ARTICLE

Clinical pharmacology information in regulatory submissions and labeling: A comparative analysis of orphan and non-orphan drugs approved by the FDA

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Abstract

Clinical pharmacology is an integral discipline supporting the development, regulatory evaluation, and clinical use of drugs for the treatment of both common and rare diseases. Here, we evaluated the recommendations and information available from select clinical pharmacology studies in the therapeutic product labeling of new molecular entities (NMEs) approved from 2017 to 2019 for both common and rare diseases. A total of 151 NMEs, including 72 orphan and 79 non-orphan drugs, were analyzed for recommendations and information available related to food–drug interaction, drug–drug interaction, renal impairment, hepatic impairment, QT assessment, and human radiolabeled mass balance studies using data collected from the original labeling and other regulatory documents. The analysis showed no statistically significant difference in the recommendations between orphan and non-orphan drugs except for renal impairment related recommendations in section 8 of the labeling. Although not significant, fewer hepatic impairment labeling recommendations were available for orphan drugs when compared with non-orphan drugs. At the time of initial approval, 79 postmarketing requirements (PMRs) and postmarketing commitments (PMCs) for 33 orphan drugs and 39 PMRs and PMCs for 19 non-orphan drugs were established; with most difference observed for drug–drug interaction, hepatic impairment, and QT assessment. Overall, although there was a trend for more labeling recommendations and fewer postmarketing studies and clinical trials for non-orphan drugs, there appeared to be no substantial differences in how these select clinical pharmacology studies are leveraged during the development and approval of orphan and non-orphan drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
As a discipline, clinical pharmacology can be leveraged to support development, regulatory evaluation, and clinical use of drugs for common and rare diseases.

However, analyses have not been performed to examine how select clinical pharmacology studies have been utilized to inform labeling recommendations and information for orphan drugs (for rare diseases) when compared to non-orphan drugs.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to compare the labeling of orphan and non-orphan drugs approved by the US Food and Drug Administration from 2017 to 2019 to understand the availability of recommendations and information from the select clinical pharmacology studies at the time of original drug approval. In addition, we assessed if any postmarketing studies and clinical trials were established to address knowledge gaps related to these studies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

There appeared to be no substantial difference in how the select clinical pharmacology studies were leveraged during the development and approval of orphan and non-orphan drugs, although there was a trend for more labeling recommendations and information as well as fewer postmarketing studies and clinical trials for non-orphan drugs.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The findings suggest that leveraging clinical pharmacology principles during drug development and evaluation can help promote therapeutic optimization, and as a result, help the right patient receive the right drug, at the right dose, and at the right time.

INTRODUCTION

Clinical pharmacology, a multidisciplinary field that bridges basic pharmacology and clinical medicine, is extensively leveraged to support drug development, regulatory evaluation, and clinical use.[1] During drug development, several in vitro, in vivo, and in silico clinical pharmacology studies are conducted to evaluate a drug's pharmacokinetics (PKs; e.g., absorption, distribution, metabolism, and excretion [ADME]), and pharmacodynamics (PDs). Some of these studies also evaluate the impact of intrinsic factors (e.g., age, sex, race/ethnicity, genomics, and organ function) and extrinsic factors (e.g., food–drug interaction and drug–drug interaction) on drug exposure and response. Clinical pharmacology relevant information from these studies is critical for characterizing the new drug, informing therapeutic product labeling, determining the need for postmarketing studies and clinical trials, and managing the lifecycle of the product.[2] In the labeling, recommendations for dosage in the general population and specific populations (therapeutic individualization) are based on information from clinical pharmacology studies. This is applicable for drugs developed to treat common diseases as well as rare diseases.

In the United States, rare disease is defined as a disease that affects fewer than 200,000 people.[3] It is estimated that there are over 7000 rare diseases affecting about 30 million Americans.[4] However, only 5% of the 7000 rare diseases currently have an approved therapy.[5] The majority of patients with rare diseases do not have drugs specifically approved to treat their diseases, thereby resulting in a high unmet medical need. To address this need, the US Food and Drug Administration (FDA) continues to develop pathways to support drug development for rare diseases. For example, drugs to prevent, diagnose, or treat a rare disease can obtain orphan drug designation that offers several incentives for drug developers. In the last decade, the number of new molecular entities (NMEs) approved by the FDA that have received an orphan designation has increased steadily. In 2017, orphan drugs accounted for 39% of all approved NMEs and was 58% in 2018, and 44% in 2019.[6] This increase is attributable to the Orphan Drug Act (ODA) passed in 1983.[4] It is important to note that the ODA did not create a different statutory standard for the approval of orphan drugs when compared with non-orphan drugs. Approval of both orphan and non-orphan drugs should be based on substantial evidence of effectiveness and sufficient information on safety.[7] Some factors that make drug development for rare diseases challenging include: (a) fewer patients are affected by a given disease and, therefore, only a limited number of them may enroll in clinical trials, (b) disease manifestation can be heterogenous, (c) the natural history of the disease and its pathophysiology may not be well understood, and (d) nearly half of all rare diseases are pediatric diseases. Given these challenges, for drugs to treat rare diseases, the FDA can exercise flexibility and scientific judgment to determine the kind and quantity of data required for drug approval.[8]

