Major Internship Report

The Use of Real World Data/Real World Evidence in Regulatory Submissions for Products Centrally Approved by the EMA in 2019

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Contents

Abstract

Introduction: Real World Data (RWD) and Real World Evidence (RWE) is increasingly used throughout a medicines lifecycle, including for regulatory submission. RWD is derived from routine healthcare data such as , EHRs, product or patient registries, etc. and RWE is evidence generated from the transformation of RWD. While its use in Phase IV studies is well documented and understood, RWD/E is being used in pre-approval phases.

Methods: To better understand how the industry uses RWD/RWE in regulatory submissions and medicines development, a survey was conducted among company representatives with relevant knowledge, representing marketing authorisation holders for products approved via EMA centralized procedure in 2019 (n=46).

Results: 15 companies respondend tot he survey for a total of 22 products. 80% of the companies reported they they regularly use RWD/RWE in product development. For 8 products in the cohort (36,4%), RWD/RWE was used in development and in case of 5 products (33.3%), RWE was submitted as part of the dopssier with the EMA. Most commonly reported uses of RWE are supplementing safery (66,7%) and efficacy (73,3%) data.

Discussion: A questionnaire aimed at the Marheting Authorisation Holders is a new and insightful way to study the place of RWD/RWE in drug regulation and development. Challenges with RWE presist in the regulatory space, but increased awareness and guidance on behalf of the regulators is needed to ensure quality uses of RWE in future regulatory applications.

Conclusion: The study provided a unique insight into how the industry uses RWD/RWE in product development. RWE is being submitted to the EMA as part of dossiers fort he approval of new products.

Layman's Summary

Before a new medicine enters the market, it undergoes a rigorous evaluation (regulatory approval) in which the manufacturer must prove the medicine's safety and efficacy. As part of that evaluation, data from randomized controlled trials is submitted as the standard evidence to demonstrate that. However, other types of data, collected in any number of healthcare settings (Real World Data, RWD) may be used to inform any type of decisions throughought the process of medicines development and ultimate regulatory approval. Real World Evidence (RWE) is evidence from such data. This type of evidence is particularly useful when assesing the long-term effects and safety of a medication after it has been approved for use. However, in many cases, such as novel cancer treatments or drugs that are aimed at very rare diseases, evidence from clinical trials may not always be enough, and RWE can play an important role in their approval.

In order to study how RWD/RWE is used by companies when developing medicines and to obtain the regulatory approval, we focused on products approved in the European Union in 2019, and created a survey directed at relevant company representatives. The survey inquired about the day-to-day use of RWD/RWE, from what sources it is derrived, information about the companies, as well as product-specific information related to the RWD/RWE use.

15 companies respondend to the survey for a total of 22 products.We found that 80% of companies rely on RWD/RWE in their operations. We also found that for 5 products, RWE was used in the regulatory application with the European Medicines Agency.

This study chose to study representatives of the company directly, as opposed to other indirect ways to establish the use of RWD/RWE, which is why it was unique. We were able to get rich data about the uses of RWD/RWE at company levels, and somewhat less data about the specific products. Our study compares well compared to existing understanding in literature about sources and uses of RWE. We were able to establish that manufacturers do sumbit Real World Evidence, aside from data from clinical trials. One limitation of RWE is that, unlike RCTs, it is often data not orinally aimed for purposes of research, meaning that methodological and other challenges may arise with regards to the quality of that data. Furthermore, medicines regulators, have issued some guidance to companies about how to use RWE to support their regulatory applications, however, our respondents have shared that a need for more guidance still exists. Limitations of our study include the fact that we had a small sample size, and that despite our best efforts, there is a possibility that the identified company experts may not have had all the knowledge or information necessary to answer the full survey.

In conclusion, this original survey approached this important question in drug regulatory science and allowed us to confirm that RWD/RWE is readily used throughout mediciens development, up to and including the process of regulatory approval. While more guidance may be needed to ensure high-quality data and sound evidence only to be included in the process fo drug approval, more resrarch on this subject matter is also needed in the future.

List of Accronyms

(US)FDA	United States Food and Drugs Agency
ATC	Anatomical Therapeutic Chemical Classification System
DARWIN	Data Analytics and Real World Interrogation Network
HEOR	Health Economicas and Outcomes Research
HTA	Health Technology Assesment
ISPOR	The Professional Society for Health Economics and Outcomes Research
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
NMPA	National Medical Products Administration (China)
PMDA	Pharmaceuticals and Medical Devices Agency
RCTs	Randomized Controlled Trials
RWD	Real World Data
RWE	Real World Evidence

I. Introduction

The use of Real World Data, hereinafter RWD, as an important factor in pharmaceutical science and industry are steadily on the rise(1), accompanying significant and exciting developments in the field. According to the European Medicines Agency (EMA), RWD is defined as "routinely collected data relating to a patient's health status or delivery of health care from a variety of sources rather than traditional clinical trials" (2). In this definition, the EMA excludes traditional clinical trials (RCTs), even if single arm, but includes pragmatic clinical trials (2). RWD can be considered complimentary to data obtained through RCTs (3). Sources of RWD are data collected in a healthcare setting, such as from electronic health records (EHRs), claims data, prescription data and patient registries, as well as data from wearable personal devices, mobile health apps and other factors related to the lifestyle and environment factors (2). Real World Evidence, hereinafter RWE, is according to the EMA definition "the evidence derived from the analysis and/or synthesis of real world data", and according to the USFDA, "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD" (4).

Given its sources, it is reasonable to suppose that, opposed to tightly controlled RCTs, RWE provides us with a more holistic understanding of an individual's health status (1). However, due to its nature, RWE does not provide actionable evidence as easily (2), and there is a reported weariness by the regulators in their understanding and acceptance when it comes to issuing marketing approvals that utilise RWE (5). Historically, RWD/RWE have been important in regulatory decision making related to safety signal evaluation and risk management that occur in post authorisation of the medicine. In pharmacovigilance, safety is to be understood in the wider context of care delivery after the medicine has entered the market, as opposed to the controlled environment of RCTs (2). The pharmaceutical industry has been using RWE also in the pre-approval phase of drug development for various purposes including describing patient populations (*Figure* 1) (3). The use of RWE is well characterised when it comes to its use in economic modelling and pricing negotiations (3). RWE also has a central spot in the HTA discussions (3).

There is an increased use of RWD/RWE in the earlier stages of drug R&D and in supporting regulatory decision-making(6). This is true both in the context of general R&D, but especially in the category of advanced therapies and orphan products, where e.g. ethical or operational challenges to conduct RCTs are more significant (2). An RWE-admissible approach is applicable for the entire cycle of medicine development, starting with their potential to be used in drug discovery, e.g. by being helpful in identifying diseases and indications significant in the population (3). In drug development, RWE can be used to increase internal validity of Phase III studies (3). RWE can help in choosing appropriate population, can help characterise the unmet medical need and standard of care (3). The impact of

RWE on trial design can be especially interesting in the context of choosing the right trial population. Given that the impact of eligibility criteria for clinical trials is not always fully understood nor tested, until the generalizability of the trial is examined at the stage of regulatory submission, RWE can be used with this regard to great advantage. Furthermore, RWE can help achieve regulatory approval, through providing data related to demonstrating efficacy and safety of the investigated medicine.

