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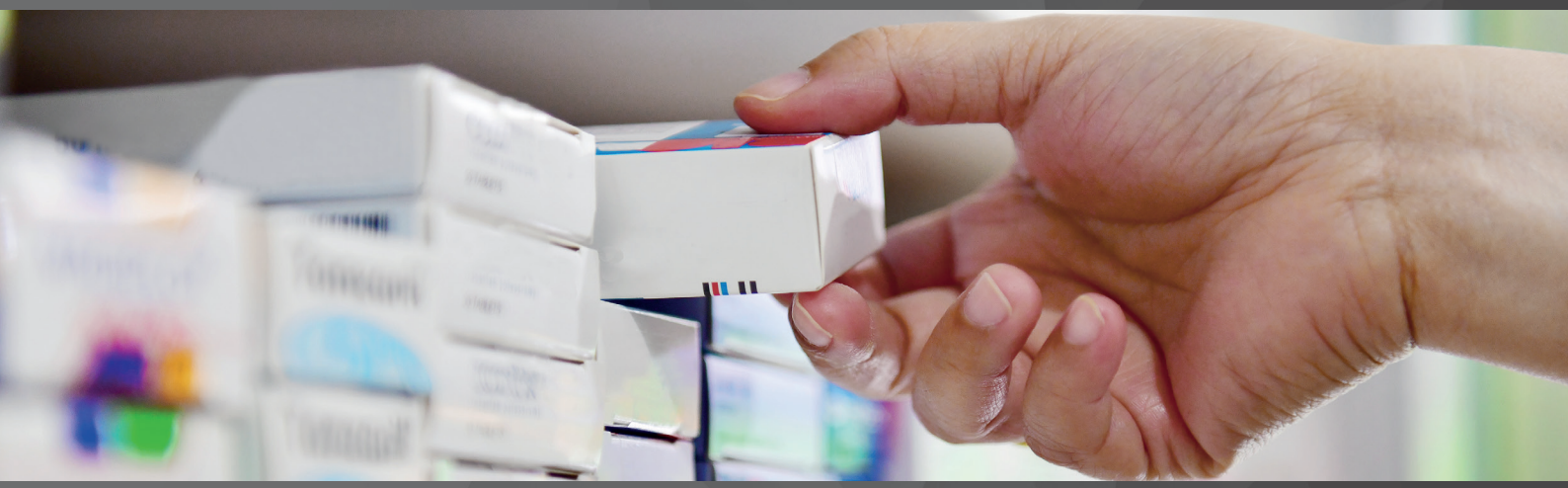

Pharmaceutical Advertising 2021

A practical cross-border insight into pharmaceutical advertising

18th Edition

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Real-World Evidence and Its Use in Advertising of Medicinal Products in the EU and U.S.


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Introduction

Interest in real-world evidence (RWE) continues to increase among industry and regulatory authorities alike, with the belief that generating such data can be a cheaper alternative to costly randomised controlled trials (RCT). RWE is also regarded as more representative of the population as a whole and of the real-life use of a product, compared to data produced in a conventional, and somewhat sanitised, clinical trial. Indeed, it was said at the "Global regulatory workshop on COVID-19 real-world evidence and observational studies" in July 2020 that: "*Evidence generated by high-quality observational research is fundamental to understanding the safety and effectiveness of medicines in everyday use by patients and doctors.*"[1]

However, up to now, the use of such data in regulatory submissions has been largely limited to post-marketing follow-up to explore areas where there is insufficient evidence pre-authorisation, or to support pricing and reimbursement approval. This chapter discusses the current position in relation to the use of RWE by regulatory authorities in the EU and U.S., and considers how such data can be used to support the advertising and promotion of medicinal products.

RWE and Its Strengths and Weaknesses

Regulatory and clinical decision-making continues to focus on the use of RCTs to evidence the safety and efficacy of a product, and to avoid bias being introduced into the data. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline E9 on Statistical Principles for Clinical Trials clearly states in Section 2.3 on Design Techniques to Avoid Bias: "*the most important design techniques for avoiding bias in clinical trials are blinding and randomisation (…)*". Clearly, blinding and randomisation can be used and carefully controlled in RCTs, which are conducted in selected populations with carefully defined eligibility criteria, and in a highly monitored setting.