Although it has been argued by some that the regulatory standards are higher for the approval of orphan drugs,[9] others have pointed out that flexibility has been utilized in the approval of orphan drugs.[10]

The nature of clinical development programs supporting drugs for common and rare diseases are different.[11] When compared with non-orphan drug development programs, fewer subjects are enrolled and fewer studies are conducted in orphan drug development programs.[11] The types of studies that are conducted can be expected to vary between orphan and non-orphan drug development programs. For example, for non-orphan drugs, multiple dose-finding studies are more common. For orphan drugs, development programs can vary with respect to enrollment of healthy volunteers or patients as well as total patient population enrolled.[12] This suggests that the FDA exercises judgment under the regulations to support an appropriate clinical pharmacology development program all the while balancing the need for information with feasibility.[13]

It may be expected that more information may be available at the time of approval for non-orphan drugs because of the number of studies and subjects enrolled in the entire drug development program. Whether information is available from a large or limited number of studies or subjects, as a discipline, clinical pharmacology is critical for informing the labeling. Particularly, studies that assess the impact of food on drug exposure (referred to as food effect [FE] study),[14] drug–drug interaction (DDI),[15] renal impairment (RI),[16] hepatic impairment (HI),[17] QT assessment,[18] and human radiolabeled mass balance (MB) studies[19] are anticipated to be leveraged similarly by both orphan and non-orphan drugs. When knowledge gaps are present, that is, specific recommendations cannot be provided in the labeling, postmarketing studies and clinical trials (i.e., postmarketing requirements [PMRs] and postmarketing commitments [PMCs]) are anticipated to be established at the time of drug approval for orphan and non-orphan drugs to obtain this information, and to subsequently inform the labeling.

Several publications have described the clinical pharmacology studies that support the development of orphan drugs.[12,20,21] However, a comparison between drugs for rare diseases and common diseases has not been done to understand if select clinical pharmacology studies were performed during drug development and how the information translated into the labeling at the time of approval. Here, we aimed to compare the labeling of orphan and non-orphan NMEs approved between 2017 and 2019 to understand the availability of recommendations and information from the select clinical pharmacology studies at the time of approval. In addition, we evaluated if any PMRs and PMCs were established for these orphan and non-orphan drugs to address knowledge gaps related to these studies.

METHODS

NMEs approved as new drug application (NDA) or biologics license application (BLA) by the FDA's Center for Drug Evaluation and Research (CDER) from 2017 to 2019 were identified using publicly available databases.[22,23] Of the NMEs approved, two were excluded from further analysis – (a) fosnetupitant and palonosetron (clinical pharmacology information for this drug combination was borrowed from previously approved drugs), and (b) brilliant blue G ophthalmic solution (which did not have information on select clinical pharmacology studies as this diagnostic agent may not need the traditional clinical pharmacology studies to characterize it).

The original labeling (at the time of NME initial approval) was used to collect recommendations related to FE, DDI, RI, and HI, as well as information on QT assessment and human radiolabeled MB study. Publicly available clinical pharmacology reviews were referred as needed. Approval letters were used to collect information on postmarketing studies and clinical trials established for the select clinical pharmacology studies listed above.

Additional information on the NME, such as route of administration, type of product, and therapeutic area were collected. Special regulatory designations, such as orphan drug designation, breakthrough therapy, priority review, and fast track, or approval pathway, such as the accelerated approval pathway, were collected.

Food effect

Section 2 (DOSAGE AND ADMINISTRATION) of the labeling was assessed for the availability of recommendations for dosing a drug in relation to food intake (i.e., take the drug "with food," "without food," and "with or without food"). When such a recommendation was unavailable in section 2, other sections of the labeling, including subsection 12.3 (*Pharmacokinetics*), section 17 (PATIENT COUNSELING INFORMATION), and Medication Guide were utilized to identify the availability of FE-related recommendations or information. All orally administered small molecule drugs were included in the analysis.

Drug–drug interactions

Section 7 (DRUG INTERACTIONS) of the labeling was assessed for the availability of recommendations related to PK-based DDIs. Additionally, when recommendations were unavailable in section 7, *Drug Interaction Studies* of subsection 12.3 (*Pharmacokinetics*) was used

to collect information on whether clinical studies were conducted to evaluate DDI concerns primarily due to alteration of metabolic enzymes or transporters. When a recommendation or information on clinical DDI studies was unavailable in either section 7 or subsection 12.3, the availability of information on PK-based in vitro studies was cataloged. PD-based DDIs were excluded from this analysis. All NDAs, except diagnostics or local administration, were included in the analysis. Antibody drug conjugate and cytokine/cytokine modulators were also included in this analysis, whereas all other BLAs were excluded.

