Confirmatory Evidence of Effectiveness Used to Support Non-Oncologic Rare Disease Novel Drug Marketing Application Approvals, CY 2020-2022

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Abstract

There are an estimated 7,000 to 10,000 rare diseases (defined as impacting < 200,000 people in the US) affecting 30 million people nationwide [1]. From 2020-2022, almost half of all non-oncologic novel drug approvals were for rare diseases. Despite rapid growth and advancements in this space, rare disease drug development remains challenging. Rare disease drug development often has challenges surrounding characterization of disease natural history, a limited understanding of disease pathophysiology, small trial sizes, and challenges with trial design. It is often not feasible to conduct multiple large clinical trials for rare disease drug development, thus confirmatory evidence (CE) of effectiveness is typically necessary to demonstrate that a novel therapeutic is effective. To gain a better understanding of how CE has been utilized to support novel drug approvals across CDER review divisions working in the rare disease space, this study categorized CE submitted in approved new molecular entity (NME) new drug applications (NDAs) and original biologics license applications (BLAs) for non-oncologic rare diseases from CY 2020-2022. The findings of this study show that mechanistic evidence and evidence from an additional clinical study (e.g. early phase dose-finding and safety studies that also collected data regarding effectiveness) were the two most commonly used categories of CE in recent non-oncologic rare disease novel drug approvals. Multiple CE types were commonly submitted to support a single, pivotal AWC trial in approved rare disease applications.

Introduction

For a novel drug to be approved for marketing under an NDA or BLA, data must show that the product is both safe and effective. Since 1962, FDA has required substantial evidence of effectiveness (SEE) to support approval of marketing applications for drugs in the US [2]. For common diseases with large patient populations, SEE is typically demonstrated through data from two or more adequate and well-controlled (AWC) trials. In cases where it may not be possible to conduct multiple AWC trials, such as in rare diseases, regulatory flexibility is needed. In 1998, FDA published the *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Product* guidance which states that substantial evidence requirements for demonstrating effectiveness can be met by evidence from two AWC trials or a single trial plus confirmatory evidence (CE) [3]. In some cases, a single, highly-persuasive, adequate and well-controlled, large multicenter trial can be used to establish effectiveness without additional CE. The 2019 *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* guidance expands upon the 1998 guidance, acknowledging the evolution of drug development and advances in science that can facilitate rare disease drug development [4]. Importantly, SEE includes both the *quality* and *quantity* of scientific evidence. Reliable evidence of effectiveness, including CE, is critical in completing risk-benefit assessments during the marketing application review process.

To gain a better understanding of what types of CE have been utilized to support rare disease marketing application approvals since publication of the 2019 *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* draft guidance [4], we reviewed and categorized CE submitted in rare disease marketing applications in NME NDAs and original BLAs from 2020 through 2022.

Methods

Utilizing FDA's internal Data Analysis Search Host (DASH) database, we compiled rare disease marketing applications (NDAs and BLAs) for novel drugs approved from January 1, 2020 through December 31, 2022. Rare disease applications were identified based on the marketing application sponsor's reporting of the product's indication as a treatment for a rare disease (defined as a condition affecting <200,000 individuals in the US) and orphan drug designation status. Applications reviewed by the Office of Oncologic Diseases were excluded from the dataset to focus on non-oncologic indications. Diagnostic products were also excluded. For the purposes of this study, CE was categorized as belonging to the following categories: clinical evidence from a related indication, mechanistic or pharmacodynamic evidence, evidence from a relevant animal model, evidence from other members of the same pharmacologic class, natural history evidence, evidence from expanded access use of an investigational drug, and evidence from an additional clinical study (e.g. early phase dose-finding and safety studies that also collected data regarding effectiveness). CE data were manually extracted from each application's internal FDA review documents by 3 independent researchers. In rare cases when a consensus for the type of CE in an application could not be reached, an additional expert in rare disease drug development and review was consulted and/or interviews with the review division were conducted. Marketing application information, regulatory action details and CE information was captured in Excel and .csv files and summary statistics were calculated using R (version 4.1.2)[5].

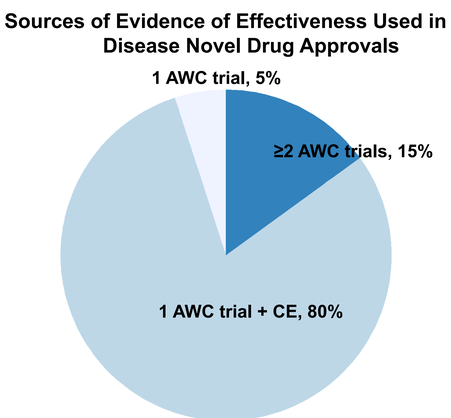

Figure 1. Sources of evidence used in non-oncologic rare disease novel drug approvals, 2020-2022. Of 40 rare disease novel drug approvals, 32 (80%) utilized 1 AWC trial plus CE, 6 (15%) utilized 2 or more AWC trials, and 2 (5%) utilized a single robust and persuasive AWC trial to meet FDA's statutory requirement for SEE. By comparison, of the 49 non-oncologic, non-diagnostic novel drugs approved for common diseases 69.4% utilized 2 or more AWC trials to demonstrate SEE.

