decision-making”* (100) and *“Develop network competence and specialist collaborations to engage with big data”* (100) which support the strategic goal “*Advancing patient-centered access to medicines in partnership with healthcare systems*” (100)
- and the *“European strategy for data”* (101) which laid the foundation for the EC’s *“Proposal for a Regulation […] on the European Health Data Space”* (90).

3.3.4 Research projects

The initiatives of the HMA, EMA and the EC to harness the potential of big data are supported and informed by various research projects. In the following, a brief summary is given of the so-called MINERVA project, a recently completed research project sponsored by the EMA. Furthermore, three research initiatives sponsored through the European research and innovation program Horizon Europe are introduced.

Metadata for data dIscoverability aNd study rEplicability in obseRVAtional studies (MINERVA) project (95)

The EMA commissioned research project MINERVA (EU PAS Register number: EUPAS39322) was aimed at addressing the need to improve data discoverability in accordance with priority recommendation III of the BDTF. (95, 102) The MINERVA project informed the creation of the previously mentioned list of metadata to characterize RWD sources and studies as well as the development of the draft *“Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources”* (103). (95, 103) Both documents are available on the EMA’s big data webpage. (11)

Horizon Europe research initiatives

In 2021, the EC published, among others, calls for proposals for the following three topics under its Horizon Europe research and innovation program:

- HORIZON-HLTH-2021-TOOL-06-03: *"Innovative tools for use and re-use of health data (in particular of electronic health records and/or patient registries)"* (104)
- HORIZON-HLTH-2022-IND-13-05: *"Setting up a European Electronic Health Record Exchange Format (EEHRxF) Ecosystem"* (105)
- HORIZON-HLTH-2022-TOOL-11-02: *"New methods for the effective use of real-world data and/or synthetic data in regulatory decision-making and/or in health technology assessment"* (106)

The research projects funded/ to be funded under these topics should help cover the needs of the EMRN's 'big data initiative' outlined in the previous section and support the delivery and optimal use of DARWIN EU® and the EHDS. In December 2021, the EMA published a note declaring its willingness to participate in projects under the umbrella of HORIZON-HLTH-2022-TOOL-11-02, for example, as a project steering group member. (107)

3.3.5 Guidance documents

Listed below are the new/ revised guidance document issued under the EMRN's big data initiative so far:

- *"Guideline on registry-based studies"* (108) – issued October 2021 (108)
- *"The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 10)"* (19) – issued June 2022 (41)

3.4 Comparative analysis of the RWD/ RWE landscapes in the USA and the EU

The RWD/ RWE landscapes in the USA and the EU described in the previous sections might look quite different at first sight but besides differences, there are many commonalities and consensus exists on many key aspects. In the following, a comparative overview is given of the RWD/ RWE ecosystems in the USA and the EU, covering the aspects: legal basis, RWD/ RWE definitions, general concepts and considerations around RWD/ RWE as well as efforts towards a learning healthcare system.

3.4.1 Legal basis

The U.S. FDA’s RWE program was launched to fulfill the RWE provisions of the Cures Act, mandating the FDA to evaluate the potential use of RWE to support regulatory decision-making on new indications for drugs already approved or to support or satisfy post-authorization study requirements. (20) For the European ‘big data initiative’, by contrast, there is no comparable legal basis. However, the recommendations made by the BDTF are in conformity with the existing European legal frameworks.

3.4.2 Definitions of RWD/ RWE

The European and the U.S. FDA’s definition of RWD are widely identical in wording. Both definitions speak of RWD to be patient health status or delivery of health care related data *“routinely collected from a variety of sources”* (20). (21) The FDA’s definition of RWD seems to be a bit broader though, since data collected in the course of traditional clinical trials are not explicitly excluded, as it is the case in the EU definition. (20, 21) With regard to the definitions of RWE, the European definition seems to include all evidence derived from the analysis of RWD, while the FDA’s definition specifies for RWE to be *“clinical [RWD-derived] evidence about the usage and potential benefits or risks of a medical product”* (20). (21) Hence, the FDA’s definition of RWE seems to be more restrictive as compared to the European one. The U.S. and the EU definitions of RWD and RWE do not contradict each other but are largely congruent. Regarding RWD, the U.S. definition is a bit broader in scope than the respective EU definition, while, on the other hand, the EU definition of RWE is broader than the FDA’s definition of this term. An illustration of this is provided in Figure 2 below.