Renal and hepatic impairment

Relevant subsections in section 8 (USE IN SPECIFIC POPULATIONS) of the labeling were assessed for the availability of recommendations related to RI and HI. Additionally, *Specific Populations* of subsection 12.3 (*Pharmacokinetics*) was assessed to identify recommendations (both explicit and implicit) for different stages of RI (i.e., mild, moderate, or severe RI, and kidney failure) and HI (i.e., mild, moderate, or severe HI). Recommendations such as "avoid use," "contraindication," "dose adjustment," "no dose adjustment," "dose reduction," and "not recommended" were counted as recommendation available. If no dose adjustment was implied, this was also counted as recommendation available. If the labeling mentioned that recommendation cannot be provided or if there was no information in the labeling on the impact of RI or HI, this was considered as no recommendation available. In order to capture the full extent of recommendations for the analysis, we pooled information from subsection 12.3 and section 8 of the labeling. As indicated or implied in the labeling, information on the type(s) of studies conducted (i.e., dedicated renal or hepatic impairment study, population PK [PopPK] analysis, or both) to determine the impact of organ impairment was collected. All NMEs were included in this analysis, except NDAs that were diagnostics or were for local administration (e.g., intrauterine, ophthalmic, and topical).

QT assessment

Subsection 12.2 (*Pharmacodynamics*) of the labeling was assessed for information related to clinical studies evaluating QT/QTc interval prolongation. When *Cardiac Electrophysiology* of subsection 12.2 was present in the labeling, additional information was collected on the study design (i.e., thorough QT [TQT], other studies, or both) used to evaluate QT interval prolongation. When subsection 12.2 was insufficient to determine the study design for a drug, the corresponding clinical pharmacology reviews were referred. All NMEs were included in this analysis.

Human radiolabeled mass balance study

Subsection 12.3 (*Pharmacokinetics*) of the labeling was assessed for the presence of information on human radiolabeled MB study using key search terms. Additionally, clinical pharmacology reviews were utilized when further information was needed. All NDAs, except peptides and oligonucleotide therapeutics, were included. All BLAs were excluded from the analysis.

Data analysis

Based on their regulatory designation, drugs were categorized as orphan or non-orphan.[24] Across orphan and non-orphan categories, descriptive statistical analyses were performed to compare the availability of recommendation or information from select clinical pharmacology studies listed above. Chi-square test (at the 0.05 level of significance) was performed for the availability of recommendation in the labeling for FE in section 2, DDI in section 7, RI and HI in section 8, and for the availability of information in the labeling for QT assessment in subsection 12.2 and human radiolabeled MB study in subsection 12.3. In addition, PMRs and PMCs established for the aforementioned clinical pharmacology studies were also compared for orphan and non-orphan drugs.

RESULTS

Of the 153 NMEs approved by the CDER from 2017 to 2019, 151 NMEs were included in this analysis. Of these, 72 NMEs (48%; 51 NDAs and 21 BLAs) were orphan drugs and 79 (52%; 61 NDAs and 18 BLAs) were non-orphan drugs.

Regulatory designations and pathways for approval

When comparing orphan and non-orphan drugs for special regulatory designations, significantly more orphan drugs received breakthrough therapy, priority review, and fast track designations or were approved via the accelerated approval pathway as compared with non-orphan drugs (Table 1).

TABLE 1 Summary of regulatory designations and approval pathway for orphan and non-orphan drugs

Regulatory designation/ pathway	Orphan (N = 72) % (n)	Non-orphan (N = 79) % (n)
Priority review*	88% (63)	49% (39)
Accelerated approval*	21% (15)	5% (4)
Breakthrough therapy*	43% (31)	16% (13)
Fast track*	53% (38)	27% (21)

*All p values were statistically significant at 0.05 level.

Overall availability of information from select clinical pharmacology studies

When comparing orphan and non-orphan drugs for the availability of recommendations in the labeling for FE in section 2, DDI in section 7, and HI in section 8, and for the availability of information in the labeling for QT assessment in subsection 12.2 and human radiolabeled MB study in subsection 12.3, there were no statistically significant differences (Figure 1). The only statistically significant difference was observed for the availability of recommendations for RI in section 8.

Overall, 52 drugs had postmarketing studies and clinical trials established for the clinical pharmacology studies listed above. This included 33 orphan drugs with 79 PMRs or PMCs and 19 non-orphan drugs with 39 PMRs or PMCs.

## Availability of recommendations related to food

The analysis included 83 NMEs (all NDAs), of which 41 (49%) were orphan and 42 (51%) were non-orphan drugs that were administered orally. Of this, 90% (37/41) orphan and 93% (39/42) non-orphan drugs had specific recommendations related to food intake in section 2 of the labeling (Figure 1). Of the four orphan drugs without recommendations in section 2, one had recommendation in the Medication Guide and all four had information related to the effect of food on drug exposure in subsection 12.3. Of the three non-orphan drugs without recommendations in section 2, one had recommendation in section 17, one had food effect related information in subsection 12.3, and one had information on food intake in section 14 (CLINICAL STUDIES).