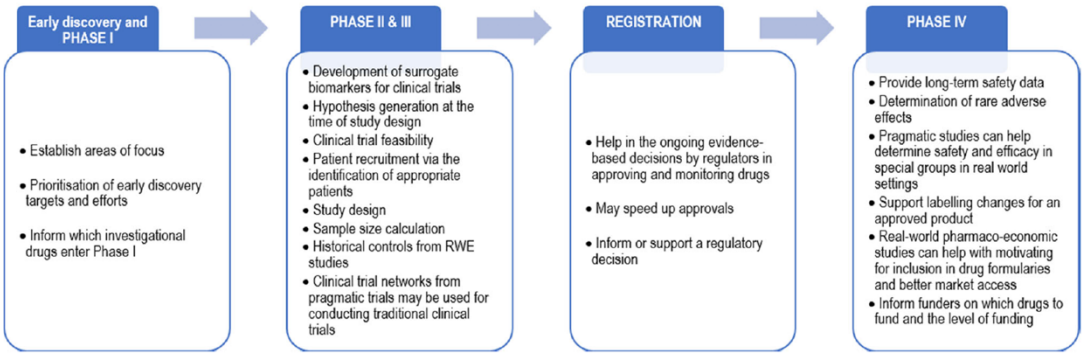

Figure 1 An overview of uses of RWE throghout the product lifecycle (Taken from Naidoo et al (7)*)*

The rise in RWE is driven in particular by the developments in biotechnology and a need for speedy, lest costly and more efficient innovation, and it can be argued that the greatest potential for the use of RWE lies in development of oncology products (8). Between the disease burden of cancer and the rise of novel cancer therapies such as CAR-T, RWE can accelerate the development and maximize the impact of new oncology therapies (8).

The attitude and experience by different regulators towards RWE is not homogenous. The US FDA reported planning on a more definitive RWE guidelines by 2021, and has in the meantime published Draft Guidance on "Submitting documents using real-world data and real-world evidence", that includes a framework for RWE use in regulatory setting (9) . According to their annual report of 2019, EMA does not have a similar guideline published yet (10). On the other hand, the role of big data and RWE have been explored by the EMA and they aim to work towards the DARWIN network, to enable better use of big data for industry and the agency itself (11). This, however, does not mean that RWE has not informed EMA decsions about marketing authorisations in the past (11).

The intricate web of the multitude sources of RWE, the still unknown applicability across different therapeutic groups as well as different regulatory approaches towards use of RWE provide a great deal of complexity. Nevertheless, the increased use of RWE represents a significant paradigm shift in R&D of medicines. In order to characterize and understand how RWE is used today to achieve regulatory approval, the multiple stakeholders: the industry, regulators, academia, etc., are to be recognized. Furthermore, guidance documents and other initiatives undertaken by regulators allow a

basic understanding of the place of RWE/RWD in regulatory science. New frameworks for assessing RWE in study designs are being published, an understanding of how medicine developers already incorporate RWD/RWE into their day-to-day practices remains elusive. Despite the fact that RWD/RWE has been well charactherized in scientific literature, researchers have not been able to quantify the use of RWD/RWE in R&D, as this type of information tends to remain privileged and confidential. Therefore, there is a need to understand the stances of the industry and engage them directly in an attempt to understand how they use RWD/RWE to support regulatory submissions and generally.

This study focused on a cohort of 38 companies who obtained marketing authorisations via the EMA Centralized Procedure for in total of 46 products in 2019. A questionnaire was developed and distributed to marketing authorisation holders (MAHs). The aim of this study was to (1) identify incidence of RWE use to support marketing authorisations, (2) discover and characterize where and from which sources RWE has been used in medicines development phase and (3) better understand how RWE is supporting regulatory submissions. Aditionally, in order to prepare the questionnaire, a literature review was performed in order to reach a deeper understanding of the topic. The literature review is included as a supplement.

II. Methods

In this research project we used an electronic survey to collect information about the sources, uses of RWD/RWE in development and regulatory sumissions from Marketing Authorisation Holders for products that went through the EMA centralized procedure and were approved in 2019. The study was complemented by a literature review for background understanding.

2.1. Product Cohort and data collection

The study cohort was pre-defined and it included all products (n=46) that have obtained an EMA marketing authorization via the centralised procedure in 2019. All human medicinal products, except for generics and biosimilars, were included in the study cohort. Exclusion criteria was justified as the generic and biosimilar medicines are expected to demonstrate their efficacy and safety cross-referencing mostly the data already assessed by the regulatory authority for an innovative product.

Respondents, i.e. relevant company representatives (n=38) were recruited for the study from either the existing contact network of the study supervisor (SE), or from direct engagement with Marketing Authorisation Holders based on the information found in the internet on the respective company websites. The respondents were identified as individuals within the respective companies with adequate internal knowledge about RWD/RWE and regulatory affairs, who were best suited to participate and/ or to coordinate the response from their respective company to the survey.

All respondents were contacted by an email and provided information about the study with a request to participate and asked for a written consent to participate in the study prior to the conduct of the study. The survey was digitally distributed to consenting participants (all 38 were included). Participants were given 4 weeks of response time, with two reminders sent and extra response time provided to those who requested it, totaling to 6 weeks of response time.

The survey included main variables such as company size, and co-variates such as company specialization, specific points in medicines R&D where RWE was used in general and at the level of the company, need for more guidance for regulators, etc.

2.2. Study design

A survey was designed to collect information about the companies, the overall uses of RWD/RWE in regulatory submissions and product development at the level of the whole company and also of the individual product in cohort. (Appendix A). The survey was designed based on the insights obtained from literature (2), (6), (10), and its structure was guided in part by the FDA draft guidance on "Submitting documents using real-world data and real-world evidence". Following the design of the survey and before its launch, the survey was piloted with 6 experts from the industry (relevant representatives of companies who were not included in the study cohort), the representatives of the regulatory body (EMA), trade association (EFPIA) and external research organisation (Technopolis). Following their feedback, the survey questions and structure were further refined prior to its finalisation and the launch.

The survey was subdivided into 5 groups of questions and included a total of 25 questions, in the form of either yes/no questions, multiple choice selection or free text questions. The first 3 groups dealt with quering details of the Marheting Authorisation Holder itself, i.e. company/respondent. Namely, in group 1, those included the company size, whether the company is specialized on certain products/therapeutic areas, whether the company has a specific RWD/RWE department and where in the organisational structure of the company RWD/RWE responsibilities reside and whether the company outsources some of RWD/RWE related tasks. In group 2, the overall use of RWD/RWE by the company was inquired about, including whether the company routinely uses RWD/RWE, from which sources RWD is commonly obtained, and at which stage of development RWD/RWE is commonly used. In group 3, the use of RWD/RWE in regulatory submissions was examined in the survey, with questions regarding EMA scientific advice, experience with submitting RWE in dossiers with the EMA and other major regulators, as well as types of regulatory submissions in which the company has experience with RWE use. This concluded the company-related part with general questions.

