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### The Commercial Aspects of Regulatory Approvals

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#### Abstract

**Objective** To investigate the regulatory approval of new medical devices.

**Design** Cross sectional study of new medical devices reported in the biomedical literature.

**Data sources** PubMed was searched between 1 January 2000 and 31 December 2004 to identify clinical studies of new medical devices. The search was carried out during this period to allow time for regulatory approval.

**Eligibility criteria for study selection** Articles were included if they reported a clinical study of a new medical device and there was no evidence of a previous clinical study in the literature. We defined a medical device according to the US Food and Drug Administration as an “instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article.”

**Main outcome measures** Type of device, target specialty, and involvement of academia or of industry for each clinical study. The FDA medical databases were then searched for clearance or approval relevant to the device.

**Results** 5574 titles and abstracts were screened, 493 full text articles assessed for eligibility, and 218 clinical studies of new medical devices included. In all, 99/218 (45%) of the devices described in clinical studies ultimately received regulatory clearance or approval. These included 510(k) clearance for devices determined to be “substantially equivalent” to another legally marketed device (78/99; 79%), premarket approval for high risk devices (17/99; 17%), and others (4/99; 4%). Of these, 43 devices (43/99; 43%) were actually cleared or approved before a clinical study was published.

**Conclusions** We identified a multitude of new medical devices in clinical studies, almost half of which received regulatory clearance or approval. The 510(k) pathway was most commonly used, and clearance often preceded the first published clinical study.

#### INTRODUCTION

Randomized controlled trials (RCTs) have been considered the gold standard to demonstrate efficacy since the 1960s.<sup>1,2</sup> While current routes to market for investigational drugs typically require at least two pivotal RCTs, these are time-consuming, costly, and produce evidence that can have limited applicability in real-world clinical practice. There is, therefore, a move towards investigating innovative ways to improve the efficiency of clinical research.<sup>3,4</sup>

The controlled nature of an RCT offers advantages in evidence generation as there are standard methods to reduce bias (like randomization and blinding), and they have comprehensive measurement of outcomes to demonstrate efficacy against both active and placebo controls.<sup>5</sup> However, RCTs do not accurately reflect real-world circumstances under which patients are treated; thus, there is often a need for observational studies to support additional evidence generation, particularly around questions of safety.

Real-world data (RWD) forms the basis for real-world evidence (RWE) and can be extracted from a broad range of sources such as patient registries, health care databases, claims databases, patient networks, social media, and patient-generated data from wearables.<sup>6-9</sup> The definitions of RWD and RWE are relatively consistent between key regulatory agencies (see Table 1).<sup>7,8,10</sup> While RWE from observational studies is well accepted for post-approval safety monitoring and to answer pharmacoeconomic questions<sup>3,11,12</sup> its contribution to regulatory decisions around effectiveness has been more limited. Indeed, evidence quality can be compromised by confounding by indication or a general lack of rigorous collection standards.<sup>5</sup> There is, therefore, a need for the development of novel trial methodologies that can take the best parts of traditional RCT and observational study designs to produce RWE that provides adequate scientific evidence for regulatory decision-making. It has already been recognised by health authorities that there is a wide spectrum of potential uses of RWD/RWE in clinical studies, some of which preserve key features such as randomization.<sup>13</sup>

## 1. REGULATORS ARE WILLING TO EMBRACE NEW APPROACHES TO RWE

While acceptance of the role RWE could play in regulatory decision-making is not universal, opinions within regulatory agencies are evolving, and there is a growing acknowledgement that the current drug approval process no longer fully meets current health care needs.<sup>14</sup> For example, Dr Janet Woodcock, Director of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research, has acknowledged that the current drug approval system is “broken” and expressed the agency’s commitment to find new ways to collect and utilize patient data to improve the process.<sup>14</sup> Dr Woodcock has said, “FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren’t studied prior to approval.”<sup>14</sup> The use of RWE to support effectiveness decisions has been used