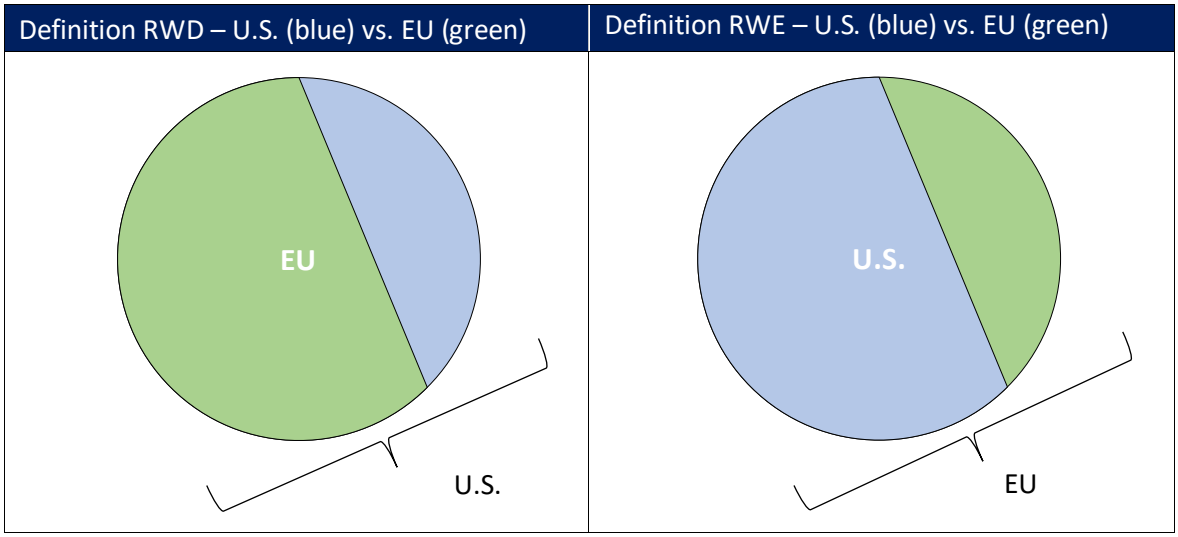

Figure 2: Visual comparison of the U.S. and EU definitions of RWD and RWE

Basically, none of the definitions is particularly specific and all leave room for interpretation, which bears the risk of inconsistent use and constitutes a potential source of misunderstandings. For instance, the term ‘traditional clinical trial’ used in the EU definition of RWD is not further defined and the phrase ‘data from a variety of sources’ which is used both in the U.S. and the EU definition of RWD is not very specific. A recently published ICMRA statement on RWD/ RWE suggests that there is agreement between European and U.S. regulators to the effect that efforts are required towards the establishment of globally harmonized definitions for RWD/ RWE *“with clear scope and level of granularity”* (30).

3.4.3 General concepts and considerations around RWD/ RWE

The concepts and considerations outlined in the U.S. FDA’s RWE framework, the European OPTIMAL framework and in other relevant publications, such as the BDTF reports or the Sentinel System five-year strategy, suggest for the FDA and the EMRN to be generally aligned when it comes to challenges and opportunities seen in the use of RWD/ big data and RWE to inform regulatory decision-making and criteria to be met for RWE to be acceptable for regulatory purposes. For example, there is mutual agreement to the effect that RWE acceptability is determined by factors such as the adequacy of the study design and the analysis methods to answer the research question as well as the quality, relevance and representativeness of the underlying data. (20, 21, 45) It is important to note though, that on the part of the EU no official document exists, comparable to the FDA’s RWE framework, which specifically addresses the EMA’s/ EMRN’s views and perspectives on the use of RWD/ RWE for regulatory purposes. Unlike the FDA’s RWE framework, the European OPTIMAL framework for regulatory use of RWE was published as an article in a scientific journal rather than as an official statement of the EMA/ EMRN. The reports of the HMA-EMA BDTF cover RWD/ RWE, but only in the wider context of big data and without providing a clear differentiation between the terms RWD and big data.

Challenges identified both by the U.S. FDA and the EMRN in regard to the use of RWD/ big data for regulatory purposes include the lack of uniformity of existing RWD sources (in terms of data quality, data elements captured, data standards used, etc.), susceptibility of observational studies to the effects of bias and confounding, issues with respect to data ethics and transparency and the lack of harmonized operational definitions of the terms RWD and RWE. (20, 21, 45, 30) There is agreement between European and U.S. regulators

that international collaboration and alignment is required to adequately address some of these challenges. This is underlined by the previously mentioned ICMRA *“call for international collaboration to enable RWE for regulatory decision-making”* (99), initiated by the EMA, the U.S. FDA and HC. (30) In this statement, ICMRA members pledge for international collaboration to achieve

- harmonization of RWD/ RWE terminologies, guidance and best practices,
- preparedness to address future public health challenges
- and enhanced transparency in regard to observational studies. (30)

A challenge which is unique to the EU, is the necessity to upscale the EMRN’s IT capabilities and capacities and to strengthen the EMRN’s expertise in big data analytics to enable the EMRN to analyze raw data to test hypotheses and validate analyses performed by applicants.

3.4.4 Efforts towards a learning healthcare system

There is agreement on the part of U.S. and EU regulators that secure RWD networks and associated RWE-generation platforms, such as the Sentinel System and the European DARWIN EU®, hold the potential of realizing the vision of a learning health system. (45, 48) As outlined in chapter 3.1.1, such systems can not only support post-marketing pharmacovigilance activities but also other research beyond the field of drug safety. While the U.S. Sentinel System is well established – it was initially launched in 2016 and has, since then, continually been expanded – the European counterpart, DARWIN EU®, as well as the associated EHDS, is currently still under development. (48, 88) Even though the FDA has readily shared their knowledge on how to set up and operate a secure distributed data network with regulators and researchers around the world, including the EU, (48) there are a number of challenges unique to the EU that need to be addressed for the EHDS to become a reality. An analysis of existing European healthcare databases, conducted a few years ago, revealed that the number of those databases that were readily accessible and met minimum requirements that would allow utilization across a range of regulatory use cases was low. (21) According to information currently provided on the website of the EC, the degree of readiness for the EHDS still varies between the EU member states. (109) Furthermore, it is stated that *"[t]o make the EHDS a reality, further digitali[z]ation is needed at national level […] [and] interoperable EU-wide infrastructures [need to be set up] to enable the cross-*

border use of health data in the EU" (109). While, on the European level, the establishment of a common health data space and the sharing and the secondary use of data across this space is challenged by the fact that the EU is an association of sovereign states with different languages, healthcare systems, country-specific regulations and disparities in clinical practice, the established U.S. systems are also faced with challenges. For example, patients in the USA, unlike in many European countries, are not assigned one unique patient identification number. (20, 21, 110) This poses challenges when it comes to long-term tracking of outcomes, as patients may move between insurance schemes. (20, 45, 110) As touched upon previously, addressing such challenges is one of the aims defined by the FDA in its RWE Framework, for example, by developing methods to address duplication of information in different RWD sources and tools to enable linkage of a single patient's data across data sets while safeguarding the patient's privacy. (20)

4. The wider picture – RWD/ RWE-related activities outside of the USA/ EU and harmonization efforts on ICH level

4.1 RWD/ RWE-related activities outside of the USA and the EU

The interest in leveraging RWD to support regulatory decision-making across the product lifecycle is not limited to the USA and the EU but is a widespread phenomenon. Several regulatory authorities across the globe have issued position papers and/ or country-specific guidance documents on the use of RWD/ RWE in regulatory contexts. Table 1 below provides a breakdown of countries in which RWD/ RWE-related guidance has been published by local authorities. Besides listing the respective guidelines, the table includes country-specific definitions of RWD/ RWE and brief overviews on the acceptance of RWD/ RWE for regulatory purposes by the respective authorities. No claims for comprehensiveness are made for the information provided in Table 1.