The participants were then asked to provide an anonymised product-specific code to answer the latter

two paragraphs of questions that related to the product of the cohort. The group 4 related to use of RWD/RWE in product development, namely at which stage of development it was used and what motivated RWE use. Finally, the survey concluded with group 5, questions related to the specific regulatory submission for the product approved in 2019, such as whether Scientific Advice from the EMA was sought, whether EMA recommended the use of RWD/RWE and whether RWE was assessed by the EMA in their evaluation and decision of the given product.

2.3. Outcomes

The main outcome of the survey was to determine the incidence of RWE use by respondents at the level of the company and the individual product. At the company level, outcomes of interest were whether companies use RWD/RWE regularly in their decision making, their specialization, size and whether those had a significant connection with RWE use. Further outcomes include the identification of sources of RWD, types of regulatory applications RWE is used to, as well as discover whether variables like therapeutic area of the product are more likely to involve RWE use in development.

2.4. Variables

The main independent variables included therapeutic area, orphan designation and company size. The dependent variables included incidence of RWE use, incidences of RWE use in particular points of drug development, as well as product-unrelated dependent variables that characterize the RWE use per MAH in general, such as general incidence of RWE use in the particular sample. For each medicinal product in the cohort, information on product characteristics and marketing authorization characteristics were collected from the "download table of medicines", retrieved on the EMA website. The product characteristics included as co-variables were the medicine name, therapeutic area per high-level ATC code (12), active substance and approved condition/indication. The marketing authorization characteristics included as co-variables were marketing authorization approval date, whether the medicine had received a conditional approval, was approved under exceptional circumstances or through accelerated assessment. Finally, the classification as an orphan medicine was captured as a co-variable.

2.5. Data Analysis

Contingency tables (cross-tabulation) and freqeuencies were used as the main descriptive method to determine associations between product characteristics and case-specific RWE use. The data obtained from the digital survey was coded and analysed in IBM SPSS Statistics 2020 (version 27.0) .

III. Results

In total 15 out of 38 MAHs responded to the survey resulting in a total 22 out of 46 products in the cohort being included in the outcomes. The response rate was 39% out of companies included and 48% out of products included in the cohort.

3.1. Product and Company Charactheristics.

To better charactherize the respondents, the first part of the survey focused on company charatheristics (*Table* A; Appendix B). 80% of the respondents described themselves as large companies (>250 employees). For a more illustrative estimate, 40% of total respondents informed that their company is currently sponsoring more than 100 clinical trials. 60% of respondents affirmed that there is a specialiazed group/department that is tasked with RWE in their companies. *Table* 1 shows a breakdown of products per therapeutic area in the cohort and for the responses.

Table 1 Cohort v. Respondent Therapeutic Area Breakdown

Therapeutic Area Breakdown	Nr (cohort)	% (cohort)	Resp.	% (of response total)	ATC classification	Nr (cohot)	% (cohort)	Resp.	% (of response total)
A: alimentary tract and metabolism	5	11%	2	9%	M: musculo-skeletal system	2	4%	1	4%
B: blood and blood forming organs	2	4%	2	9%	N: nervous system	8	18%	2	9%
C: cardiovascular system	1	2%	1	4,5%	R: respiratory system	1	2%	1	4%
H: systemic hormonal preparations, excluding sex hormones and insulins	1	2%	1	4,5%	S: sensory organs	1	2%	0	-
J: antiinfectives for systemic use	6	13%	3	13%	V: various	3	7%	2	9%
L: antieoplastic and immunomodulating agents	14	31%	7	31%	Not assigned	1	2%	-	-

3.2. RWD/RWE use at the company-level

66.7% of respondents stated that their company outsources some or part of generating RWD and analysing RWE. An overview of reported company specialization is outlined in the Table C in Appendix B. Overall MAH Use of RWE in Development and Regulatory Decision Making.

A key finding was that 80% of respondents reported that they routinely use RWD in product development. In terms of using RWD/RWE in specific phases of R&D (*Table* A; Appendix B), the most reported uses were those that are supplementing safety or efficacy data obtained from clinical trials,with 66.7% and 73.3%, respectively (*Table* 2). Most uses for pre-approval phase were reported in defining target population for the product at 60%, as well as optimizing clinical trial designs at 46.7%.

In terms of sources of RWD, almost even distribution of the most common ones was noted, with 60% of companies claiming that they have been using RWD from claims, product registries, patient registries and chart reviews (*Table* A; Appendix B). 53,3% have used RWD from EHRs in the past, while patient-generated data (e.g. from wearables) was used by 33,3% respondents.

80% of respondents reported that they *sometimes* rely on RWE for internal decision-making, while only 1 respondent (6.7%) stated that they *never* do so, furthermore, 2 respondents (13,3%) stated that their companies *always* rely on RWE for internal decision-making.

Table 2 Key survey findings on Marketing Authorisation HolderThe overall Use of RWD/RWE in Regulatory Submissions

Item (MAH level, total 15)	YES		NO		N/	
Company Size: Large (Y)/Small (N)	12	80%	3	20%	-	-
Number of sponsored trials >100	6	40%	9	60%	-	-
Routine Use of RWE	12	80%	3	20%	-	-
RWE Use: Supplementing safety data	10	66.7%	5	33.3%	-	-
RWE Use: Supplementing efficacy data	11	73,33%	4	26.7%	-	-
RWE Submitted in Previous MAAs with EMA	9	60%	6	40%	-	-
Need for more guidance from Regulators	12	80%	2	13.43	1	6.7%

With regards to the use of RWE in regulatory submissions (*Table A, Appendix B*), 60% of respondents have reported that they have submitted RWE in applications while seeking marketing authorisations from the EMA, and 73.3% have sought Scientific Advice from the EMA in relation to the use of RWE in regulatory submissions. 6 (40%) companies submitted RWD/RWE with US FDA, 5 (33.3%) with PMDA and Health Canada and 3 (20%) with NMPA. In terms of the type of regulatory applications , most uses of RWE were noted in adding new populations (60%), and at obtaining full MAAs and adding/modifying an indication (53%).

Finally, 80% of respondents stated that they believe there is a need for more guidance from regulators when it comes to using RWE in regulatory submissions.

3.3. Product-specific Uses of RWD/RWE in Development

RWE use was reported in 8 out of 22 products (36.4%) on which the response was received. All participants that used RWE in their product development also reported that their companies routinely used RWE. As to what constituted the motivation for using RWE, 5 (33.3%) respondents listed availability of RWE, 3 (20 %) have listed cost-related aspects of development, and 3 (20%) listed low population size or rarity of the targeted disease. No respondents listed ethical reasons (such as the target being an orphan disease) as a motivator for use. Besides the question of whether RWE was used for the development of the product approved in 2019, a significant number of respondents, 12 (80%) did not respond to the questions that aimed at identification of different uses of RWE in development for the given product. The same pattern of non-response was observed to the questions that related to the motivation for using RWE for the specific product submission.

In the decoding process, the product therapeutic area was attributed to each product on which the response was received. The comparison to the therapeutic area breakdown of the entire cohort is presented in Table 2.