in rare diseases, as highlighted by the examples of BAVENCIO and BLINCYTO (Case study boxes 1 and 2), both of which received accelerated approval using data from external, historical controls.<sup>15,16</sup> The case of BLINCYTO is of particular interest, as it was subsequently approved as a treatment for minimal residual disease in patients with acute lymphoblastic leukemia.<sup>17</sup> This approval was based on the results of a single-arm trial supported by RWE providing benchmarking information and was the first example of the FDA approving a drug for minimal residual disease.<sup>18</sup> A randomized clinical trial incorporating pragmatic design elements was also recently used to support a label extension for a drug treating a more common condition, schizophrenia, as demonstrated by the example of INVEGA/SUSTENNA (Case study box 3).<sup>19-21</sup> This demonstrates the willingness of regulatory authorities to consider RWE for regulatory decision-making when there is an unmet medical need.<sup>22</sup>

Regulators (including the FDA and European Medicines Agency [EMA]), data science companies (eg, Flatiron Health, New York, NY, USA, and IQVIA, Research Triangle Park, NC), and pharmaceutical companies are actively evaluating ways to embrace RWE to optimize the drug development cycle.<sup>23</sup> While the FDA and EMA are often seen to be at the forefront of these changes, other agencies are also leading the way in producing their own guidance, sharing different perspectives and approaches based on their specific needs and region characteristics.

The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has recently updated its regulations and published guidelines to encourage the use of RWD to satisfy post-safety requirements and has shown a willingness to expand its application to regulatory

|                                     | RWD                                                                                                                       | RWE                                                                                                                   |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| FDA<br>(United States) <sup>6</sup> | “Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources” | “Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD” |
| EMA<br>(Europe) <sup>7</sup>        | “Health care related data that is collected outside of randomized clinical trials”                                        | “Evidence coming from registries, electronic health records, and insurance data”                                      |
| PMDA<br>(Japan) <sup>10</sup>       | “Data that is electronically generated and stored by medical institutions”                                                | <i>No official definition has been issued at this time</i>                                                            |

**TABLE 1** Definitions of RWD and RWE from some key international regulatory authorities

Case study box 2.

BLINCYTO (blinatumomab) Developed by Amgen

- Received accelerated approval by the FDA (2014) and EMA (2015) for the treatment of relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia based on a single-arm, open-label, phase 2 study.<sup>16,99</sup>
- Historical controls who received standard of care were used to show effectiveness based on weighted analysis of patient-level data from medical chart reviews.<sup>100</sup>
- Full approval was subsequently granted (2017 FDA; 2018 EMA) based on confirmatory phase 3 data.<sup>101</sup>

Abbreviations: EMA, European Medicines Agency; FDA, United States Food and Drug Administration.

Case Study Box 3.

INVEGA SUSTENNA (paliperidone palmitate) Developed by Janssen

- Data were added to the previously approved FDA label (January 2018) for this long-acting form of INVEGA, indicated for the treatment of schizophrenia, on the basis of a randomized, open-label, pragmatic clinical trial.<sup>19-21</sup>
- This trial was conducted in real world clinical practice and included flexible treatment interventions, active comparators, and relaxed exclusion criteria to include higher-risk patients. It evaluated time to first treatment failure, defined in terms relevant to the clinician and the patient.
- The study included patients who had prior contact with the criminal justice system and was the first example of the use of RWE from a pragmatic trial in schizophrenia to support a regulatory decision, in this case, an expansion of the label.

Abbreviation: FDA, United States Food and Drug Administration.

Case study box 1.

BAVENCIO (avelumab) Developed by Merck KGaA in alliance with Pfizer and Eli Lilly

- Received accelerated approval by the FDA (2017) for the treatment of metastatic Merkel cell carcinoma and urothelial carcinoma.
- Received conditional approval by the EMA (2017) for the treatment of Merkel cell carcinoma.
- These approvals were based on findings from a single- arm, open-label, Phase II study, JAVELIN Merkel 200 (<https://clinicaltrials.gov/ct2/show/NCT02155647>). Historical controls that met the enrollment criteria were identified using McKesson's iKnowMed electronic healthcare records and a German patient registry, and were used as a benchmark to characterize the natural history of the disease.<sup>15</sup>