One orphan and one non-orphan drug had a PMR established to further evaluate the effect of food on exposure or response to the drugs (Figure 2).
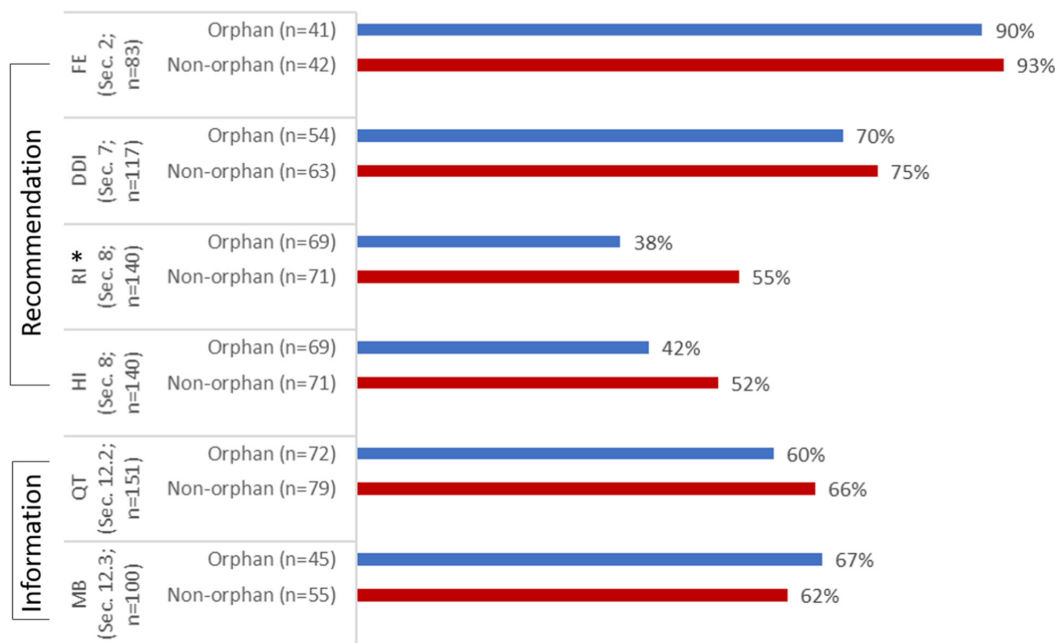
FIGURE 1 Clinical pharmacology recommendation or information availability in the original labeling of orphan and non-orphan drugs. *RI recommendation availability was statistically significant in Section 8 of the labeling ($p < 0.05$) between orphan and non-orphan drugs. See Methods for inclusion and exclusion criteria for each study category. DDI, Drug-drug Interaction; FE, Food Effect; HI, Hepatic Impairment; MB, human radiolabeled Mass Balance study; RI, Renal Impairment; Sec., Section of the labeling.
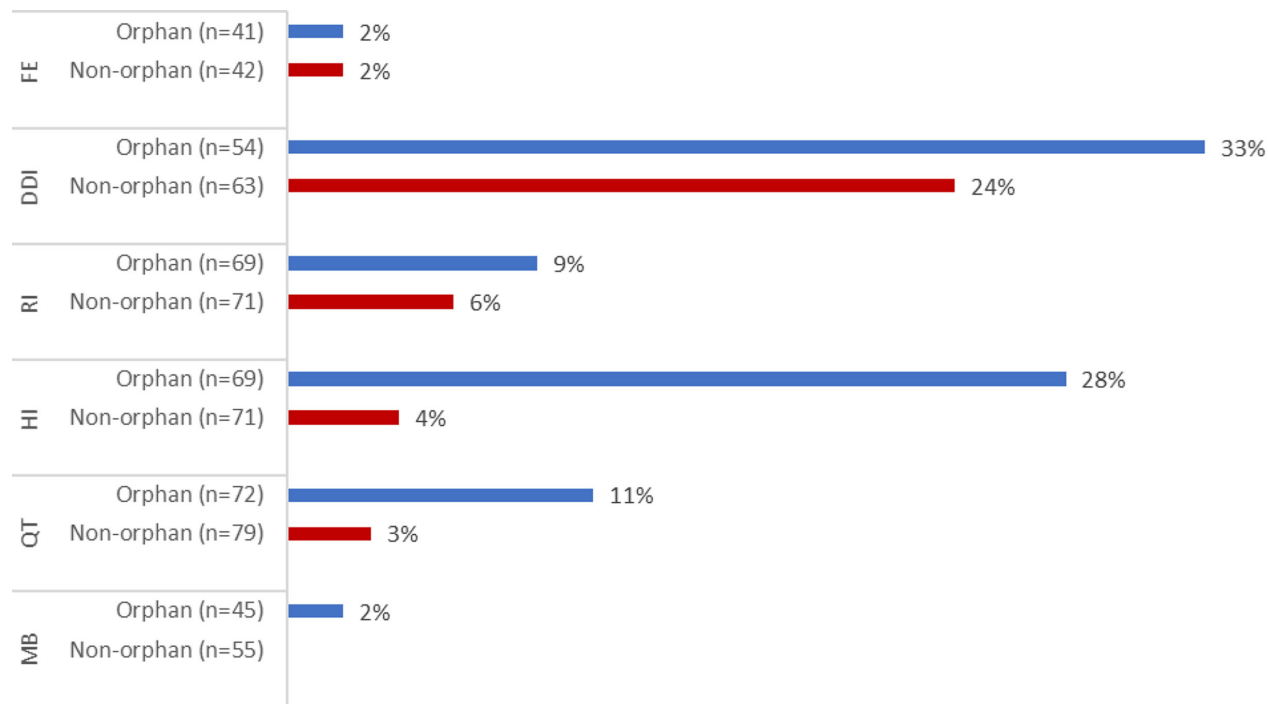
FIGURE 2 Postmarketing studies established for orphan and non-orphan drugs for the select clinical pharmacology studies. Postmarketing studies include both postmarketing requirements (PMR) and commitments (PMC). The percentages presented reflect the number of drugs with postmarketing studies established rather than the total number of postmarketing studies established. DDI, Drug-drug Interaction; FE, Food Effect; HI, Hepatic Impairment; MB, human radiolabeled Mass Balance study; RI, Renal Impairment.