To determine the distribution of RWE use across therapeutic areas, the therapeutic area of products, as per ATC classification, was crosstabulated with RWE use (Table 3). While products classified as anti-infestives for systemic use had 2 reported uses of RWE, 1 use was reported in other categories. The therapeutic area L: antineoplastic and immunomodulating agents (cancer mediciens) did not have a higher than average reported incidence of RWE use in development

Table 3 RWE Use/Therapeutic Area Crosstabulation;

TA * RWEUSE Crosstabulation		
Count		
Therapeutic Area	RWEUSE	
	YES	Total
A: alimentary tract and metabolism	0	2
B: blood and blood forming organs	1	2
C: cardiovascular system	0	1
H: systemic hormonal preparations	1	1
J: : antiinfectives for systemic use	2	3
L: antieoplastic and immunomodulating agents	1	7
M: musculo-skeletal system	1	1
N: nervous system	0	2
R: respiratory system	1	1
V: various	1	2
Total	8	22

Furthermore, reported company size was crosstabulated with RWE use and 2 out of 3 small companies that responded to the survey used RWE in their pdocut development, and more than a half of the large respondents did so as well.

5 companies (33.3%) that used RWE in the product development, submitted RWE in their dossiers of the product part of the cohort to the EMA, indicating that RWE was assessed by the EMA as part of those dossiers (*Table B, Appendix B)*. Two companies (13.3%) sought Scientific Advice from the EMA, and both received a positive opinion on using RWE in their dossier. Similarly to the previous section, a significantly high number of respondents opted not to respond to the specific questions pertaining to the regulatory submission of the product approved in 2019.

IV. Discussion

The survey established that in 8 out of the 22 products respondend for, RWD/RWE was used in development. . Our study confirms the notion that RWD/RWE is readily used in different phases of development and that a clear majority of surveyed companies has experience with using RWD/RWE both in development and in regulatory submissions, which is in line with the growing impact of RWD/RWE (13).

The study informs us in a rich way on how RWD/RWE is used in product development and it allowed us an insight in its use in regulatory submissions. When it came to RWD sources, the most common sources were identified (Claims, EHRs, Product Registries, Patient Registries, Chart Review and Patient-generated data). The findings of a systemic analysis that aimed at mapping out generic sources of RWD listed administrative data sources, followed by claims data and HERs as the most found data sources(14). While it did not take into accound disease-specific sources of RWD, this illustrates that

we observed sources consistant with reports of RWD sources in Europe(14). A couple of respondents indicated further that they consider data published in scientific publications as sources of RWD. While this type of data most certainly fits in the definition of RWD that we used in our research, data from scientific publications are not often listed as common sources of RWD in literature. It is worth highlighting is that our respondents reported less frequent use of patient-generated data, which is in line with both the focus of our study on development, and the fact that that category of data is somewhat less established than other sources. In terms of relying on RWE for internal decision-making related to drug development, textual responses of the participants are also illustrative. While some stated that they aim to use RWE for regulatory decision-making on a more routine basis, others stressed that post-approval applications remain the central place for RWE use.

Furthrmore, HEOR (Health Economis and Outcomes Research) modelling was highlighted, as well as the use in early access schemes. While the phases in development and company operations where RWE uses were reported are comparable to the expected, namely that RWE can support safety or efficacy evidence for a product, what was striking is that companies with different profiles or specializations find different uses for RWD/E. This confirms the perception, that there is no single approach to RWD/E and that its use in regulatory submissions may be applicable in some instances and for some applicants, but not for others.

The most significant consideration raised when discussing the use of RWE in medicine development and regulatory decision making, is the one of what constitutes high-quality RWE, i.e. RWE of sufficiently high quality to be considered *regulatory grade* RWE. Different authors propose different criteria, including the notion that RWE should be traceable, complete, transparent, generalizable, timely and scalable (8). Another postulation is that RWD analysis, in order to be successful, needs to be "MVET" – Meaningful, Valid, Expedited and Transparent (15). Other frameworks for evaluating RWE for regulatory decision making have been published, including the SPACE frameworks proposed by Gatto et al or the framework developed by ISPOR (16,17). *A priori* defining of evidentiary standards may, however not be futile at all, according to some authors (15), and those evidentiary standards are far from being set. Challenges related to RWE are classified as methodological (unsobserved confounders, lack of universtal methodological standards), and data realated (e.g. missing/ data, rick of false positives). The increasing use of RWE in the regulatory setting means that there is a better evolving understanding on how to overcome them (18). These considerations occupy both the industry and the regulators, and confirming that RWE is used readily to complement safety and efficacy data means that much of the RWE that is included in regulatory submissions is at some point judged as regulatory-grade.

When it comes to regulatory submissions in general, a majority of companies reported experiences with the EMA in submitting RWE as part of an application. Most of the purposes of RWE in regulatoy submission were to include a new population, new indication or support the initial marketing authorisation. In addition, companies referred to similar experiences with other major regulators (USFDA, PMDA, NMPA). Most participants sought Scientific Advice from the EMA with relation to RWE, and indicated that there is need for more guidance on RWD/RWE in general to be issued by the regulators. While the participants welcome the EMA's draft guideline on disease-registry-based studies for generating Real World Evidence(19), and while such guidance will bring much needed, some gaps such as placement and format of RWE in dossiers have been noted. This draft guidance emphasizes the need for pre-planning of such studies, with the regulator, e.g. in the form of Scientific Advice, which our study to some extent confirms is already practice when including RWD/RWE in dossiers. Furthermore, all studies that generate RWE need to be pre-planned with special care. While some other regulators, such as the FDA are somewhat ahead in this process than the EMA, the participants expressed a need for more internationally standardized guidance with regards to the regulatory use of RWD/RWE. The draft guideline represents part of a larger effort for standardizing and introducing more policies and initiatives related to RWD/RWE in the EU (11).

The questions which related to the specific products approved in 2019 by EMA revealed that for 6 products in the cohort the RWE was used in development of the product. When it came to submitting RWE as part of regulatory application, the responses indicated that RWE was submitted only in two dossiers. There was therefor a marquedly lower level of responses received for product-specific questions related to RWE submissions. This is expected given the number of cases in which RWE was used and that companies may be hesistant to disclose such information despite the anonimisation was ensured. However, literature provides insights in how regulatory policy is impacted by the predsence of RWE.

The methodology by which this study attempts to examine the use of RWD/RWE is seldomly used. Having designed a survey with the input from relevant experts and study of academic literature and focused on a cohort of product approved in a period of one year, this study is distinguishable from case studies that academic publications on RWE are well saturated with.

While little previous research that uses similar methods exists to be able to compare findings of this study, a 2020 study (20) of RWE use for FDA approvals of new oncologic products approved between 2015 and 2020 found that for 8% of approvals for oncologic treatments RWE was used to support the regulatory filing. This study focused only on oncology products and employed a different methodology (regulatory records review), however, it is a useful comparator as it gives some idea about the rate of

use of RWE/RWD. Our study ascertained that 6 products (13%) in a year-long cohort (2019) of all products used RWE in their development and more importantly that for 2 products (13%) RWE was submitted with the EMA. 2 products in a haphazard sample across all therapeutic areas is somewhat consistent with the rate for oncologic approvals with the EMA. However, while it was expected before the study that there would be a higher level of RWE use and submission for products from the oncology therapeutic area, this was not the case in the studied sample. This, however, may be positively interpreted as the protrusion of the use of RWE in other therapeutic areas, that has been observed previously. This study also corroborates the findings of Varnai et al. (21) that, especially as a means of supplementing RCT data in obtaing regulatory approval, RWE can in some instances lead to regulatory approval, given that such type of use is the most commonly reported by the respondents.