Table 1: Breakdown of countries in which RWD/ RWE-related guidance has been issued by local authorities

Australia
Guidance documents/ official statements regarding RWD/ RWE
In response to a review commissioned by the Australian 'Therapeutic Goods Administration' (TGA) regarding the usage of RWE and patient reported outcomes (PROs) in the Australian medicines and medical device regulation, the below statement and report was published in 2021: *"Real world evidence and patient reported outcomes in the regulatory context, Version 1.0"* – November 2021" (49) (available online: https://www.tga.gov.au/sites/default/files/real-world-evidence-and-patient-reported-outcomes-in-the-regulatory-context.pdf) (49)
Definitions of RWD/ RWE
The adoption of an Australian definition of RWE is planned for 2022. (111) According to the above-mentioned publication, *"the TGA should consider adopting a broad definition of [.] RWE [..] in the regulatory context based on [that] of the US FDA and Health Canada: RWE: 'clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of Real World Data, usually collected outside of the clinical trial (for therapeutics) or investigational testing (for medical devices) setting'"* (49).
Acceptance of RWD/ RWE
• RWE is already considered by the TGA for regulatory purposes, mainly in the post-approval phase in the context of drug/ medical device safety. (49) • According to the above-mentioned statement and report, well designed clinical trials are foreseen to *"remain the main means of evidence generation in most cases"*(49), but TGA sees potential for RWE to help inform decisions about extensions of indications, potential repurposing of drugs, or in situations where the conduct of RCTs is not feasible or ethical. (49) • Over the coming years, the TGA intends to undertake a set of actions to foster the use of RWE in appropriate pre-market settings, including potential adoption or adaptation of relevant guidance documents developed by regulators such as the EMA, the U.S. FDA or HC. (49, 111) • Early consultation with regulatory authorities is recommended for applicants intending to submit dossiers including RWD-based evidence to underpin the application. (49)
Canada
Guidance documents/ official statements regarding RWD/ RWE
The following official statements regarding the use of RWE in the context of regulatory decision-making on drugs and medical devices are available on the official website of the Government of Canada: • HC's notice on *"Optimizing the Use of RWE to Inform Regulatory Decision-Making"* (50) – April 2019 (available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html),

Canada (continued)
Guidance documents/ official statements regarding RWD/ RWE
• the accompanying document *"Elements of RWD/E Quality Throughout the Prescription Drug Product Life Cycle"* (112) – March 2019 (available online: https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html) • and HC's *"A strategy to optimize the use of real world evidence across the medical device life cycle in Canada"* (113) – March 2020 (available online: https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/real-world-evidence-medical-device-strategy.html). (50, 112, 113)
Definitions of RWD/ RWE
The Canadian definitions of RWD and RWE are almost identical in wording to the RWD/ RWE definitions adopted by the U.S. FDA in 2018. As per the publication on 'Elements of RWD/E Quality Throughout the Prescription Drug Product Life Cycle', RWD/ RWE are defined as follows: • RWD *"are data relating to patient status and/or the delivery of health care routinely collected from a variety of sources"* (112). • RWE *"is the evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD"* (112).
Acceptance of RWD/ RWE

• RWE already plays a part both in Canada's pre- and post-market drug regulatory processes. (50)
• Prospectively planned clinical trials are still deemed the most robust tool for generation of sound evidence to inform marketing authorization decisions, but HC encourages applicants to submit high-quality RWE to support regulatory decisions
  ○ about possible expansions of indications for populations often excluded from clinical trials and
  ○ about drugs in areas where controlled clinical trials are unethical or unfeasible. (50)
• According to HC, the quality of RWE is, inter alia, determined by the quality of the underlying data, the scientific question of interest, the study design, the statistical analyses and methods used as well as the manner in which the results are interpreted. (50, 112) In regard to protocol development for RWE studies, HC requests consideration of certain key elements which are reflective of the 'ENCePP Protocol Checklist' and the 'Guidelines for Good Pharmacoepidemiology Practices' defined by the ISPE (112)
• Prior consultation with HC is required from applicants intending to submit dossiers including RWE as pivotal evidence to underpin a MAA. (50)

China
Guidance documents
In 2020 and 2021, the below guidelines on the use of RWD/ RWE in the context of regulatory decision-making on drugs were published in China: • National Medical Products Administration (NMPA) Announcement No. 2020/1: *"Guidelines for Real World Evidence Supporting Drug Development and Review (Trial)"* (114) – January 2020 (non-official English translation available in the Clarivate™ 'Cortellis Regulatory Intelligence' (RI) database),