In contrast, RWE is collected, by definition, without these controls being in place. Real-world data (RWD) is broadly defined as routinely collected health data, for example, from electronic healthcare records, disease registries and observational studies, or data collected via wearable devices. This data, when analysed to make inferences about treatments, produces RWE. The benefit of RWE is seen as the ability to collect data that are often not collected in the context of RCTs, and to answer research questions that might not have been studied. RWE is increasingly seen as a complement to RCT data, and which can provide information on the population as a whole, and on how factors such as the clinical setting and health system may influence treatment effects and outcomes.

However, many regulatory authorities are still cautious about using RWE. In particular, the data encompasses large data sets from a variety of sources, of uncertain quality, which leads to issues related to completeness, accuracy and consistency. RWD is often collected for a number of reasons, and not specifically to answer a pre-determined question, and is then subjected to post-hoc analyses to support regulatory decisions. There are also concerns about the methodology used in collecting and analysing such data, and in merging data sets from multiple sources. Editors of peer-reviewed journals have commented on the value of RWE,[2] and have noted that lack of randomisation in RWE studies may produce results prone to error or larger treatment effects than RCTs and, therefore, use should be limited. However, others noted that improvements in data collection and statistical methods to address potential differences between comparison groups and data sets meant that high-quality RWE could be generated, and such studies could contribute to the best available evidence for a product, particularly given the problem that clinical trial data might only be able to be extrapolated to relatively small patient populations.

Legal Framework in the EU

There is currently no established legal framework in the EU on the use of RWE in regulatory or clinical decision-making, and there is limited guidance available. Article 8(3)(i) of Directive 2001/81/EC states that the applicant for a marketing authorisation should provide "*the results of: - pharmaceutical (physico-chemical, biological or microbiological) tests; - pre-clinical tests;- clinical trials*". While this does not specifically refer to non-interventional studies (NIS) or RWE, this wording has not prevented the European Medicines Agency (EMA) from accepting data from uncontrolled trials in marketing authorisation applications. However, the use of RWE in regulatory submissions for new products or indications has been confined to a limited number of orphan products where RCTs are more difficult to conduct.[3]

The EU regulatory authorities are continuing to develop an understanding of the strengths and limitations of RWE. In March 2017, the Heads of Medicines Agencies (HMA) and the EMA established a Joint Big Data Task Force to explore how regulators might use RWE. This group produced a report in December 2019, and the joint HMA/EMA Big Data Steering Group has since been set up to implement the recommendation from the task force.[4] The EMA regulatory science strategy to 2025 also includes goals to promote use of high-quality RWD in decision-making and develop network competence and specialist collaborations to engage with big data.[5] However, as yet, there are no concrete principles or guidelines for authorisation holders or applicants on how RWE can be used or on the parameters of such use.

One area where RWE is more frequently used is in pricing and reimbursement decisions. A report published by the London School of Economics[6] analysed key pricing and reimbursement stakeholders' opinions of RWE across five European countries. Results showed that RWE was used to some extent in all countries, generally in accelerated access and re-review situations, but that there were a number of areas where improvement was necessary if RWE use was to become more commonplace. More recently, it has been reported[7] that RWE featured in almost all submissions for single-technology appraisals of cancer drugs by the National Institute for Health and Care Excellence (NICE) in the UK. While sources of RWE were routinely criticised as part of the appraisal process, the use of RWE was rejected in only two cases.

Legal Framework in the U.S.

Government authorities in the United States have recognised the value of RWE, particularly RWE that provides additional insights in evaluating and guiding the safe and effective use of medicinal products, and many companies are exploring the utility of RWE in regulatory applications. RWE has already been used as part of original and supplemental applications to the U.S. Food and Drug Administration (FDA), particularly in the oncology field. Moreover, with the COVID-19 pandemic highlighting the importance of RWE collection and use, many are arguing for rapid expansion of RWE use in product development and approvals, including as a "synthetic" control to accelerate clinical trials.