4.1. Limitations

Limitations of this study stem from the study design, and response rate. While the response rate was rather good for a survey study (39%), the sample itself was still relatively small. Furthermore, the survey was responded to by predominantly large companies, meaning that the generalizability of the results is appropriate for large companies, but not otherwise. Engaging and confirming the participation of a larger part of the cohort could have yielded a somewhat higher response rate. The small sample size meant that statistical inferences and predictions about RWD/RWE use were impossible to make. Despite the fact that RWE use is often mentioned in the context of orphan products, there were no orphan designated products in the sample of responses received, which made it impossible to determine whether this was the case for the products approved in 2019. Additionally, while it was aimed to finding the correct individuals who would have capacities to answer or coordinate the answers to the entire survey, the responsibility being given to one representative of the company may not be ideal. The reluctance to answer the survey or particular questions, that may have influenced the response rate, was most likely caused by the sensititve nature of the data to be disclosed, despite the fact that the survey was fully anonymized. The respondents may have also lacked full knowledge or awareness on the topics of inquiry and/or were not able to obtain this information from their colleagues. Finally, the setup of the survey made it difficult to detect more nuanced responses and contexts in which RWE was used.

4.2. Future research

Future research should aim at getting a more detailed view, employing a similar methodology on a larger cohort, for example by including more years. This would allow for more detailed statistical analyses to be ran and patterns of use to be determined. Furthermore, a qualitative study of the same cohort could provide more insight into the uses of RWD/E, as well as provide more detailed answers

on the use of RWD/E in the internal decision-making process of the companies in the cohort, also by identifying participants with more specific expertise. In addition, this study did not examine what are barriers or motivators for RWD/E use are, which would complete the understanding of the matter. Finally, studies aimed at understanding the regulators' perspectives in a global scale would complete the picture on RWE use in regulatory submissions.

V. Conclusion

This study provides unique insights directly from the Marketing Auhtorisation Holders on their use of RWD/RWE. It evaluats systematically a cohort of products approved in a predefined time period across different therapeutic areas. The study confirmed that for 6 products centrally approved in 2019, the RWE was used in development and that for 2 of the products the RWE was part of the regulatory submission. The study also established that in terms of sources of RWD, the most frequently used sources of RWD are claims, product and patient registries. Having also observed that the majority of respondents have previously used RWE in product development and submitted it both with the EMA and other regulators, we can conclude that RWE use in product development is relatively common among large pharmaceutical companies. This applies especially for supplementing safety and efficiacy information, both for new applications and line extensions.

In conclusion, this survey approached the questions on how was RWD/RWE used for product development in 2019. The emergence of RWD/RWE in the space of drug regulation, and the ongoing paradigm shift by which RWD/RWE is entering drug development and regulatory submissions for new applications, are and will remain for the time being a significant topic in drug regulatory science. It appears that companies are already submitting RWE to the EMA and other major regulators, and have been doing so for some years now. Better understanding of RWE use for regulatory purposes by manufactures remains needed. The emergence of more specific regulatory guidance by the EMA is also needed and requsted by the medicines developers. It will lead to an increased and more constructive use of Real World Evidence in future regulatory submissions and across the medicines R&D process pre and post the regulatory approval.

VI. Supplement: Literature Review

1. Sources of RWD and RWE

Sources of RWD include data from case reports, retrospective studies (literature), electronic health records (EHRs), administrative and claims data, patient registries and patient-generated data from websites, wearable sensors, social determinants of health and environmental exposures measurements (13). Each type of RWD source has specific benefits and limitations, as well as specific methodologies used to turn them into RWE(22). Such limitations, can be overcome by consistently documenting them, with harmonisation across datasets as the key priority (22). Several of these limitations have been well documented so far. Claims data tend to lack clinical results and endpoints, while patient registries lack follow-up and reliability. Data from wearables and smartphones are prone to selectivity bias and are associated with personal data security concerns . In order to be reliable and suitable for regulatory decision-making, RWE must be generated from high-quality data, obtained from relevant sources, properly harmonized to fill in gaps that are common in data not initially generated for research purposes, and importantly, the use of RWD/RWE for decision making needs to include endpoints (22).

The rising use of Electronic Health Records (EHRs) is an important breakthrough in feasibility of collecting RWD. In the EU, there is a noticable movement to increase the quality of RWD through integrating and harmonizing EHRs across member states, and using data from EHRs for research purposes (23). Benefits of EHR use are that they lead to information from substantial and likely unselected patient populations, that can be useful in an array of studies, most notably in phase IV clinical or observational trials (23). Shortcomings mostly stem from the difficulty in linking, organising and analysing data from different sources, that reside in distinct databases and lacking proper methods for extracting such data in a manner protective of patient data privacy (23). An abundance of data that resides in the EHRs is not straightforward to compute, as it is unstructured free-text data (13). Such free-text data may, however, have benefits being a richer data source especially in safety signalling (13).

In the EU, there is a disharmony between member states in terms of the EHR databases in terms of terminology, formats and quality of data, currently being addressed by introducing common data models(24). While the EU has very rich data, due to universal healthcare present in all member states, many heterogeneities are present. For example, the data from EHRs may not be as readily accessible nor usabile in a regulatory sense, and skews heavily to originating from the Western and Northern Europe (24). Finally, the EHR data may not always be freely available in Europe, given that in some EU member states the insurance market is responsible for collecting and storing, thus they might be commercially owned (23).

Patient registries are another important source of RWD especially for rare diseases and cancer (23), to produce guidance on methodology and governance of patient registries and the EU has made initiatives on the patient registries and about their harmonization (23). In the cancer therapeutics space, population-based cancer registries are yet another source of RWD (23).

Some less obvious sources of RWD have been also described in literature, such as data from expanded accesss schemes (25), i.e. pre-approval access to medicines in tightly controlled and treatment-justified settings. For instance, a cross-sectional study of the EMA and FDA found that data from early access scehemes, traditionally a treatment procedure not used for research purposes, are a source of RWD and have been used increasingly while seeking regulatory approval in cases of high unmet medical need or for an orphan designation (25).

2. Uses of RWD

The best known application of RWD for regulatory decision making is to demonstrate drug safety in the post-marketing phase of drug development (13). However, RWD is used throughout the process of R&D of medicines as well as beyond. R&D of medicines begins with drug discovery and identification of an unmet medical need, and moves toward the development phase, with preclinical development, clinical trials Phases I-III, and post-marketing approval studies (Phase IV). RWE/RWD can be used at any number of phases of R&D. RWD can be used in the conduct of specific clinical trials, such as hybrid trials or single-arm trials, where a traditional RCT is not feasible or ethical. Futhermore, many specific cases, such as development of treatments for rare diseases and oncological treatments are documented.

RWE is used in post-approval safety considerations and establishing and updating side-effects that are may not be detected in phase III trials. This part of the drug life-cycle has seen one of the first examples of regulatory adoption of RWE, which was the USFDA Sentinel Initiative (13), and since then a steady rise in similar passive monitoring followed globally, to be used both by regulators and the industry.