Results

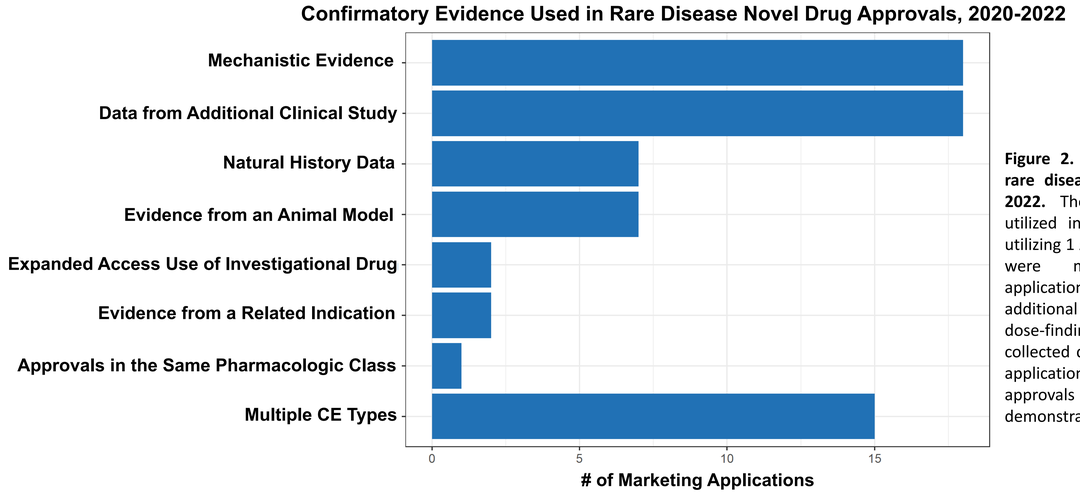

Figure 2. CE submitted in non-oncologic, rare disease novel drug approvals, 2020-2022. The most common categories of CE utilized in the 32 rare disease approvals utilizing 1 AWC trial + CE to demonstrate SEE were mechanistic evidence (n=18 applications) and efficacy data from an additional clinical study (e.g. early phase dose-finding and safety studies that also collected data regarding effectiveness; n=18 applications). Notably, 15 (46.9%) of these approvals utilized multiple CE types to demonstrate SEE.

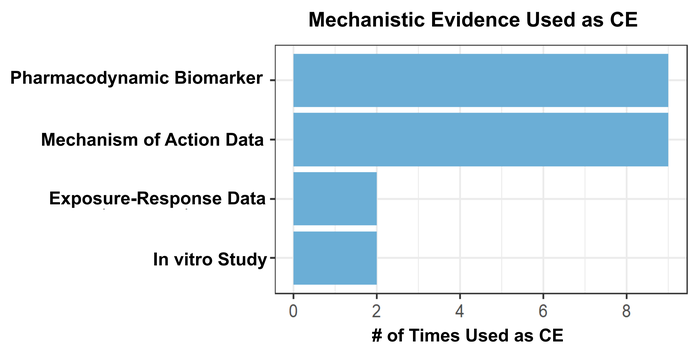

Figure 3. Mechanistic Evidence Used as CE. Data from mechanistic and translational studies was cited as CE in 18 of the 32 novel drug approvals that utilized 1 AWC trial + CE to meet SEE requirements. Four applications utilized two or more types of mechanistic evidence as CE. We subcategorized mechanistic evidence into the following categories: pharmacodynamic biomarker (n=9), mechanism of action data (n=9), exposure-response data (n=2), in vitro study (n=2).

Conclusions

Rare disease marketing applications are complex and often rely on 1 AWC trial plus CE to demonstrate a drug's efficacy. Mechanistic evidence and data from additional clinical studies are commonly submitted in rare disease novel drug marketing applications as CE. These results build a foundation for future regulatory research that can contribute to better transparency, understanding, and communication of CE used in rare disease drug development and facilitate FDA's review of CE data in rare disease drug development programs. To help meet CDER's Prescription Drug User Fee Act (PDUFA) VII commitments to familiarize review staff with the challenges associated with rare disease marketing applications and strategies to address these challenges, the results from this study will be shared broadly across FDA in coordination with other training efforts.

References: 1. Genetic and Rare Disease Information Center, National Center for Advancing Translational Sciences, https://rarediseases.info.nih.gov ; 2. Section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 26); 3. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, Guidance for Industry, FDA, May 1998, https://www.fda.gov/media/71655/download; 4. Demonstrating Substantial Evidence of Effectiveness for Human and Drug Biological Products, Draft Guidance for Industry, FDA, December 2019, https://www.fda.gov/media/133660/download; 5. R: A language and environment for statistical computing. R Core Team. R Foundation for Statical Computing, Vienna Austria, 2021, https://www.R-project.org/.