However, FDA, the Department of Justice (DOJ), the Office of the Inspector General of the Department of Health and Human Services (OIG-HHS) have also focused on compliance risks raised by RWE studies. As early as 1994, OIG-HHS expressed concern about payments to healthcare professionals (HCPs) in connection with studies "*of questionable scientific value and requir[ing] little or no actual scientific pursuit*".[8] For example, the government has characterised payments to physicians for entering RWD into registries as kickbacks where there is evidence that the company had no scientific need for the data or never used the data for any legitimate scientific or medical purpose.[9] Similarly, payments to HCPs in connection with data collection activities involving commercially-available products can raise significant risks under the Anti-Kickback Statute.

Even where payments are not involved, RWE studies can raise significant risks under the Federal Food, Drug, and Cosmetic Act (FDCA) and related laws, if not properly structured. FDA does not regulate the practice of medicine, and physicians are free to exercise their independent judgment on whether to prescribe a particular product. However, scientifically unsound RWE collection can also be used as evidence that such activities are intended to support false or misleading activity, in an attempt to avoid the necessary time, expense and regulatory oversight of well-controlled trials. Moreover, FDA has made clear that where data from an RWE study is being used to support an FDA approval or labelling change, the sponsor company is responsible for the soundness of the data submitted. Whistle-blowers and their lawyers are increasingly focused on perceived study integrity issues in RWE activities developed to support product labelling claims, including where purported data collection activities focus on scientifically unsound methodologies or unvalidated endpoints.[10]

Use of RWE in Advertising Claims in the EU

In relation to advertising and promotion, the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code includes provisions on NIS, which are a method of collecting RWE.[11] NIS must be conducted with a primary scientific purpose and similar to the concerns expressed in the U.S., the EFPIA Code makes clear that they must not be disguised promotion, and must not constitute an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. However, the EFPIA Code does not address how the data from NIS may be used in advertising and promotional materials.

Given the lack of concrete guidance in this area, it is necessary to consider the use of RWE from first principles to judge what is acceptable, depending on how the RWE will be used.

For example, EU law and guidance does not require pharmaceutical companies to obtain RCT data to support comparative claims and, therefore, does not prevent pharmaceutical companies from using RWE to support claims about their products.

There is, however, a general requirement under Directive 2001/83/EC that promotion must encourage the rational use of the product in question, by not being misleading and "*by presenting it objectively and without exaggerating its properties*".[12] It is also important that all advertising claims are in line with the product information and do not amount to off-label use. To this end, all the information contained in the promotional materials for a product must be not only accurate, up-to-date and verifiable, but also "*sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned*".[13] There is, therefore, a requirement for companies to reflect accurately and in a balanced way the results of the research available at the time the claims are made, including aspects of studies that might not be positive to the company product and any other relevant details that would enable HCPs to put the claims made in context.

In the UK, it is clear from the cases investigated by the Prescription Medicines Code of Practice Authority (PMCPA) that RWE is being used by companies as part of their advertising campaigns and to support claims made about products. The ICH Guideline on bias and randomisation has been quoted and used by the PMCPA in numerous cases regarding the quality of evidence substantiating claims made by marketing authorisation holders. The PMCPA's view on RWE is that such data can be used, provided it is not misleading and is compliant with the Code. Indeed, the Association of the British Pharmaceutical Industry (ABPI) Guidance on RWD published in 2011[14] states:

> "*There are many different ways in which RW data can support the marketing of a medicine. With its increasing acceptability, it can be considered as an alternative methodology to a randomised clinical trial to generate new evidence or to increase the robustness and credibility of existing claims.*"[15]

The PMCPA has reflected this in cases, in particular in relation to patient experience claims, for example stating:

> "*The Panel noted that the Code did not prohibit the use of retrospective observational studies that utilised prescription records to estimate outcomes as a means of substantiating a claim provided that the claim complied with the requirements of the Code.*"[16]

The critical issue is, therefore, the nature of the claim and the relative robustness of the data. Ultimately, whether a claim can be made will depend on what the statement is and whether the specific research supporting the claim can be considered robust, taking into account all available data. An overarching issue will likely be the quality of the data and the methodology used in its analysis. In general, where the claim relates to efficacy and/or safety, it is likely that results from RCTs will be viewed as more robust and reliable than studies based on RWE. In contrast, RWE may generate results that a randomised study was not designed to answer, and may support broader claims that might be made.