Main opportunities for using RWD in the development of medicines are in identifying populations of interest for new treatments, disovering subtypes or subpopulations with a more pronounced unmet medical need and in facilitating trial recruitment (26). One application is the use of single-arm experimental trials. While traditional RCTs remain the “gold standard”, this standard is not always within reach, due to ethical, financial or other reasons (13), (27). Single-arm trials are trias where a historical control or other controls derived from RWD/RWE sources (e.g. EHRs) are used (27). This trial design is reported to be controversial among authorities (18). Advancements in regulatoy policy related to RWD/RWE demonstrate the changing attitudes of regulators toward RWD/RWE (13).

Applications of this trial design remain restricted to well-understood diseases and treatments that are expected to have a substantial and rapid effect (13).

RWD is also used in the realm of RCTs to better inform trial design. One key aspect is patient recruitment, for which there is a well-documented increase in RWD use by sponsors of clinical trials (13). That would in turn benefit more from the new therapies. In addition, practical implications, such as selecting optimal trial location and enabling more efficient recruitment thus decreasing the length of the trial, are examples of RWD use. Furthermore, use of RWD might increase in some cases the statistical power and generalizability of the trial (13). RWD can also be used to improve clinical trial design, and aim for a more efficient data collection, with effectiveness in data collection being reported as a bottleneck in R&D. This can be done by informing the trial design as to what variables carry most clinical significance, and which of them may be redundant (13).

Another subtype of clinical trials that benefits from RWD are pragmatic clinical trials (PCTs). PCTs are such trials that aim to "measure strength of associations between exposures and outcomes in real world settings, rather than to prove causal relationships" (13). EHR data may prove valuable in enabling the understanding of typical practices and patterns for the disease of interest, thus enabling the trial protocols to be closer to clinical practice (13).

RWD applications in the medicine development setting may also be used for establish efficacy as well as comparative effectiveness. RWD is even more useful when it comes to inclusion of special populations, routinely excluded from RCTs, such as pregnant and brestfeeding women, children or chronic kidney disease patients or other comorbidities in cardiovascular-related trials (13). One of the the most ubiquitious application of RWD is in the development of orphan-designated treatments, where trials are not feasable. Furthermore, some specific disease-areas such as oncology are widely seen as special areas of interest for applications of RWD/RWE, especially when it comes to the regulatory approval of new therapies (28). Immuno-oncology treatments, that have been on the rise in the past decade, have especially benefit from application of RWD . A good example is the PD-L1 checkpoint inhibitor approved by EMA in 2017, on the basis of a single-arm trial, that had to take place due to high unmet medical need for patients with aggressive skin cancer and the rarity of the specific condition (28). It is not uncommon in the oncology space that new indications, especially for checkpoint inhibitors, are supported by RWD. One example being an accelerated approval of nivolumab for a new indication by an USFDA in 2018, which is small-cell lung cancer that was also based on a single-arm trial with a historic comparator (28). In the oncology space, and increasingly in other therapeutic areas (29), RWD can also be applied in the early access tools for medicines, such as conditional approvals as well as adaptive regulatory pathways.

The findings of a 2020 retrospective study of regulatory approvals issued by USFDA and EMA associated with the use of RWD for new drug applications and line extensions reveal that in the period between 1998 and 2019, there were 17 identifiable cases where RWE was used to support a regulatory approval and 10 cases where it supported a line extension (30). The study also found that most common application of RWD was in oncology and metabolic drugs. The study also found that drugs from the new marketing approval applications were initiallty marketed as orphan drugs (30). Despite the fact that the aforementioned study was not by any means exhaustive, it demonstrates well how the RWD is currently used in the regulatory decision making.

3. "Regulatory Grade" RWE; Limitations of RWD/RWE

While the usefulness and importance of RWE is somewhat universally accepted, there is much debate as to what constitutes "regulatory-grade"' RWE, i.e. such RWE that is of sufficient quality to support regulatory decision-making. To understand this, some key methodological challenges related to RWE have to be examined. For the use of RWD in informing regulatory decision-making when it comes to clinical trials, unobserved co-founders have been reported in literature (16), especially when it comes to physician-made decision regarding patient care, that are reflected in EHRs, one of key sources of RWD. Historical control arms for clinical trials do not necessarily reflect the fact that medical care changes significantly over periods of time and the unreliable historical control is prone to creating more bias (26). Special trials that use RWD/RWE also lack the ability to closely monitor the adverse effects that are generally more easily detected with traditional RCTs (26). Finally, as previously addressed, there is a persisting issue with completeness of data and loss of follow-up, especially in EHRs (26), (22).

Randomization is seen as an especially valuable aspect of traditional RCTs, that significantly boosts their validity. While the blinded studies protect against biased interpretation of data, most study designs that utilize RWD are not blinded (31). In order to justify the use of RWD, it must be of sufficient quality . Some authors interpret this that the RWD sources need to be adequately qualified in their context by using most applicable designs and where the outcome measures are based on RWD practices (31). To advance the further use of RWD in the regulatory setting, and to eliminate biases present in RWD analyses, suggestions have been made in literature to integrate multiple designs using RWD to triangulate effects, to leverage novel statistical approaches to study cause-effect relationships, and finally to keep increasing the robustness of databases (26). RWD must ultimately remain fit for original purpose, and quality and completedness of it must be unimpeachable in order for it to be as admissible as RCTs (22). In order to further strengthen RWD analyses to meet the scientific and regulatory criteria, further technological developments in sourcing and analysing RWD will likely be the key (32). Finally, the regulatory-grade RWE must eventually be approached in

transparent and fully standardized ways (33).

4. Regulatory Policy towards RWD/RWE in the EU and US

Ensuring the quality of RWD/RWE that can be used in regulatory submissions will ultimately reside with regulators who need to develop standardized policies and guidance for the industry (34,35). In order for an RWD study to be utilised in the regulatory decision making, the sponsors of such studies would need to engage early with regulators to align objectives, validate study design and ensure that the regulator sees such data as fit-for-purpose (27)

In the US, pursuant to the 21st Century Cures Act of 2016, the US FDA launched a RWE Program to be instituted across both the drug and biological drug review processes (36). The FDA program covers both prospective non-interventional clinical trials, such as pragmatic trials, as well as retrospective observational studies using a historic comparator (36). In 2019, a Draft Guidance document was released (9), (30), which further demonstrated the agency's willingness to consider alternative study designs and provided some much-needed guidance to the industry. The guidance provides a detailed definition of RWD, a non-exhaustive list of sources of RWD as well as a definition of RWE. In terms of use of RWE in regulatory submissions, FDA recommends that the purpose of using RWE needs to be justified, that the study design needs to be explained and RWD sources should be listed (9).

Until 2020, the EMA had not issued formal guidance on using RWE in regulatory submissions but it is known that EMA accepts the RWE in its evaluations, on an *ad hoc* basis (11). A draft guideline (19)has been published for public comments in 2020. There have been notable initiatives, however, including a Big Data taskforce that was established in 2017 to explore challenges and opportunities for use of Big Data, including RWD, for the purpose of regulatory decision making (30). The taskforce identified 10 priorities for the agency, and EMA highlighted the most ambitious of it being "an establishment of an EU platrofm to access and analyse healthcare data from across the EU" – the DARWIN network (10). Guided by the notion that while the EU is extremely data-rich, yet still unable to harness the power of that data, the DARWIN network project aims at closing that gap. Initially this will be done by taking a closer look into the use and quality of EHRs to support regulatory decision-making, and further expanding towards other RWD sources, including claims and registry data (10).