China (continued)
Guidance documents
• Center for Drug Evaluation (CDE) Notification No.2020/22: *"Technical Guidelines on Pediatric Drug Development and Review Supported by Real-World Evidence (Trial)"* (115) - August 2020 (non-official English translation available in the Clarivate™ Cortellis RI database), • CDE Notification No.2021/27: *"Guidelines for Real-world Data used to Generate Real-world Evidence (Tentative)"* (22) – April 2021 (non-official English translation available in the Clarivate™ Cortellis RI database). (114, 115, 22)
Definitions of RWD/ RWE
The Chinese definitions of RWD/ RWE are similar in wording to the RWD/ RWE definitions adopted by the U.S. FDA. As per the above-mentioned CDE Notification No.2021/27, • RWD are defined as *"data relating to patient health status and/or the delivery of diagnosis, treatment and health care collected from routine practice"* (22) • and RWE is defined as *"the clinical evidence regarding the use and potential benefits-risks of a drug obtained from proper and sufficient analysis of fit-for-use RWD"* (22).
Acceptance of RWD/ RWE
• As per the NMPA's announcement no. 2020/1, the systematic use of RWE for regulatory decision-making in China is still in its early stages. (114) • The concepts around RWD/ RWE outlined in the guidance document no. 2020/1, which include considerations around benefits and limitations of RWE use in a regulatory context, possible regulatory use cases of RWE, clinical research settings that can generate RWE as well as quality aspects of RWD/ RWE and ways to manage challenges in that respect, are broadly in line with the concepts presented in the U.S. FDA's framework for its RWE program of 2018. (114) • Applicants intending to use RWE to support a marketing authorization are recommended to consult with the regulatory authorities prior to initiation of the respective RWE study/ies. (114)
Japan
Guidance documents/ official statements regarding RWD/ RWE
In recent years, several RWD/ RWE-related notifications and administrative notices were published in Japan. Listed below are those guidelines and statements for with English translations are available on the official website of the Japanese 'Pharmaceutical and Medical Devices Agency' (PMDA): • *"Guidelines for the Conduct of Pharmacoepidemiological Studies in Drug Safety Assessment with Medical Information Databases"* (116) – March 2014 (available online: https://www.pmda.go.jp/files/000240951.pdf),

Japan (continued)
Guidance documents/ official statements regarding RWD/ RWE
• Pharmaceutical Safety and Environmental Health Bureau (PSEHB)/ Pharmaceutical Evaluation Division (PED) Notification No. 0221-1: *"Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs"* (117) – February 2018 (available online: https://www.pmda.go.jp/files/000243761.pdf), • PSEHB/ Medical Device Evaluation Division (MDED) Notification No.1219-4: *"Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Medical Devices"* (118) – December 2018 (available online: https://www.pmda.go.jp/files/000243762.pdf), • PMDA: *"Procedures for Developing Post-marketing Study Plan"* (119) – January 2018 (available online: https://www.pmda.go.jp/files/000226080.pdf), • PSEHB/ PED Administrative Notice: *"Questions and Answers (Q&A) on Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Drugs"* (120) – June 2019 (available online: https://www.pmda.go.jp/files/000243763.pdf), • PSEHB/ MDED Notification No.0323-4: "*Points to Consider for Ensuring the Reliability of Post-marketing Database Study for Regenerative Medical Products"* (121) – March 2020 (available online: https://www.pmda.go.jp/files/000243764.pdf), • PSEHB/ PED/ MDED Notification No.0323-1: *"Basic principles on Utilization of Registry for Applications"* (122) – March 2021 (available online: https://www.pmda.go.jp/files/000240806.pdf), • PSEHB/ PED/ MDED Notification No.0323-2: *"Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications"* (123) – March 2021 (available online: https://www.pmda.go.jp/files/000240807.pdf), • PMDA Chief Executive's statement on *"Utilization of Real World Data - PMDA's approaches"*(124) – March 2021 (available online: https://www.pmda.go.jp/english/about-pmda/0004.pdf). (116–124)
Definition of RWD
The Japanese definition of RWD is similar in wording to the U.S. FDA's definition of RWD. As per the above-mentioned PSEHB/ PED notification no. 0323-1, RWD is defined as: *"Data on patient's health conditions and/or provided medical practices routinely collected from various data sources"* (122).
Acceptance of RWD/ RWE
• RWD/ RWE already plays a part in Japan's regulatory process, both in the context of drug safety and efficacy evaluations. (15) • The evidence of efficacy and safety required for a marketing authorization should, from the PMDA chief executive's perspective, be produced through the conduct of RCTs. Notwithstanding this, PMDA may accept RWE of adequate quality in some cases, for instance, if the conduct of a controlled clinical trial is not feasible, evidence derived from a RWD-based external control arm may be considered. (15) • Prior consultation of PMDA is recommended for applicants intending to include RWD/ RWE in a regulatory submission, especially if the demonstration of product efficacy and safety is based on RWE as the major evidence. (15)

South Korea
Guidance documents
In 2019, the following guidance on the application of RWE to support medical device licensing or review was published by the Korean 'Ministry of Food and Drug Safety' (MFDS): *"Guideline on Application of the Real-World Evidence (RWE) for Medical Devices (Instructions to Civilian Applicants)"* (125) – February 2019 (non-official English translation available in the Clarivate™ Cortellis RI database). (125) According to the latest version, dated June 2022, of the 'Clarivate™ Regulatory Summary on Clinical Research for South Korea', available in the Clarivate™ Cortellis RI database, regulatory guidance on the use of RWD for post-marketing safety studies of drugs is provided in the MFDS guidelines listed below: • Guide-0020-06: *"Guideline on Risk Management Plan (RMP) for Medicines"* (126) – December 2020*, • Guide-1128-01: *"Guidelines for Research on Medical Information Databases"* (126) – June 2021*. (126)
Definitions of RWD/ RWE
In the context of the Korean medical device regulation, RWD and RWE are defined as follows: • RWD *"is a comprehensive [.] term for various types of medical data not collected in clinical trials conducted by existing interventional methods"* (125). • *"RWE refers to clinical evidence related to results, potential benefits or risks of the use of medical devices obtained by analysis of real-world data"* (125).
Acceptance of RWD/ RWE
According to the aforementioned Clarivate™ Regulatory Summary on Clinical Research for South Korea of June 2022, the MFDS's activities regarding the use of RWE in the drug regulatory process are currently focused on post-market safety surveillance. (126)
Switzerland
Guidance documents/ official statements regarding RWD/ RWE
In July 2022, the 'Swiss Agency for Therapeutic Products', Swissmedic, published a position paper on RWE on their official website, the *"Swissmedic position paper on the use of real world evidence"* (127) – July 2022 (available online: https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl/positionspapier-verwendung-real-wordl-evidence.pdf.download.pdf/Positionspapier%20RWE_EN.pdf). (128)
Definitions of RWD/ RWE
The Swiss definitions of RWD/ RWE come close to the EU definitions cited in section 2.2.2 of this thesis. According to the aforementioned position paper, Swissmedic defines RWD and RWE as follows: • RWD is *"all data other than those collected through a clinical trial conducted as per ICH GCP"* (127).