Availability of recommendations for drug–drug interaction

The analysis included 117 NMEs (90% NDAs and 10% BLAs), of which 54 (46%) were orphan and 63 (54%) were non-orphan drugs. Of this, 70% (38/54) orphan and 75% (47/63) non-orphan drugs had PK-based DDI recommendations in section 7 of the labeling (Figure 1).

Drugs without a PK-based DDI recommendation in section 7 ($n = 32$; 16 orphan and 16 non-orphan drugs) were analyzed further for information on PK-based clinical DDI studies in subsection 12.3 and subsequently for information from in vitro DDI studies in the same subsection (Data S1). For 27 drugs (12 orphan and 15 non-orphan), clinical and/or in vitro DDI studies were described in subsection 12.3 of the labeling. For one of the five drugs without any information in section 7 and subsection 12.3, in vitro studies were done (negative DDI finding) but information was not in the original labeling. For the other four drugs, DDI was not anticipated based on the drug properties.

Eighteen of the 54 orphan drugs had a total of 44 postmarketing DDI studies, including 29 established as PMRs and 15 established as PMCs (Figure 2). Six of these were established for in vitro, 32 for clinical, and six for in silico studies. Fifteen of the 63 non-orphan drugs had a total of 25 postmarketing DDI studies, including 15 established as PMRs and 10 established as PMCs (Figure 2). Five of these were established for in vitro, 17 for clinical, and three for in silico studies.

Availability of recommendations for renal impairment

The analysis included 140 NMEs (75% NDAs and 25% BLAs), of which 69 (49%) were orphan and 71 (51%) were non-orphan drugs. Specifically looking at section 8 of the labeling, 65 drugs, 38% (26/69) orphan and 55% (39/71) non-orphan drugs, had specific recommendations related to RI (Figure 1). When looking at both section 8 and subsection 12.3, 115 drugs, 78% (54/69) orphan and 86% (61/71) non-orphan drugs, had recommendations for various RI stages (Figure 3). Of the 140 drugs, 25 (15 orphan and 10 non-orphan) drugs had no information on RI, or it was stated in the labeling that a recommendation cannot be provided.

When further looking at the 115 drugs for specific RI stages (Figure 3), recommendations for mild RI were available for 98% (53/54) orphan and 100% (61/61) non-orphan drugs. Recommendations for moderate RI were available for 98% (53/54) orphan and 97% (59/61) non-orphan drugs. Recommendations for severe RI were available for

57% (31/54) orphan and 77% (47/61) non-orphan drugs. Recommendations for patients with kidney failure were available for 31% (17/54) orphan and 44% (27/61) non-orphan drugs, respectively.

Of the 54 orphan drugs with recommendations available across various RI stages, for 49 drugs, the labeling had information on the type of study used to characterize the effect of renal function on PK. This included PopPK ($n = 37$), dedicated RI study ($n = 10$), and both ($n = 2$) (Data S2). Of the 61 non-orphan drugs with recommendations available, for 55 drugs, the labeling had information on the type of study used to characterize the effect of renal function on PK. This included PopPK ($n = 22$), dedicated RI study ($n = 30$), and both ($n = 3$; Data S2). Information about the type of the study was unavailable in the labeling for five orphan and six non-orphan drugs (Data S2).

Six of the 69 orphan drugs had six postmarketing RI studies, including five PMRs and one PMC. Four of the 71 non-orphan drugs had four postmarketing RI studies, including three PMRs and one PMC (Figure 2).