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Appendix A : The Electronic Survey

Title: *The Use of RWD/RWE Study of Innovative Products Centrally Approved by the EMA in 2019*

Introduction to the Survey

Dear Respondent,

Thank you for agreeing to participate in this study concerning the use of Real World Data/Real World Evidence (RWD/RWE) in medicines development and regulatory decision making.

The aim of this study is to understand how RWD/RWE is used to support medicines development at different points of the medicine's lifecycle from discovery to clinical development and in the pre-approval phase especially with regards to regulatory submission. We also hope to gain knowledge about how RWD/RWE is used in regulatory submissions by the applicants and in turn how the EMA responds to RWD/RWE use as part of the regulatory submission.

As a representative of one of the companies identified as Marketing Authorisation Holder of product(s) that received an EMA Marketing Authorisation using the Centralized Procedure, you are asked to respond to a number of questions divided into 5 groups related to this subject:

- Parts 1-3: General questions related to your company characteristics, RWE use in development, RWE use in regulatory decision-making;
- Parts 4-5: Product specific questions related to RWE use in development, RWE use in regulatory decision-making.

The total time the survey should take is XX minutes.

Please note that the Part I about the company characteristics is included due to the high diversity of MAHs in our survey, companies ranging from large and small, and from companies that are specialized for one type of product to those that produce many kinds. The Parts IV-V explore information on the specific approved product/products as part of our cohort. Please refer to the introduction email of this survey in case you are unsure which product/products are of concern.

In order to participate in the survey to the best of your ability, we are sharing with you two definitions to keep in mind while responding.

Real World Data (RWD): According to the EMA, RWD are defined as "routinely collected data relating to a patient's health status or delivery of health care from a variety of sources rather than traditional clinical trials". In this definition, the EMA excludes traditional clinical trials (RCTs), even if single arm, but includes pragmatic clinical trials.

Real World Evidence (RWE): According to a broadly accepted definition, analytically processed RWD, in such a manner that yields valid evidence. Sources of RWD are data collected in a healthcare setting, such as electronic health records (EHRs), claims data, prescription data and patient registries, as well as data from wearable personal devices, mobile health apps and other factors related to the lifestyle and environment factors.

In addition to these two key definitions, the definitions of key terms used in this survey will be provided in places where we deemed further explanations might be necessary.

Data treatment and confidentiality

We will treat all data received in strict confidence. We have established processes to ensure the security of the data and information that we collect and hold. The data you provide here will be anonymized using a specialized key, which will be kept separate from the survey results and is only

accessible to an independent researcher at Utrecht University[needs to be explained in more detail]. Some of the questions, and moreover the answers, might fall under the category of sensitive information. The information will not be attributed to individual companies unless an explicit written consent is obtained. Due to the anonymization process, the researchers will not be able to connect any of that information to any particular company. Only the aggregate level of results will be included in the report, which we aim to publish in a peer reviewed scientific journal. The conduct of this survey complies in its entirety with the EU General Data Protection Regulation. Please let us know if you in addition require bilateral confidentiality agreement

Timeline

You will have X weeks to respond to this survey. We look forward to receiving your response **latest by day, mm.dd.yyy.** The study will complete by XX Jun 2021 and we are happy to share the outcomes with you.

Further information and contact

Should you have any questions/suggestions/concerns or other feedback, do not hesitate to contact us.

For technical questions of the survey, please contact Mr Aleksandar Gigov, BSc, Master's Student at Utrecht University Title, email, Telephone. If you have questions about further background of the study, please contact Ms Sini Eskola, MSc Pharm, Professional PhD Candidate, University of Utrecht, s.m.eskola@uu.nl, Telephone: +32470217237.

Please note that Ms Eskola works also at European Federation for Pharmaceutical Industries and Associations (EFPIA) as Director Regulatory Affairs, Drug development and manufacturing. This study is independent from EFPIA and only connected to the research at University of Utrecht.

Marketing Authorisation Holder Survey

1. Company Characteristics

The first four questions are related to your company and its broad characteristics. We are inquiring about these to better understand if there are trends related to company size or specialization and RWE use.

1.1. Is the company small/medium sized? (<250 employees) or large (>250 employees)?

Small □ Large □

1.2. To better estimate the size of the company, how many clinical trials are ongoing in the company at this moment?

- □ <10,
- □ 10-50,
- □ 50-100,
- □ >100

1.3. Is the company narrowly specialized for a certain type of products (tick the answer that applies)?

- □ No specialization
- □ Vaccines
- □ ATMPs

- □ Orphan drugs
- □ A disease area (please specify _____)
- □ Other(s) (please specify _____)

1.4. Is there a specialized department/group with tasks related to RWE in the company?

Yes □ No □

2. General questions about RWE use in development

The following 11 questions aim to assess pre-approval use of RWE in drug development, as it has (or hasn't) been done by your company in the past. Note that here we do not inquire about any particular product, but rather about past trends.

RWE Use & Sources of RWE

2.1 Does your company routinely use or generate RWD during product development?

Yes □ No □

2.2. Does your company routinely use 3rd party RWD in product development? (e.g. from EHRs, medical reimbursement claims or billing data)

Yes □ No □

2.3. Has your company used RWD derived from product registry and/or disease registry data?

Yes □ No □

RWE in Research and Development

2.4. To what extent does your company rely on Real World Insights for internal decision-making related to drug development?

Never	Rarely	Sometimes	Often	Always
□	□	□	□	□

2.5. Has your company ever used RWE in drug discovery and/or lead selection?

Yes □ No □

2.6. Has your company ever used RWE in clinical trial design, e.g. to define the trial population?

Yes □ No □

2.7. Has your company ever used RWE to supplement efficacy data to data obtained through RCTs?

Yes □ No □

2.8. Has your company in the past used RWE to supplement safety data to data obtained through RCTs?

Yes □ No □

2.9. Has your company in the past used RWE in defining the target population for a product?

Yes □ No □

2.10. Has your company in the past used RWE in early development, e.g. to differentiate the product from current clinical practice?

Yes □ No □

2.11. Has your company used in the past RWE for establishing the safety-profile of a product?

Yes □ No □

3. General questions about RWE use in regulatory decision-making

The following group of questions looks into how regulatory decision making with regards to RWD/RWE and experiences with RWD/RWE when seeking regulatory approval.

3.1. Does the company have experience with submitting RWE in dossiers when seeking marketing authorisations with the EMA?

Yes □ No □

3.2. Does the company have experience with submitting RWD/RWE in seeking regulatory approval with other major regulatory authorities? (tick all that apply)

- □ US FDA
- □ PMDA
- □ Health Canada
- □ NMPA
- □ None of the above

3.3. Did the company ever seek Scientific Advice from the EMA in relation to RWE?

Yes □ No □

3.4. Do you feel that there is a need for more guidance from the regulators when it comes to using RWE in regulatory submissions?