Switzerland (continued)
Definitions of RWD/ RWE
• *"RWE is defined as information derived from analyses of RWD"* (127).
Acceptance of RWD/ RWE
• Swissmedic requires data from adequate clinical trials for new MAAs and variation applications aimed at broadening the therapeutic indication of a medicinal product. In these regulatory settings, RWE is only accepted as a complement to clinical trial data. (127) • Post-marketing variation applications affecting risk minimization measures or aimed at modifying the therapeutic use of a medicinal product may be based solely on RWE, provided the evidence is of adequate quality. (127) • Swissmedic recommends applicants intending to submit RWE to support a MAA or variation application aimed at broadening the therapeutic indication of a medicinal product to seek for a pre-submission meeting. (127)
Taiwan
Guidance documents
In 2020 and 2021, the following guidance documents on the use of RWD/ RWE in the context of regulatory decision-making were published by the Taiwan Food and Drug Administration (TFDA): • TFDA Announcement No.1091405905: *"Guidance on Basic Considerations on Drug Development Supported by Real-world Evidence"* (129) – July 2020 (non-official English translation available in the Clarivate™ Cortellis RI database), • TFDA Announcement No.1091413558A: *"Study Design with Real World Evidence: Keypoints to Consider in Pragmatic Clinical Trials"* (130) – January 2021*, • TFDA Announcement No.1101401345A: *"Real World Evidence: Consideration for evaluating data relevance and reliability"* (130) – March 2021*, • TFDA Announcement No.1101406217A: *"Issues on Using Real-world Data/Real-world Evidence as Drug Review Technical Dossier for Drug Application"* (131) – July 2021 (non-official English translation available in the Clarivate™ Cortellis RI database). (129, 131, 130)
Definitions of RWD/ RWE
The Taiwanese definitions of RWD/ RWE come close to the RWD/ RWE definitions adopted by the U.S. FDA. As per the above-mentioned announcement no. 1091405905, TFDA defines RWD and RWE are as follows: • RWD *"refers to many types of data that are routinely collected in relation to patient health status or that are obtained from the health care process"* (129). • RWE *"refers to clinical evidence that is produced by applying appropriate analytic methods to real-world data sources"* (129).

Taiwan (continued)
Acceptance of RWD/ RWE
• The TFDA's considerations on drug development supported by RWE, as set out in its announcement no. 1091405905, take up many aspects of and are generally in line with the U.S. FDA's framework for its RWE program of 2018. • As per the aforementioned announcement, possible areas of application of RWE include *"improving and aiding clinical trial design, secondary evidence of drug pre-market efficacy, post-market drug monitoring and safety evaluations, and post-market package insert information modifications"* (129). • TFDA encourages the inclusion of RWE in regulatory submissions but recommends applicants to consult with the regulatory authorities at an early stage of study planning to ensure the RWE generated is suited for supporting regulatory decision-making. (131)
United Kingdom (UK)
Guidance documents
In 2021, two guidance documents on the use of RWD to support regulatory decisions were published by the UK 'Medicines and Healthcare products Regulatory Agency' (MHRA): • *"MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions"* (132) – December 2021 (available online: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions), • *"MHRA guideline on randomi[z]ed controlled trials using real-world data to support regulatory decisions"* (133) – December 2021 (available online: https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guideline-on-randomised-controlled-trials-using-real-world-data-to-support-regulatory-decisions). (132, 133)
Definitions of RWD/ RWE
The UK definitions of RWD and RWE come close to the EU definitions cited in section 2.2.2 of this thesis. As per the above-mentioned guidance on the use of RWD in clinical studies, MHRA defines RWD as follows: *"RWD are defined as data relating to patient health status or delivery of health care collected outside of a clinical study"* (132). With regard to RWE, the aforementioned guideline states: *"When such [real-world] data are analy[z]ed, the information produced may be referred to as real-world evidence (RWE)"* (132)
Acceptance of RWD/ RWE
• As per the guidance on the use of RWD in clinical studies, *"the MHRA encourages sponsors to explore the opportunities presented by the utili[z]ation of RWD"* (132) and invites those interested in using RWD in their development programs to seek MHRA scientific advice on specific proposals. (132)

United Kingdom (continued)
Acceptance of RWD/ RWE

• Regarding RCTs using a RWD source, the corresponding MHRA guideline states that
  ○ evidence derived from such a trial is not principally considered less valuable for supporting regulatory decisions than evidence generated from a traditional RCT, provided that the RWD using trial is well-designed and the data is robust. (133)
  ○ these kinds of trials are considered most suitable for supporting regulatory decisions on label changes for products already authorized, extensions of indications, repurposing of existing medicinal products, or changes in dose or route of administration. However, the MHRA does not rule out further RWD use cases, including the investigation of new drugs. (133)
• There is currently no specific MHRA guidance on other types of studies that could be conducted using RWD, for example, observational studies, or clinical trials using RWD as a control arm.

* Currently no English translation of this document available in the Clarivate™ Cortellis RI database or on the website of the respective competent authority

As mentioned in the previous chapter, the U.S. and the EU definitions of RWD and RWE are not fundamentally different but largely congruent. Table 2 below compares the RWD/ RWE definitions adopted in the countries listed in Table 1 against the U.S. and EU definitions. Table 3 provides an overview of whether reference is taken to U.S. and/ or European RWD/ RWE-related literature in the country specific guidance documents/ official statements regarding RWD/ RWE cited in Table 1 above. Table 2 and 3 show that often both U.S. and European literature is taken reference to and that the 'rest of the world' RWD/ RWE definitions are either largely in line with the U.S. or the EU RWD/ RWE definitions with a tendency towards more 'U.S.-like' definitions. This represents a solid foundation and important starting point for efforts towards a global harmonization of definitions of RWD and RWE.