Availability of recommendations for hepatic impairment

The analysis included 140 NMEs (75% NDAs and 25% BLAs), of which 69 (49%) were orphan and 71 (51%) were non-orphan drugs. Specifically looking at section 8 of the labeling, 66 drugs, 42% (29/69) orphan and 52% (37/71) non-orphan drugs, had specific recommendations related to HI (Figure 1). When looking at both section 8 and subsection 12.3, 107 drugs, 74% (51/69) orphan and 79%
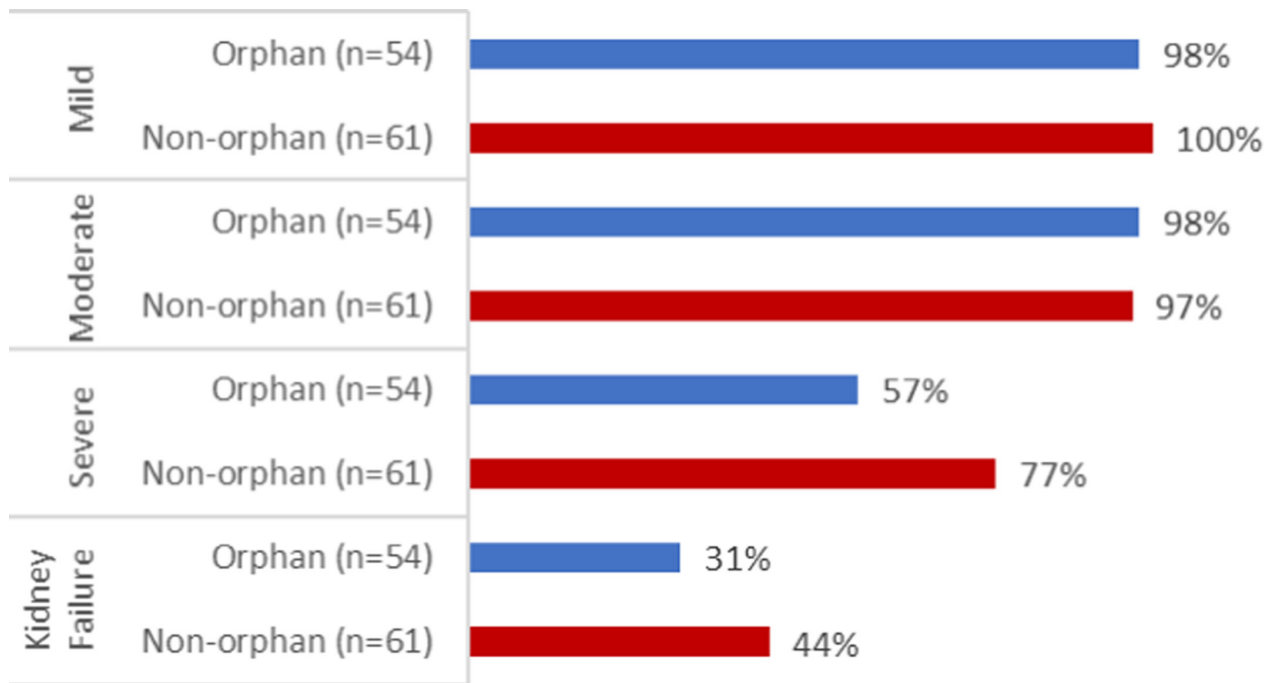
FIGURE 3 Availability of recommendation by renal function stages. 115 drugs with recommendations for various renal impairment stages in Section 8 and Subsection 12.3 of the labeling were included. See Methods for additional details.

FIGURE 4 Availability of recommendation by hepatic function stages. 107 drugs with recommendations for hepatic function stages in Section 8 and Subsection 12.3 of the labeling were included. See Methods for additional details.
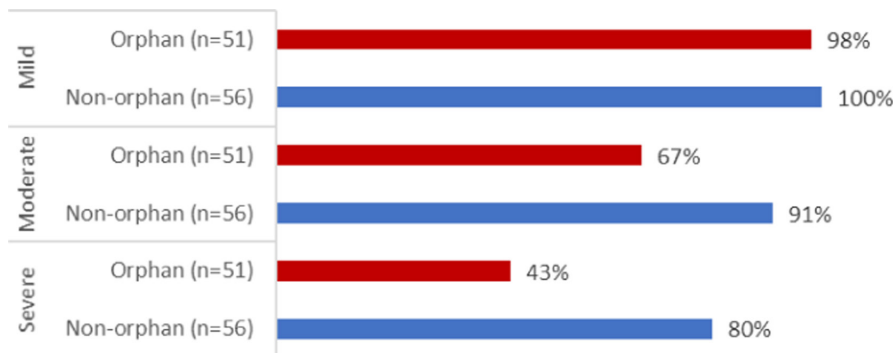
(56/71) non-orphan drugs, had recommendations for various HI stages (Figure 4). Of the 140 drugs, 33 (18 orphan and 15 non-orphan) drugs had no information on HI, or it was stated in the labeling that a recommendation cannot be provided.

When further looking at the 107 drugs for specific HI stages (Figure 4), recommendations for mild HI were available for 98% (50/51) orphan and 100% (56/56) non-orphan drugs. Recommendations for moderate HI were available for 65% (33/51) orphan and 91% (51/56) non-orphan drugs. Recommendations for severe HI were available in 43% (22/51) orphan and 80% (45/56) non-orphan drugs.