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

how RWE has already been used for regulatory labelling.<sup>41</sup> Indeed, Health Canada has begun to consider RWE as part of the totality of evidence to support its regulatory decisions, as illustrated by the fact that in April 2019 they approved an expansion of the existing approved pediatric indication for Prevnar 13 to include acute otitis media in children 6 weeks to 5 years of age using real-world data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey.<sup>42,43</sup> Health Canada is also collaborating with Health Technology Assessment (HTA) partners to establish a joint document that aims to formalize and optimize the use of RWE throughout the drug life cycle.<sup>44</sup> Similarly, in Europe, the report of the HMA-EMA joint big data taskforce has also reinforced the need for collaboration across all stakeholders, from regulators to payers, HTA bodies, patients, academia, and industry to assess how RWE can contribute to effectiveness decisions.<sup>25</sup>

## THE EMERGING RULES FOR RWE THAT IS FIT FOR REGULATORY PURPOSES

The 21st Century Cures Act and PDUFA VI requires the FDA to accelerate drug development and approval processes, and more specifically, to produce guidance on how to incorporate patient perspectives and innovative study designs, including RWE, into the drug development process.<sup>45-47</sup> The recently published FDA framework for evaluation of how RWE can be incorporated into the regulatory approval process highlights the key topics for which full evaluation will be undertaken.<sup>8</sup>

| Details of the Initiative                                                                                                      |                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Guidance to submit documents using real-world data and real world evidence to FDA for drugs and biologics (2019) <sup>24</sup> | This guidance is intended to encourage sponsors and applicants who are using RWD to generate RWE as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format. |
| HMA/EMA Joint Task Force on Big Data (2019) <sup>25</sup>                                                                      | This document provides recommendations for a path towards understanding the acceptability of RWE from “Big data” sources to support regulatory evaluation and monitoring.                                          |

|                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Framework for FDA: Real-world evidence program (2018) <sup>8</sup>                                                               | The FDA published a framework to help evaluate the potential use of RWE to support new indications for drugs already approved or to satisfy post-approval study requirements. This framework demonstrates a commitment to transforming the drug development cycle.                                                                                                                                                                                                                                                                                                                  |
| Guidance on the use of Electronic Health Records (FDA) (2018) <sup>26</sup>                                                      | The focus of this guidance is on data integrity. It emphasizes the need to cite the “data originator” and preserve the audit trail. It also reinforces that RWE may be used to inform approval of new indications for approved drugs and to satisfy post-approval study requirements.                                                                                                                                                                                                                                                                                               |
| Brigham and Women's Hospital/Harvard Medical School/Aetion study, RCT DUPLICATE (FDA funded) (Started end of 2017) <sup>27</sup> | This initiative explores whether results from 30 clinical trials (previously used for approval decisions and from multiple therapeutic areas) can be replicated with RWE. FDA also recently announced, the expansion of their demonstration project, using real-world evidence to predict the results of seven ongoing Phase IV trials.<br>Along the same lines, another study (REPEAT; ENCePP registration number: EUPAS19636) is also underway independently of the FDA ( <a href="https://www.repeatinitiative.org/">https://www.repeatinitiative.org/</a> ).                    |
| MyStudies mobile App (FDA) (2018) <sup>28</sup>                                                                                  | This is a validated and publicly available software application (App) from the FDA, aiming to provide a template for the collection of RWD.                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Complex Innovative Trial Designs Pilot Program (FDA) (Started 2018) <sup>29</sup>                                                | This pilot program offers drug developers a chance to increase their interactions with the FDA to discuss and develop innovative trial designs and analysis plans. This could include the use of RWD to generate RWE.                                                                                                                                                                                                                                                                                                                                                               |
| Clinical Trials Transformation Initiative (FDA) (Started 2017) <sup>30</sup>                                                     | Established by the FDA and Duke University, this public–private collaboration aims to create and disseminate recommendations for improving clinical trials. Several of their initiatives encourage the increased use of RWD. This initiative is also responsible for the Sentinel IMPACT-Afib international, prospective, cluster-randomized pragmatic study, which is currently testing the effect of early educational intervention on real-world clinical practice. <sup>31,32</sup>                                                                                             |
| Patient registries initiative (EMA) (Started 2015) <sup>33</sup>                                                                 | This project aims to facilitate the establishment and systematic approach to use of patient registries in order to collect high-quality data for regulatory decision-making.                                                                                                                                                                                                                                                                                                                                                                                                        |
| Adaptive pathways (EMA) (2014-2016) <sup>34</sup>                                                                                | This initiative aims to use current European regulatory framework to speed up patient access to medicines. It encouraged principles such as iterative development/approvals, RWD as a supplement to trial data, and early discussions with patients and health-technology-assessment bodies. In parallel, the Innovative Medicines Initiative (IMI) launched the ADAPT-SMART initiative ( <a href="https://www.infographic.adaptsmart.eu/">https://www.infographic.adaptsmart.eu/</a> ), which brought together stakeholders to develop better ways to achieve “adaptive pathways.” |
| IMI GetReal (EMA is a member) (2013-2016) <sup>35-37</sup>                                                                       | IMI is a partnership between the European Union and the European pharmaceutical industry that collaborates on a range of initiatives aimed to advance and accelerate patient access to medicines, particularly where there is unmet need. The GetReal project discussed, proposed, and created tools to support new robust methods of RWE synthesis for use throughout the drug lifecycle, including regulatory decision-making. Although the initial project has formally finished, their work continues through the IMI GetReal initiative launched in 2018.                      |