Table 2: Comparative overview of U.S., EU and 'rest of the world' RWD/ RWE definitions

Country	Definition of	Level of accordance with EU (green) or U.S. FDA's (blue) RWD/ RWE definitions		
		Basically identical	Minor differences	Major differences
Australia	RWD	No official RWD/ RWE definitions adopted as of October 2022		
	RWE			
Canada	RWD			
	RWE			
China	RWD			
	RWE			
Japan	RWD			
	RWE	No RWE definition available to the author		
South Korea	RWD			
	RWE			
Switzerland	RWD			
	RWE			
Taiwan	RWD			
	RWE			
UK	RWD			
	RWE			

Refers to the U.S. Refers to the EU

Table 3: U.S./ European literature taken reference to in the documents listed in Table 1

Country	U.S. (blue)/ European (green) literature that is taken reference to in the guidance documents/ official statements listed in Table 1
Australia	FDA's RWE framework, RWD/RWE-related FDA guidance documents
	EMA draft guideline & discussion paper on the use of registries for regulatory purposes

Country	U.S. (blue)/ European (green) literature that is taken reference to in the guidance documents/ official statements listed in Table 1
Canada	No reference sections included in the HC publications listed in Table 1
China	FDA’s RWE framework, other RWD/RWE-related U.S. literature
	European RWD/ RWE-related literature
Japan	No reference to RWD/ RWE-related U.S./ European literature is made in the Japanese guidance documents listed in Table 1
South Korea	FDA guidance on RWE use to support regulatory decision-making for medical devices, other RWD/RWE-related U.S. literature
	European RWD/ RWE-related literature
Switzerland	No reference section included in the Swissmedic publication listed in Table 1
Taiwan	FDA’s RWE framework, RWD/RWE-related FDA guidelines, other RWD/RWE-related U.S. literature
UK	FDA’s RWE framework
	HMA-EMA Joint BDTF Phase II report, other European RWD/RWE related literature

Refers to the U.S. Refers to Europe

4.2 RWD/ RWE- related harmonization efforts at international level

There is widespread agreement among regulators that there is an urgent need for international harmonization of terms and terminologies in relation to, as well as of guidelines on, RWD/ RWE to reduce confusion around this topic and foster an effective integration of RWD/ RWE into regulatory decision-making. Only recently, following an ICMRA workshop on RWD/ RWE, co-organized by the U.S. FDA, the EMA and HC, and attended by representatives from the ‘World Health Organization’ (WHO) and from regulatory authorities of more than 40 countries, a joint ICMRA statement was published calling for international collaboration in this regard. (134) Actually, harmonization efforts are already ongoing. In recent years, several international organizations such as the ISPE, the ICMRA, the ISPOR and the ‘Council for International Organizations of Medical Sciences’ (CIOMS) have launched initiatives and working groups dedicated to RWD/ RWE, which serve as fora for transnational knowledge exchange and collaboration and are aimed at fostering the establishment of global standards in regard to the utilization of RWD for research purposes. (135–138) Furthermore, relevant harmonization work is currently ongoing under the umbrella of the ICH. An overview of this work is provided in the following sections. It is important to note

though, that no definitions or proposals for definitions of the terms RWD and RWE have been published on the part of the ICH to date.

4.2.1 GCP renovation - Modernization of existing ICH guidelines

In 2017, the ICH 'Renovation of GCP' project was initiated in response to concerns conveyed to the ICH regarding a lack of flexibility offered by the ICH E6(R2) GCP guideline in terms of the management of varying levels of risk inherent to different types of trials and regarding the guideline's limited scope. (40) The ongoing GCP renovation initiative is not limited to the revision of the E6 guideline though, the project also included an update of the ICH E8 *"General Considerations for Clinical Studies"* (139) guideline, which is already finalized. (40, 139)

Modernization of the ICH E8 'General considerations for clinical studies' guideline

The ICH E8 guideline on 'General Considerations for Clinical Studies', which was first adopted in 1997, defines general principles on the conduct of clinical studies. (140) The revised version of the E8 guideline, E8(R1), was finalized in October 2021. (139) A renovation of the E8 guideline was deemed necessary to address the increased diversity and complexity of clinical study designs and the enhanced range of data sources. (140) Furthermore, quality by design considerations and approaches were included in the revised guideline. (141, 142) In chapter five of the guidance document, covering *"design elements and data sources for clinical studies"* (142), some references are made to observational studies and data sources commonly regarded as RWD sources, such as EHRs. (142) However, the concepts around RWD / RWE are not specifically addressed in the E8(R1) guideline and no definitions for RWD/ RWE are provided.

Renovation of the ICH E6 'Good Clinical Practice' guideline

The ICH E6 guideline on GCP was first adopted in 1996 and subjected to a revision in 2016. (143) The currently ongoing revision R3 is aimed at expanding the scope of the guideline to account for the increased variety of clinical trial types, data sources and technologies utilized to support regulatory decision-making on medicines. (144) The ICH E6(R3) guideline is sought to provide scientific and ethical guidance that is relevant and flexibly applicable across the full range of clinical trial designs and innovative technologies utilized. (144) As per the ICH E6(R3) final concept paper, the revised guideline will be composed of three

parts: an overarching principles and objectives document and two annexes. The first annex is to address traditional interventional clinical trials and the second annex non-traditional interventional clinical trials, such as pragmatic and decentralized clinical trials as well as trials using RWD. (144) Initially, the development of a third annex to cover non-interventional study designs, i.e. observational studies, patient registries, etc., had been proposed but the ICH Management Committee agreed in 2020 for the work on this topic to be deferred. (40) A draft, work in progress version of the revised overarching principles was published by the ICH in 2021. (143) The adoption of the final versions of the revised GCP principles and of the Annex I, which will replace the current E6(R2), is anticipated for August 2023. (145) The work on the Annex II is currently ongoing. (145)

4.2.2 Proposed new ICH guidelines

Besides the activities of the GCP renovation expert working group (EWG), work on topics relevant to RWD/ RWE and secondary use of data is currently ongoing in two more ICH groups. The members of the ICH M11 EWG and the recently established informal ICH M14 WG are engaged in the development of two new ICH guidelines, the ICH M11 *"Clinical electronic Structured Harmoni[z]ed Protocol"* (146) guideline and the ICH M14 *"Use of real-world data in pharmacoepidemiological studies"* (147) guideline.