Use of RWE in Advertising Claims in the U.S.

There are significant limitations on when RWE may be disseminated in a manner consistent with applicable U.S. regulatory promotional requirements. Promotional labelling or advertising claims of safety or efficacy that lack adequate substantiation may be deemed false or misleading under the FDCA, rendering a drug or device "misbranded".[17] False or misleading statements, including overstatements as to the importance of particular data or a failure to disclose limitations on data, can also form the basis for false claims and other fraud allegations.

FDA generally requires promotional treatment benefit and safety claims to be substantiated by "substantial evidence". Under the FDCA and FDA regulations, the "substantial evidence" standard may be met by at least one "adequate and well-controlled study".[18] FDA has specifically noted that uncontrolled studies or partially controlled studies are generally not acceptable as the sole basis to substantiate promotional claims of effectiveness. For example, according to FDA, "*[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered*" as sufficient substantiation.[19]

That said, FDA has acknowledged in guidance that information that is not found in approved labelling but is nonetheless "consistent" with FDA-required labelling (or CFL) may be utilised in product promotion. To be truthful and non-misleading, such communications must "*be grounded in fact and science and presented with appropriate context…any data, studies, or analyses relied on should be scientifically appropriate and statistically sound to support the representations or suggestions made in a CFL promotional communication*".[20] Given that RWE is not subject to the same methodological controls as RCTs, RWE can often have limited utility in product promotion and can be used, at least at this time, primarily to supplement or explain more controlled data, with transparency and disclosures as to the limitations of the RWE.

RWE currently plays a bigger role in promotional communication of healthcare economic information (HCEI) to payors, such as health insurers and other entities making coverage and reimbursement decisions on a population basis. Section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA 114) allows a manufacturer to convey HCEI relating to on-label uses of a drug or biologic to payors when substantiated by "*competent and reliable scientific evidence*".[21] Such claims describe the economic consequences of a particular treatment without making claims about its safety or efficacy. Under that standard, and with appropriate disclosures, RWE can be used as part of validated pharmacoeconomic methodologies to develop analyses that can be utilised to promote the cost-effectiveness or other economic aspects of the particular drug in an approved indication. Notably, claims substantiated under the FDAMA 114 standard must be truthful, non-misleading, consistent with the approved label, and meet other relevant requirements. Moreover, while RWE can be used to support clinical assumptions for economic claims to payors, FDAMA 114 is not a vehicle for conveying clinical claims to payors that do not otherwise meet applicable standards.

Practical Considerations When Using RWE to Support Advertising Claims

Given the above, we set out some points that should be considered when seeking to rely on RWE to support advertising claims. The overarching factor of whether RWE will be accepted will depend on the quality and completeness of the data, and the relevance of and purpose for which it will be used.

- Understand **why** the RWE was collected. For example, was it collected to answer a specific relevant question (with a pre-defined protocol), or has a post-hoc analysis been undertaken?
- Understand **how** the RWE was collected. For example, what was the study design and methodology? What analytical methods where used? Were adequate controls utilised to ensure that payments for RWE conform with legal requirements relating to kickbacks or bribes to physicians or healthcare institutions, ensure integrity of the data, and comply with privacy requirements?
- Describe other available data that might answer the question you are trying to answer, or that may conflict with the RWE. Otherwise, there will be a risk that the claims will be considered as not being balanced and not being based on an up-to-date evaluation of all the evidence and reflecting that evidence clearly.
- Describe **why** you want to use the RWE and that the data is fit for purpose to answer the relevant question or support the relevant claim. The acceptability of the use of RWE will depend on what is the focus of the claim (e.g. efficacy versus clinical effectiveness) and what questions are not answered by the RCT, or the scope of other evidential uncertainties.
- Ensure the use of RWE is consistent with the contents of the Summary of Product Characteristics (SmPC) or approved labelling, and meets applicable substantiation standards. Care should be taken where RWE goes beyond the RCT data.
- Remember that there are real differences of opinion among authorities and ethics committees about the collection and use of such data, so ensure you are aware of the regulatory framework and the current views on whether the data collected will be able to be used for the intended purpose.