Yes □ No □

If Yes, please elaborate _____

3.5. Did the company ever **attempt** to use RWE to support regulatory submissions or any type of labelling change, including (tick all that apply)

- □ Full MAA
- □ Conditional MAA
- □ Adding/modifying an indication
- □ Changes in dose, dose regimen or administration route
- □ New population

- Adding comparative effectiveness information
- Adding new safety information
- Other labelling change, namely: _____

3.6. Did the company ever **successfully** use RWE to support submissions or any type of labelling change, including (tick all that apply)

- Full MAA
- Conditional MAA
- Adding/modifying an indication
- Changes in dose, dose regimen or administration route
- New population
- Adding comparative effectiveness information
- Adding new safety information
- Other labelling change, namely: _____

4. Product-specific questions about RWE Use in Product Development

As you are by now aware, one or more of your products have been identified as part of our cohort. In this segment we are asking you to answer these questions for that specific product.

4.1. Has the company used RWE in drug discovery for the product developed in 2019?

Yes □ No □

4.2. What decision motivated the use or RWE (tick all that apply)

- Ethical reasons as RCT was not feasible
- Low population/rare disease
- Cost-aspect of the development programme
- Availability of RWD (e.g. from literature)
- Something else, namely _____

4.3. Has there been an observational study performed or planned in relation to the product ?

- Before regulatory approval
- After regulatory approval
- An observational study was not performed

4.4. Was RWE used to define the target population of the product?

Yes □ No □

4.5. Has the company used RWE in early development, e.g. to differentiate the product from current clinical practice for the product?

Yes □ No □

4.6. Has the company used RWE in clinical trial design, e.g. to define the trial population for the product?

Yes □ No □

4.7. Has the company used RWE to supplement efficacy data to data obtained through RCTs?

Yes □ No □

4.8. Has the company used RWE to supplement safety data to data obtained through RCTs?

Yes □ No □

4.9. Has the company used RWE to supplement RCTs for special populations? (tick all that apply)

- □ Paediatric indications
- □ Use in pregnancy and lactation
- □ Use in geriatrics
- □ None

5. Product-specific questions about RWE in regulatory decision-making

The final questions are related to whether RWE was used in the marketing authorisation application for the product in question?

5.1. Did the company seek Scientific Advice from EMA in relation to the use of RWE for obtaining the MAA for this product?

Yes □ No □

5.2. If Scientific Advice from EMA was sought did EMA recommend that RWE be used in the submission?

Yes □ No □

5.3. Was RWE data submitted as part of the dossier while seeking the MA from EMA?

Yes □ No □

Appendix B: Responses Summary Tables

Table A: Summaries of responses on: Company Charactheristics, RWE Use and Sources and RWE Use in Regulatory Submissions at the MAH level

Company Characteristics (15 total)	**YES**		**NO**		**N/A**	
Large (Y)/Small (N)	12	80%	3	20%	-	-
Number of sponsored trials >100	6	40%	9	60%	-	-
Presence of Specific RWD department	9	60%	5	33,33%	1	6,67%
Outsourcing of RWD responsibilities	10	66,67%	2	13,33%	3	20,00%
RWE Use and Sources at MAH Level (15 total)	**YES**		**NO**		**N/A**	
Routine Use of RWE	12	80%	3	20%	-	-
RWE Use: Drug discovery/lead selection	2	13,33%	13	86,67%	-	-
RWE Use: Optimizing clinical trial design	7	46,67%	8	53,33%	-	-
RWE Use: Supplementing safety data	10	66,67%	5	33,33%	-	-
RWE Use: Supplementing efficacy data	11	73,33%	4	26,67%	-	-
RWE Use: Defining the target population	9	60%	6	40%	-	-
RWE Use: Differentiating the product from current clinical practice	9	60%	6	40%	-	-
RWE Use: Establishing the safety profile of the prod.	7	46,67%	8	53,33%	-	-
RWD Sourced from Claims	9	60%	6	40%	-	-
RWD Sourced from Product Registries	8	53,33%	6	46,67%	-	-
RWD Sourced from Patient Registries	9	60%	6	40%	-	-
RWD Sourced from Chart Reviews	9	60%	6	40%	-	-
RWD Sourced from Patient-Generated Data (e.g. apps and wearables)	5	33,33%	10	66,67%	-	-
RWE Use in Regulatory Submissions at MAH level (15 total)	**YES**		**NO**		**N/A**	
RWE Submitted in Previous MAAs with EMA	9	60%	6	40%	-	-
Scientific Advice Sought from EMA on RWE USE	11	73,33%	3	20%	1	6,67%
RWE Submitted With Other Major Regulators*	7	67,77%	8	53,33%	-	-
Need for more guidance from Regulators	12	80%	2	13,33%	1	6,67%
Submitted RWE for a Full MAA	8	53,33%	7	26,67%	-	-
Submitted RWE for a Conditional MAA	2	13,33%	13	86,67%	-	-
Submitted RWE for Adding/Modifying Indication	8	53,33%	7	46,67%	-	-
Submitted RWE for Changes of Dose, Dose Regimen or Administration Route	5	33,33%	10	66,67%	-	-
Submitted RWE for inclusion of a New Population	9	60%	6	40%	-	-
Submitted RWE to Add Comparative Effectiveness Information	3	20%	12	80%	-	-
Submitted RWE to Add New safety information	6	40%	9	60%	-	-

Table B: Summaries of responses on: RWE use for development and regulatory submission for the Product approved in 2019

RWE Use for Development of the Product Approved in 2019 (22 total)	**YES**		**NO**		**N/A**	
RWE Used	8	63,6%	14	36,4%	-	-
RWE Used in Early Development	1	4,5%	7	31,8%	14	63,6%
RWE Used to Support/Optimize an RCT	3	13,6%	5	22,7%	14	63,6%
RWE Used to Supplement Safety Data obtained from an RCT	3	13,6%	5	22,7%	14	63,6%
RWE Used to Supplement Efficacy Data obtained from an RCT	2	9,1%	6	27,3%	14	63,6%
RWE Used to Supplement Data for Special Populations	2	9,1%	6	27,3%	14	63,6%
RWE use motivated by low population size/rarity of the target disease	3	13,6%	9	40,9%	10	45,4%
RWE use motivated by cost-aspect of the development	3	13,6%	9	40,9%	10	45,4%
RWE use motivated by availability of RWE	5	22,7%	7	31,8	10	45,4%
RWE Use in the EMA Regulatory Submission for the Product Approved in 2019 (22 total)	**YES**		**NO**		**N/A**	
Scientific Advice sought from EMA	2	9,1%	6	27,3%	14	63,6%
EMA recommended the use of RWE in submission after Scientific Advice	2	9,1%	0	-	20	90,9%
RWE submitted as part of the dossier while seeking the MAA	5	22,7%	3	13,6%	14	63,6%
EMA reviewed RWE as part of the dossier and used it in the evaluation and decision	5	22,7%	3	13,6%	14	63,6%

Table C : Company specialization breakdown

Is the company specialized in a certain type of product and/or disease area?		
Answer	Count	Percentage
No specialization (SQ001)	4	26,67%
Vaccines (SQ002)	2	13,33%
ATMPs (SQ003)	1	6,67%
Orphan drugs (SQ004)	3	20,00%
Generics/biosimilars (SQ005)	2	13,33%
All of the above (SQ006)	1	6,67%
A specific disease area (SQ007)	4	26,67%
Other*	7	46,67%