ICH M11 'Clinical electronic Structured Harmonized Protocol (CeSHarP)' guideline

The ICH M11 EWG is tasked with developing internationally harmonized standards for clinical study protocols in terms of protocol structure and content. (148) The new M11 guideline is proposed to include a protocol template and *"a technical specification that uses an open, nonproprietary standard to enable electronic exchange of clinical protocol information"* (148). It is aimed for the M11 guideline to cover a wide range of study types and to provide flexibility to comply with local requirements. (148) The objective of the harmonization efforts is to improve the efficiency of drug development by facilitating the initiation, review and conduct of clinical research for sponsors, regulators and other stakeholders. (149) Furthermore, it is anticipated for the harmonization of study protocols to enhance data accessibility and enable comparative data analysis across different clinical studies. (150) The adoption of the M11 guideline is anticipated for 2023. (151)

ICH M14 'Use of real-world data in pharmacoepidemiological studies' guideline

The yet to be established ICH M14 EWG will be tasked with the development of a new ICH guidance document on *"General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines"* (152). This topic was endorsed by the ICH Assembly in June 2021, in response to the globally increased number of pharmacoepidemiologic studies utilizing RWD conducted for regulatory purposes and the lack of harmonized guidance in this area. (152, 147) Aspects to be addressed in the proposed M14 guideline include

> *"defining the research question, data source selection/generation, study design, definitions of target populations, exposure and outcome(s), covariates, data source fit-for-purpose evaluation, sources of and methods to address confounding and bias, analytic approaches, and format and content of reporting"* (152).

Although the focus of the proposed guideline will be on non-interventional studies using RWD to generate RWE to inform drug safety assessments, the principles to be defined in this new guideline may also be applicable to studies out of scope of the future M14 guideline, such as RCTs or single arm trials, if these include the use of RWD sources. (152) The finalization of the M14 guideline is anticipated for 2025. (153)

5. Final summary, discussion and outlook

This thesis provides a comprehensive overview and a comparison of the regulatory landscapes around RWD/ RWE in the USA and the EU, a brief overview of RWD/ RWE related guidance available in other countries and some insight into harmonization efforts with relation to RWD/ RWE ongoing on ICH level. Furthermore, basic definitions and terminology around RWD/ RWE are covered. But when talking about RWD and RWE, what types of data and sort of evidence do these terms refer to exactly? Since no globally harmonized definitions of RWD and RWE exist to date and the definitions available lack specificity, this question cannot be conclusively answered within this work. However, the literature reviewed for this thesis indicates a common understanding among regulators that the term 'real-world', when used in connection with 'data', refers to health-related data routinely collected in everyday clinical practice settings. Also, there seems to be widespread agreement to the effect that RWD may be primary or secondary data. When reducing the various existing definitions of the term RWE to a common denominator, then RWE refers to the

knowledge derived from the analysis of RWD. Positions are less clear when it comes to the question if and to what extend interventional trial designs, especially RCTs, can generate RWE. This certainly adds to the air of confusion that seems to exist around RWD/ RWE and underlines the importance of common definitions for the terms RWD and RWE to be agreed on *“with clear scope and level of granularity”* (30), as called for by international regulators, including the EMA and the U.S. FDA, in a recently published ICMRA statement.
The information presented in this thesis makes apparent that there is great interest among regulators around the globe in leveraging RWD/ RWE to support regulatory decision-making throughout the drug product lifecycle. As outlined in the previous chapter, RWD/ RWE related initiatives are not only ongoing in the USA and the EU. In recent years, guidance documents and/ or position papers on the use of RWD/ RWE for regulatory purposes have been issued in many of the leading industry nations and numerous international fora exist that are dedicated to this topic. Also, a number of countries have established or are interested in building the infrastructures for secure RWD networks and analysis platforms similar to the U.S. Sentinel System or the EHDS and the associated DARWIN EU® platform currently under construction. (48)

According to the literature reviewed for this work, regulators seem to be generally open-minded about the use of RWE in various regulatory use cases, provided the evidence is based on fit for purpose RWD and scientifically sound methodology. RWE is already routinely considered by the U.S. FDA, the EMA and several other regulatory agencies in drug safety-related assessments in the post-authorization phase. For new drugs not yet authorized in any indication, the general tenor is for RCTs to be, and to certainly remain, the gold standard for demonstrating efficacy and safety. This approach is reasonable, to the effect that a high degree of internal validity, as it can be achieved in highly controlled RCTs, is required to reliably establish causality between a treatment and an outcome, whereas in the context of drug safety, a high degree of generalizability across populations and contexts is essential, which can be best achieved in study settings reflecting usual clinical care. In areas of high unmet medical need, when efficacy of a treatment is sufficiently demonstrated in RCTs but uncertainties remain in regard to long-term safety and effectiveness, post-authorization observational studies represent a widely accepted method for such uncertainties to be addressed. Notwithstanding the above, many regulatory authorities seem