Future Developments

The EMA has acknowledged in the HMA-EMA Joint Big Data Taskforce Phase II report, "Evolving Data-Driven Regulation", that: "*It is clear that the data landscape is evolving and that the regulatory system needs to evolve as well.*"[22] It is also clear that the regulatory authorities are hoping to meet that challenge. They continue to explore how RWE can be exploited, and how the collection and analysis of such data can be standardised so data sets can be more easily combined, and there are a number of ongoing discussions and consultations about the use of RWE in regulatory decision-making.

For example, at the end of 2020, the EMA ran a consultation on RWE and the use of registry-based studies.[23] The guidance aims to optimise the use of registry-based studies as a source of RWE that can be used in the context of the benefit-risk evaluation of medicinal products. In addition, a number of collaborations between agencies, academic institutions, patient groups and pharmaceutical companies have been launched recently, including, in February 2021, RWE4Decisions[24] and, in April 2021, GetReal Institute.[25] These are aimed at reducing barriers to the use of RWE in healthcare decision-making, and developing best practices for generating and using RWE.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued draft guidance[26] on RTCs generating RWE that will be used to support regulatory decisions. It is intended to be the first in a series of guidance documents addressing RWE. It sets out the factors that need to be considered when collecting RWD as part of a clinical trial. In terms of using RWE for regulatory submissions, the MHRA says there is nothing barring the use of RWE to gain an initial approval or approval of a new indication – it is not the source of the data that is the critical question, but whether the data quality is "robust" and the trial is "*designed in a way which allows it to provide the evidence required to answer the regulatory question*". For low interventional

trials, the MHRA will accept the data for regulatory purposes "*if the key endpoints necessary to make the regulatory decision are routinely collected in the database and are sufficiently objective such that they would not be subject to meaningful bias from the knowledge of treatment allocation in an open-label setting*". Notwithstanding this, the consultation states that an RWE approach is likely to be most suited to labelling changes and adding a new indication.

In the U.S., FDA has developed a framework for its RWE programme, and produced guidance on RWE use in regulatory submissions and in supporting regulatory decision-making for medical devices, as well as on the general use of electronic health records in clinical investigations.[27] The agency has also provided grants for entities exploring the use of RWE in regulatory decision-making. In addition, legislation that will be considered in the coming year, including a "21st Century Cures 2.0" proposal and reauthorisation of FDA user fees that help fund the drug and medical device review processes, will likely include new provisions to further advance the role of RWE in drug and medical device development and approval processes.