|                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Regulatory Update for Promoting RWD Utilization (PMDA) (Started 2017) <sup>38</sup> | To encourage RWD utilization, the ministerial ordinance (Good Post-Marketing Study Practice, or GPSP) was amended in October 2017 and implemented on April 1, 2018. MID-NET (Medical Information Database Network) was also formally launched on April 1, 2018, allowing certain stakeholders to utilize this database. The next five years will be an important period for considering and expanding the use of RWD to support regulatory processes. |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

There is a need to define the rules for RWE that is fit for regulatory purposes. However, while the development of innovative trial designs is being actively encouraged by the major regulatory agencies, particularly with the FDA's Complex Innovative Trial Designs Pilot Program and Clinical Trials Transformation Initiative and the EMA's adaptive pathways initiative, the required standards to produce RWE that is acceptable for regulatory decision-making have not yet been fully defined.<sup>29,30,34</sup> Although regulators are open to proposals for studies with RWD and receiving RWE, the decision to pursue an innovative study design as part of a clinical development program and regulatory approval strategy is not straightforward, as the routes to obtaining pilot guidance are complex and the “rules” for acceptance of evidence in regulatory decision-making are not yet firmly defined. It is therefore essential to engage with regulatory authorities early to obtain alignment on objectives, inform the study design, and ensure the study design and data are acknowledged as “fit-for-purpose” before conducting a study that may not meet the regulatory goals.

To aid this process, several stakeholders have published frameworks and recommendations for the creation of RWE suitable for use in regulatory decisions. The Duke-Margolis Center for Health Policy, with support from the FDA, released a white paper on the regulatory use of RWE in 2017 following open consultation with academics, patients, and industry.<sup>48</sup> Emphasizing considerations for developing RWE that is fit for regulatory purposes, they identified several areas for practical improvement, including the need to ensure that the appropriate RWD sources are matched with appropriate study designs and data collection and handling methods to address the research question. They also encourage the formation of transparent collaborations and the sharing of datasets. Professional societies have also weighed in here too, with the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology publishing recommendations for good procedural practices for RWE, aiming to build trust and expand its current use in health care decision-making.<sup>49</sup> Many of the recommendations made in these aforementioned publications have been formalized in the FDA framework document.<sup>8</sup>

An important part of planning innovative studies to produce RWE that provides adequate scientific evidence for regulatory decision-making is preparation of a thorough analytical plan at the outset of the study. This is already an integral part of most traditional pivotal and post-safety trials and should reasonably be extended to effectiveness studies that use RWD. Some also argue that pivotal and safety outcome RCTs and observational post authorization safety studies should be registered on appropriate repositories (eg, ClinicalTrials.gov or the EU PAS Register) prior to study initiation as a requirement of the regulatory process. Whether RWE studies will be required to be registered in such a way is a topic of ongoing debate, with opinion sharply divided. Registration by itself is no guarantee of study quality, and any benefit from registration would be heavily dependent on what information would be required to be posted (eg, study protocols, methodological details, etc.). Further discussions between stakeholders will be required before a consensus develops.