to be open towards considering RWE for efficacy evaluations in some circumstances. For instance, if RCTs are not feasible for any reason (e.g. because of a small patient population) or not ethical (e.g. in case of life-threatening diseases with no existing satisfactory treatment options), the use of sound RWE to contextualize the results of non-randomized trials is generally deemed acceptable. In 2017 and 2018, two CAR-T cell therapies (based on T-cells genetically modified to express a Chimeric Antigen Receptor (CAR)) for the treatment of certain life-threatening cancers were approved in the USA and the EU (tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®)). (154–157) The approvals for both therapies were based on the results of single-arm trials with response rates confirmed through comparison with datasets partially derived from RWD sources. (21, 158, 159) Decisive factors for RWD-derived evidence to be accepted by the regulatory authorities in these cases included the rareness of the respective diseases and the significant unmet medical need. (21) The literature reviewed for this work also suggests a general openness among regulators when it comes to the use of appropriate RWE to support decisions about repurposing of drugs or assessments of extension of indication applications for existing drugs. One recent example is the U.S. FDA’s approval of the expansion of indication for tacrolimus (Prograf®) for use in combination with other immunosuppressant drugs to prevent organ rejection in patients receiving a lung transplantation, which was based on an observational study that compared data from a registry with data from historical controls. (31) This approval can be regarded as significant as it demonstrates that adequate and well-controlled non-interventional studies have indeed the potential to meet a stringent regulatory authority’s scientific evidentiary standards for demonstrating efficacy.

Currently, the use of RWE to support efficacy decisions is still rather an exception and applicants wishing to use RWE to support regulatory decisions about new or expanded indications are generally recommended to consult with the respective regulatory authority/ies early in the process on the conditions of RWE acceptability. However, in the light of the rapidly evolving scientific and technology landscapes and the emerging trends towards precision medicine and products for rare conditions, it can be anticipated for RWE to gain importance for regulatory decision-making in the coming years. As touched upon in chapter three, there are numerous research projects ongoing in the USA and the EU aimed at building expertise in the application of RWD/ RWE across the spectrum of possible use cases. Intelligence gathered from these research projects and lessons learned from RWE-

supported approvals like those mentioned above will certainly help to build confidence in the use of RWD/ RWE as, with growing experience, regulators and researchers will be better able to evaluate the validity of RWE. In the opinion of the author, an important step for reducing uncertainty and concerns about the use of RWE for regulatory purposes will be the successful realization of the harmonization efforts ongoing at the international level, especially the finalization of the ICH GCP renovation works and the completion of the ICH M14 guideline which will define general principles for non-interventional RWD-based safety studies that may also guide the planning, design and analysis of RWD studies outside of the field of safety.

As indicated by the literature reviewed for this thesis, regulators in the USA and the EU also share a common vision of establishing national/ regional – or eventually one global – learning healthcare systems. To realize this vision, great promise is seen in the establishment and expansion of privacy-preserving distributed data networks and accompanying analytic infrastructures designed to enable the secondary use of health data to generate robust RWE to inform regulatory and public health decision-making and, subsequently, to evaluate the effectiveness of the decisions taken. A pioneer role in this regard can be attributed to the U.S. Sentinel System. Initially created to monitor the risks associated with drugs, the Sentinel System has, in the meantime, grown into a multi-purpose national evidence-generation platform used by different stakeholders to inform a wide range of research questions as well as serving as an engine for methodological innovation and for the advancement of the science of RWE. (48) The FDA has shared their knowledge on how to build up, operate and govern such a platform with regulators and researchers from around the world, for example, from Canada, the EU, Japan, Taiwan, South Korea and China. (48) Today, the CDM developed for the Sentinel System is also used in data networks outside of the USA. Countries that have fully or partly transformed their national data networks into the Sentinel CDM include Canada, Taiwan and Denmark. (48) The use of the same CDM across different national data networks allows for identical, and hence comparable, RWD studies to be conducted in the respective countries and can help facilitate cross-border collaboration between regulators and researchers. (48) In the EU, the foundation for a pan-European health data network has been laid with the launch of the EHDS by the European Commission in May 2022. (160) The latter tying in with a central recommendation of the

EMA-HMA BDTF to establish DARWIN EU®, a European platform to access and analyze health data from across the EU, in order to deliver RWE on diseases, populations, drug use and performance. DARWIN EU®, which is currently under development, is anticipated to be fully operational in 2023. (88)

Even though initiatives towards the establishment of new or expansion of existing health data networks to support learning healthcare systems have been ongoing in many countries before the COVID-19 pandemic hit the globe, the pandemic can certainly be regarded as representing one major engine for these initiatives. Virtually from one day to another, RWD was urgently needed to help answer a wide range of pandemic related questions (e.g. about counts of COVID-19 cases, the natural history of the disease, occupancy rates of intensive care units, etc.) and, thus, inform, guide and evaluate health policy decisions and support the development of COVID-19 medicines and vaccines. Thus, the pandemic has raised further awareness for the spectrum of possible RWD use cases and for the benefits of RWD infrastructures and analysis capacities being in place as well as enhancing the expertise of researchers and regulators in analyzing and evaluating RWD and RWE. Furthermore, the pandemic has been a catalyst for the implementation of digital tools and services and certainly contributed to an enhanced acceptance of such digital solutions in the healthcare context. In the opinion of the author, the COVID-19 pandemic has created a lot of momentum for efforts towards the digital transformation of healthcare and the establishment and expansion of data infrastructures and analysis capabilities to support learning healthcare systems across the globe. In a few years’ time, RWE obtained through platforms such as Sentinel or DARWIN EU® might be routinely embedded in the decision-making processes of regulators, HTA bodies, payers, policy makers and researchers and help them to take sound, data-driven decisions. From the author’s perspective, an important factor for the successful realization of RWD-based learning healthcare systems will be to build and maintain trust among citizens that the privacy of their personal health data is protected. Solid data protection regulations and frameworks, such as the European GDPR, certainly represent important pillars for building public trust and acceptance for the secondary use of health data for research and innovation, policy-making and regulatory purposes, that is, ultimately, for the benefit of public health.

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Erklärung

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

München, 15. November 2022

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