Endnotes

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3. "Use of Real-world Data for New Drug Applications and Line Extensions", Bolislis *et al.*, *Clinical Therapeutics*, 24 April 2020 (https://doi.org/10.1016/j.clinthera.2020.03.006).
4. "Big data", *European Medicines Agency* (https://www.ema.europa.eu/en/about-us/how-we-work/big-data).
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7. "Real-world evidence use in assessment of cancer drugs by NICE", Bullement *et al.*, *International Journal of Technology Assessment in Health Care*, 10 July 2020 (https://www.researchgate.net/publication/342850358_Real-world_evidence_use_in_assessments_of_cancer_drugs_by_NICE).
8. OIG-HHS, Special Fraud Alert: Prescription Drug Marketing Schemes, 59 Fed. Reg. 65,372, 65,376 (19 December 1994); *see also* OIG-HHS, Publication of OIG Special Fraud Alerts, 59 Fed. Reg. _____, FR Doc. No. 94-31157 (19 December 1994) (identifying as a fraudulent activity, a "*research grant program in which physicians were given substantial payments for de minimis recordkeeping tasks…[t]he physician administered the drug manufacturer's product to the patient and made brief notes, sometimes a single word…upon completion… the physician received payment from the manufacturer*") (internal quotations omitted).
9. For example, in 2006, Serono resolved a civil fraud investigation focused, in part, on non-FMV payments to physician "investigators" associated with two post-marketing observational studies related to Serostim®. Physicians participating in these two studies were Serostim® prescribers who were allegedly paid hundreds of dollars to fill out one-page questionnaires which did not ask substantive questions about observational data and which were allegedly never used by Serono. In some instances, physicians were also alleged to have paid a per-patient enrolment fee, which was considered by the government to be an unlawful inducement. Together, these allegations supported the government's theory that the Serono observational studies did not serve a legitimate purpose (e.g., helping answer a scientific question) but rather evidenced an improper intent to reward and increase referrals of Serostim®. *See*, e.g., Second Amended Class Action Complaint, *Government Employees Hospital Association v. Serono*, 1:05-cv-11935-PBS, para. 11 (D. Mass. filed 21 March 2006); Third Amended Class Action Complaint, *Government Employees Hospital Association v. Serono*, 1:05-cv-11935-PBS, paras 11-12, 153 (D. Mass. filed 16 October 2006). *See also* Serono Settlement Agreement (October 2005), para. H.iii. (resolving allegations that, *inter alia*, Serono caused the submission of false claims to federal healthcare programmes through allegedly unlawful SALSA and SeronAIDS survey payments).
10. *See*, e.g., Corrected First Amended Complaint, *ex rel. Petratos v. Genentech, Inc., et al.*, 2:11-cv-03691-MCA-LDW (D.N.J. filed on 16 April 2015) (alleging the sponsors of Avastin failed to properly design RWE studies required to support FDA approval and failed to fully disclose to FDA negative safety data from RWE studies).
11. Article 18, with similar provisions in Clause 22 of the 2021 ABPI Code.
12. Article 87.3.
13. Article 92.1 of Directive 2001/83/EC.
14. "ABPI Guidance demonstrating value with Real World Data: A practical guidance", May 2011.
15. Section 4 of the "ABPI Guidance demonstrating value with Real World Data: A practical guidance", May 2011.
16. AUTH/3135/12/18 – *Complainant v. Astellas* (https://www.pmcpa.org.uk/cases/completed-cases/auth31351218-anonymous-complainant-v-astellas/#:~:text=CPRD%20was%20a%20real-world%20research%20service%20supporting%20retrospective%20and%20prospective%20public%20health%20and%20clinical%20studies.%20).
17. 21 U.S.C. 352.
18. 21 C.F.R. 314.126.
19. 21 C.F.R. 314.126(e). Further, in the context of promotion, FDA regulations caution against "*pooling data from various insignificant or dissimilar studies in a way that suggests either that such ['statistics'] are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case*". 21 C.F.R. 202.1(e)(6)(xiv).
20. "Medical Product Communications that are Consistent with FDA-Required Labeling – Questions and Answers, Guidance for Industry", *Food and Drug Administration*, June 2018 (https://www.fda.gov/media/133619/download).
21. 21 U.S.C. 352(a), as amended by Section 114 of the Food and Drug Modernization Act of 1997.
22. HMA-EMA Joint Big Data Taskforce Phase II report: "Evolving Data-Driven Regulation", EMA/584203/2019.
23. "Guideline on registry-based studies", *European Medicines Agency* (https://www.ema.europa.eu/en/guideline-registry-based-studies).
24. https://rwe4decisions.com.
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26. "MHRA draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions" (https://www.gov.uk/government/consultations/mhra-draft-guidance-on-randomised-controlled-trials-generating-real-world-evidence-to-support-regulatory-decisions).
27. *See* "Real-World Evidence", *Food and Drug Administration* (https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence).

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