In a separate framework on the regulatory use of RWE, Dreyer (2018) has discussed the requirement and transferability of key RCT study design elements to real-world studies. This builds on the current thinking around clinical outcomes from RWD analysis, suggesting that outcomes should be patient-centric and should be observable and relevant to daily clinical practice. Specific issues are addressed, such as blinding, which is routinely used in RCTs, but is often impractical to achieve under “real-world” circumstances, especially when comparing pharmacologic and nonpharmacologic treatments and when using a selection of “standard of care” comparators, which differ by locale, and while informative, would be impossible to blind. Furthermore, blinding might not be necessary for objective outcomes such as the results of a blood tests and imaging, for example, where in most cases, third-party raters, such as pathologists, are essentially blinded to treatment.<sup>50</sup> The importance of using data sources that are “fit for purpose” and the familiarity of researchers with potential sources of bias or error so that the most appropriate study methodology is employed is also emphasized. Analytical methods should be transparent, defined up front, and optimized to answer the research question.

Regulators and industry have acknowledged the value of scientifically rigorous and innovative study methodologies as the key route to achieving the standard of substantial evidence for RWE.<sup>8,48,51</sup> As a means to achieve this, the FDA framework proposes that the following should be considered: (a) whether the RWD are fit for use; (b) whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question; (c) whether the study conduct meets FDA regulatory requirements (eg, for study monitoring and data collection).<sup>8</sup> It should be noted that strict applicability of these rules, particularly for monitoring, is rarely feasible for studies that rely on existing data, since the identities of patient and care providers are masked to protect privacy in most secondary data sources.

Similarly, the EMA in its recent report on the use of large datasets for RWE made several recommendations to improve the quality of RWE, including the need to define standard formats for documenting datasets, protocols, and tools used to ensure study reproducibility. In addition, it emphasizes the need to ensure that outcome measures from novel data sources such as wearables should be reflective of a defined clinical benefit.<sup>25</sup> If these considerations and recommendations are fully addressed by novel study methodologies, the quality of RWE will improve, and studies using RWD could increasingly be used in support of decisions about therapeutic effectiveness. The development of sufficiently robust RWE will ultimately depend on the ability of experts such as pharmacoepidemiologists, statisticians, data scientists, and academics to develop these new methodologies to optimize hybrid study designs, RWD collection and analysis in a way that is compliant with our current understanding of best practice for RWE generation, and open to regulatory scrutiny.<sup>8</sup> Sponsors and data owners should proactively identify and develop standard

**TABLE 3** Examples of FDA and EMA accelerated approvals, full approvals, and label expansions that used RWE to support regulatory decision-making in the past decade

| Drug                                     | Indication (Health Authority, Year)                                                                                                 | RWE Use Examples                                                                                                                                                                                                                                                               |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lumizyme/Myozyme<br>(alglucosidase alfa) | Pompe Disease (FDA, 2010)                                                                                                           | The approval relied on a placebo-controlled trial, in late-onset Pompe disease, supported by clinical outcomes data in infantile-onset patients from the Pompe Registry, which was launched as a post-marketing commitment for the 2006                                        |
|                                          |                                                                                                                                     | Myozyme approval in Europe. The registry data showed increased survival at 18 months in Lumizyme patients compared with age- and disease-matched historical controls. The Myozyme approval also relied on a comparison to a 61-patient historical control group. <sup>56</sup> |
| Carbaglu (carglumic acid) tablets        | Hyperammonia caused by N-acetylglutamate (NAGS) deficiency (FDA, 2010)                                                              | The approval relied on a retrospective review of 23 NAGS deficiency patients who received Carbaglu for a median of approximately eight years, and on data from 3 patients with NAGS deficiency treated in a prospective trial. <sup>59</sup>                                   |
| Voraxaze (glucarpidase)                  | Toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function (FDA, 2012) | The chemotherapy toxicity reversal agent approval was supported by clinical evidence from 22 patients in two efficacy studies, including an open-label non-randomized compassionate use protocol. <sup>56,60-62</sup>                                                          |
| NovoSeven (Coagulation Factor VIIa)      | Glanzmann's thrombasthenia with refractoriness to platelet transfusions (Treatment of bleeding episodes and                         | The approval was based upon evidence collected from the global Glanzmann's Thrombasthenia Registry (218 patients with 1,073 bleeding and surgical events) and the Hemostasis & Thrombosis Research Society Registry (7 patients with 23                                        |