Of the 51 orphan drugs with recommendations available across various HI stages, for 43 drugs, the labeling had information on the type of study used to characterize the effect of hepatic function on PK. This included PopPK ($n = 28$), dedicated HI study ($n = 13$), and both ($n = 2$; Data S3). Of the 56 non-orphan drugs with recommendations available, for 48 drugs, the labeling had information on the type of study used to characterize the effect of hepatic function on PKs. This included dedicated HI study ($n = 31$), PopPK ($n = 12$), and both ($n = 5$; Data S3). Information about the type of the study was unavailable in the labeling for eight orphan and eight non-orphan drugs.

Nineteen of the 69 orphan drugs had a total of 20 postmarketing HI studies established as PMRs. Three of the 71 non-orphan drugs had three postmarketing HI studies established as PMRs (Figure 2).

Availability of information on QT assessment

The analysis included 151 NMEs (74% NDAs and 26% BLAs), of which 72 (48%) were orphan and 79 (52%) were non-orphan drugs. Information related to QT assessment in subsection 12.2 was not available in 56 NMEs (37%). Of the remaining 95, 60% (43/72) orphan and 66% (52/79) non-orphan drugs had specific information related to QT assessment in subsection 12.2 of the labeling (Figure 1). For orphan drugs, 40% (17/43) had conducted TQT studies, 51% (22/43) had relied on other types of studies, and 9% (4/43) had utilized both TQT and other types of studies to provide information on the risk of QT prolongation. For non-orphan drugs, 60% (31/52) had conducted TQT studies, 28% (15/52) had relied on other types of studies, and 12% (6/52) had utilized both TQT and other types of studies to provide information on the risk of QT prolongation (Data S4).

Eight of the 72 orphan drugs had eight postmarketing QT assessment studies established as PMRs. Two of the 79 non-orphan drugs had two postmarketing QT assessment studies established as PMRs (Figure 2).

Availability of information from human radiolabeled mass balance study

The analysis included 100 NDAs, of which 45 (45%) were orphan and 55 (55%) were non-orphan drugs. Of this, 67% (30/45) orphan and 62% (34/55) non-orphan drugs had specific information from human radiolabeled MB study in subsection 12.3 (Figure 1). Although not picked up in the keyword search of the subsection 12.3, eight additional non-orphan drugs had information on human radiolabeled MB studies in the clinical pharmacology review resulting in 76% of non-orphan drugs with MB studies.

One orphan drug had one PMR established to conduct a human radiolabeled MB study. None of the non-orphan drugs had PMRs or PMCs established for human radiolabeled MB studies (Figure 2).

DISCUSSION

Overall, more orphan drugs had received special regulatory designations or were approved via the accelerated pathway. This is not surprising, as these special designations and programs, such as fast track, breakthrough therapy, priority review, and accelerated approval, were established to facilitate and expedite development and approval of new drugs that address unmet medical needs.[7,22,24]

Our analysis showed no statistically significant difference in recommendations or information availability for FE, DDI, HI, QT assessment, and MB studies between orphan and non-orphan drugs, except for RI related recommendations in section 8 of the labeling (Figure 1). More postmarketing studies and clinical trials were established for orphan drugs when compared with non-orphan drugs (Figure 2). The findings for orphan drugs in this analysis were similar to what was observed for drugs of neurological rare diseases in another study, which found that the effects of intrinsic or extrinsic factors were adequately characterized in most of the drug applications.[21]

Food effect

Food–drug interactions can affect systemic drug exposure and consequently can have a significant impact on the safety and efficacy of orally administered drugs.[14] Therefore, it is important to determine the impact of food during new drug development to assess the effect on systemic drug exposure. This allows for dosing recommendations to be provided in the labeling in relation to food consumption (e.g., on an empty stomach, or with food).

If dosing of a drug in relation to food consumption is important to the efficacy or safety of the drug, that information should be clearly stated in section 2 (DOSAGE AND ADMINISTRATION) of the labeling.[25–27] These expectations outlined here apply to the development and approval of both orphan and non-orphan drugs.

As expected, there was no significant difference in the availability of recommendations related to FE between orphan and non-orphan drugs in section 2 (over 90%; Figure 1). When considering all sections of the labeling, all small molecule drugs included in the analysis had a recommendation and/or information on the effect of food.

With respect to PMRs and PMCs, no difference was observed between orphan and non-orphan drugs (one PMR each was established). Although both drugs had specific recommendations in section 2 of the labeling, more information (e.g., impact of food intake or exposure with a low-fat meal) was needed to determine the optimal dosing recommendations in relation to food resulting in a PMR for these two drugs.