|                                |                                                                                               |                                                                                                                                                                  |
|--------------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                | the peri-operative management)                                                                | bleeding episodes). <sup>63</sup>                                                                                                                                |
|                                | (FDA, 2014)                                                                                   |                                                                                                                                                                  |
| Blinicyto                      | Philadelphia chromosome-negative                                                              | The main study supporting this accelerated approval was a Phase 2, multicenter,                                                                                  |
| (blinatumomab)                 | (Ph -) relapsed or refractory positive                                                        | open-label, single-arm trial that included a core study of 185 patients to assess                                                                                |
|                                | B-cell precursor acute lymphoblastic                                                          | the treatment efficacy and safety. The results of this study were compared to a                                                                                  |
|                                | leukemia (ALL) (FDA 2014, EMA                                                                 | retrospective pooled analysis of historical data on 1139 patients from 1990 to                                                                                   |
|                                | 2015)                                                                                         | 2014 on hematological remission rates and survival among adult patients with                                                                                     |
|                                |                                                                                               | relapsed/refractory ALL treated with standard of care therapy. This historical                                                                                   |
|                                |                                                                                               | database was assembled by combining existing databases from the USA and                                                                                          |
|                                |                                                                                               | European Union from 1139 patients that had similar characteristics to the                                                                                        |
|                                |                                                                                               | patients in the main study with respect to previous treatment status. <sup>16,64-66</sup>                                                                        |
| Cholbam (cholic acid)          | Bile acid synthesis disorders (FDA,                                                           | The approval was based on a retrospectively devised case report form from chart                                                                                  |
|                                | 2015)                                                                                         | review of patients in the open-label, single-arm expanded access protocol and a retrospective literature review to construct a historical control. <sup>56</sup> |
| Vistogard (Uridine triacetate) | Emergency treatment of certain types of chemotherapy overdose (FDA,                           | Vistogard was approved as an emergency treatment for patients who receive                                                                                        |
|                                | 2015)                                                                                         | overdoses of two chemotherapy drugs or exhibit severe adverse reactions to the                                                                                   |
|                                |                                                                                               | drugs following open-label safety and efficacy trials of 135 patients. The patient                                                                               |
|                                |                                                                                               | had either received overdoses of fluorouracil or capecitabine or presented with                                                                                  |
|                                |                                                                                               | severe or life-threatening toxicities within four days following administration of                                                                               |
|                                |                                                                                               | either chemotherapy drug. The agency also utilized historical data, including its                                                                                |
|                                |                                                                                               | evaluation of 25 historical case reports of patients who received overdoses of the two chemotherapy agents and who did not receive Vistogard. <sup>58,67</sup>   |
| ProVay Blue                    | Acquired methemoglobinemia (FDA,                                                              | The ProVay Blue accelerated approval was based on retrospective case reports                                                                                     |
| (methylene blue)               | 2016)                                                                                         | found in a multicenter chart review along with cases found in literature search.                                                                                 |
|                                |                                                                                               | Like many of the orphan products approved with RWE, ProVay Blue used the                                                                                         |
|                                |                                                                                               | 505(b)(2) NDA pathway, which allows for data not developed by the sponsor to be incorporated in the application. <sup>56,68-71</sup>                             |
| Zalmoxis (allogeneic T cells)  | Hematopoietic stem cell transplantation with high-risk hematological malignancies (EMA, 2016) | For this approval, a control group was collected from the European transplant                                                                                    |
|                                |                                                                                               | registry based on the same criteria used in the control group of an ongoing Phase III trial and a specific sets of matching parameters. <sup>72-74</sup>         |
| Exondys (eteplirsen)           | Duchenne muscular dystrophy (FDA 2016)                                                        | The Accelerated approval was based on matching and comparison of eteplirsen arm with historic control arm from the Italian DMD Registry database. <sup>75</sup>  |

|                                                                                                                        |                                                       |                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kalydeco (ivacaftor)                                                                                                   | 10 cystic fibrosis (CF) mutations to 33 (FDA, 2017)   | The label expansion was based on post-marketing registry data and mechanistic information from lab studies. <sup>56</sup>                                                                                                                         |
| Soliris (eculizumab)                                                                                                   | Paroxysmal nocturnal hemoglobinuria                   | Soliris was initially restricted to use in patients with a certain disease severity. The                                                                                                                                                          |
|                                                                                                                        | where evidence of clinical benefit is                 | expanded indication was based on disease registry data to help demonstrate                                                                                                                                                                        |
|                                                                                                                        | demonstrated in patients with                         | effectiveness. The registry was established at the time of authorization of Soliris                                                                                                                                                               |
| Drug                                                                                                                   | Indication (Health Authority, Year)                   | RWE Use Examples                                                                                                                                                                                                                                  |
| haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (EMA, 2017) |                                                       | with the twin aims of evaluating the safety of Soliris and also characterizing disease progression, clinical outcomes, morbidity, and mortality. The registry included data from both Soliris treated and untreated patients. <sup>74,76,77</sup> |
| Brineura (cerliponase alfa)                                                                                            | Batten disease (EMA and FDA 2017)                     | The FDA approved Brineura as a treatment for a form of Batten disease, following a                                                                                                                                                                |
|                                                                                                                        |                                                       | single-arm study which used a natural history control. Brineura was the first                                                                                                                                                                     |
|                                                                                                                        |                                                       | FDA-approved treatment to slow loss of walking ability in patients with late                                                                                                                                                                      |
|                                                                                                                        |                                                       | infantile neuronal ceroid lipofuscinosis type 2 (CLN2). The clinical trial                                                                                                                                                                        |
|                                                                                                                        |                                                       | establishing Brineura's efficacy was a non-randomized, single-arm dose                                                                                                                                                                            |
|                                                                                                                        |                                                       | escalation clinical study in 22 symptomatic pediatric patients. The control or                                                                                                                                                                    |
|                                                                                                                        |                                                       | comparator consisted of 42 untreated patients with CLN2 disease from a natural history cohort. <sup>56,58,78-82</sup>                                                                                                                             |
| Bavencio (avelumab)                                                                                                    | Metastatic Merkel cell carcinoma (FDA and EMA 2017)   | Accelerated approval based on a single-arm, open-label study compared with historical control from electronic health records. <sup>15,83</sup>                                                                                                    |
| Yescarta (Axicabtagene Ciloleucel)                                                                                     | Diffuse large B-cell lymphoma (FDA 2017 and EMA 2018) | The full approval was granted for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy based on the findings                                                                              |
|                                                                                                                        |                                                       | of the single-arm ZUMA-1 study which compared the treatment response with historical controls from scientific literature. <sup>84,85</sup>                                                                                                        |
| Tepadina (thiotepa)                                                                                                    | Reduce the risk of rejection in pediatric             | The label expansion was based on a retrospective study of pediatric patients with                                                                                                                                                                 |
|                                                                                                                        | call 3 beta-thalassemia (FDA, 2017)                   | class 3 beta-thalassemia who underwent allogeneic hematopoietic stem cell                                                                                                                                                                         |
|                                                                                                                        |                                                       | transplantation.                                                                                                                                                                                                                                  |

## AIM AND OBJECTIVE

### Aim:

A review of successful regulatory approvals and the sequences between them was completed for companies that achieved US Food and Drug Administration (FDA) premarket approval or new drug approvals (NDAs) or device clearances in the fields of fluorescent imaging agents, open surgery imaging devices, and their approved medical indications.

### CONCLUSION:

The optimal framework for the regulatory approval of medical innovations remains unclear. This study suggests that many new devices do receive regulatory approval but often lack clinical trial data supporting their safety and effectiveness. The IDEAL model makes several proposals for the staged introduction of innovations in surgery (and other disciplines that offer complex interventions), including randomised

controlled trials to assess safety and effectiveness. At present, few relevant randomised controlled trials are published, and fewer still meet current quality standards for optimal reporting. Changes in the regulatory approval of devices that would require trials for proof of safety and effectiveness might promote adherence to the IDEAL model.

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