Drug–drug interaction

DDIs can either reduce therapeutic efficacy or enhance drug toxicity.[28] Recently, the FDA issued several guidances describing a systematic, risk-based approach for assessing the DDI potential and for providing recommendations to mitigate them.[15,29–32] First, an in vitro assessment to evaluate the potential interaction between drugs with cytochrome P450 enzymes and transporters should be conducted.[29] When results from in vitro studies suggest a clinical DDI study needs to be conducted, such studies should follow.[15] If the investigational drug is a therapeutic protein that may modulate expression and thus function of CYP enzymes, such as a proinflammatory cytokine or a cytokine modulator, evaluation will need to be considered to evaluate the impact on exposure of other concomitant drugs that are primarily eliminated by CYP-mediated metabolism.[30] In addition, if gastric pH elevation by acid-reducing agents or drug interaction with combined oral contraceptives are of concern, evaluation will be needed to assess if an interaction in vivo may occur and whether that may affect the concentrations of the investigational drug or contraceptives leading to adverse impact on efficacy and/or safety.[31,32]

Depending on the need, DDI information typically appears in section 7 (DRUG INTERACTIONS) and subsection 12.3 (*Pharmacokinetics*) apart from other sections of the labeling.[25] Section 7 contains actionable recommendations to prevent or manage drug interactions. *Drug Interaction Studies* within subsection 12.3 include more

details of in vitro and clinical DDI studies, including both positive and pertinent negative results.[25,27] These expectations outlined here apply to the development and approval of both orphan and non-orphan drugs.

Overall, the availability of recommendation or information related to DDI was not significantly different for orphan and non-orphan drugs (Figure 1). As not all drugs will have recommendations in section 7, subsection 12.3 was further analyzed. Of those without recommendation or information on clinical DDI in section 7 or subsection 12.3, some had relied on in vitro DDI studies to conclude a lack of clinically significant drug interactions. This may explain why some drugs had no clinical DDI studies documented as the in vitro results may have already ruled out the need for a clinical study. Additionally, the conduct of in vitro studies is not expected to be significantly different between orphan and non-orphan drugs.

With respect to PMRs and PMCs, irrespective of whether a drug was orphan or not, DDI was the most common type of postmarketing study established. This is not surprising given the complexity of the DDI assessment landscape (i.e., multiple mechanisms for PK-based interaction), including drug metabolizing enzyme-based, transporter-based, as well as based on other mechanisms such as changes in gastric pH with acid reducing agents. Even within drug metabolizing enzymes and transporters, several enzymes and transporters may need to be investigated to assess the potential for DDI from the perspective of the investigational drug being a substrate (i.e., victim) and as an inducer or an inhibitor (i.e., perpetrator). The number of postmarketing DDI studies established was numerically higher for orphan drugs (Figure 2). Although a majority of the PMR/PMC studies established for both orphan and non-orphan drugs were clinical DDI studies, in vitro and in silico studies were also established depending on the knowledge gap. Overall, the need to establish a PMR or PMC was generally based on the need to evaluate the PK of the investigational drug and concomitant medication to assess the magnitude of increase or decrease in drug exposure so as to provide appropriate labeling recommendations.

Renal impairment

The kidneys play an important role in the elimination of drugs, and impairment or renal function can alter the PKs of drugs.[33] Changes in exposure can potentially impact the response (safety or efficacy) to a drug, thereby necessitating different dosage recommendations when compared with patients with normal renal function. Based on the exposure differences and understanding of the

exposure-response relationships of a drug, labeling recommendations can range from no dose modification to contraindication in specific organ function stage.[16] The FDA draft guidance provides recommendation on when characterization of the impact of RI on drug PKs should be considered, as well as the design and conduct of dedicated RI studies and considerations for when and how to utilize PopPK to characterize the impact of RI on PKs. It also provides recommendations on how to derive the dose for patients with RI.[16]

A concise summary of any clinically important differences in response and recommendations for use of the drug in specific populations defined by renal function should be reported in section 8 (USE IN SPECIFIC POPULATION) of the labeling unless the specific population was not assessed.[25] In certain circumstances, if describing the absence of data provides important information for the prescriber, the heading should be retained.[25] In addition, *Specific Populations* of Subsection 12.3 (*Pharmacokinetics*) should include descriptions and results of studies and analyses conducted to identify potential PK differences as well as changes in both the parent drug and any relevant metabolites.[27] These expectations outlined here apply to the development and approval of both orphan and non-orphan drugs.

In this analysis, we observed that a lower proportion of orphan drugs had recommendations related to RI in section 8 of the labeling compared with non-orphan drugs, and this difference was statistically significant. Although no obvious rationale was identified, this difference may be attributed to a number of factors. For example, the excretory routes may not be evenly distributed between orphan and non-orphan populations or the orphan drug may have been approved for a population that may not have an underlying RI and therefore less emphasis would have been placed on adding that information. It might also be a reflection of the labeling requirement for section 8 because only clinically important differences in response or recommendations for use of the drug in the specific population are included.[2,25]

When looking in both section 8 and subsection 12.3, no difference was observed between orphan and non-orphan drugs for mild and moderate RI. However, lack of information (e.g., unknown or no study done) was the most commonly reported finding for severe RI and kidney failure stages for both orphan and non-orphan drugs. As disease severity progressed, recommendations became scarce for both orphan and non-orphan drugs, and was more pronounced for orphan drugs. This may be because patients with severe RI or kidney failure are often excluded from clinical trials[34] and the labeling might be more conservative in the absence of data in the specific subpopulation.

Based on the labeling language, orphan drugs more often relied on PopPK analyses compared with non-orphan drugs. This may be reflective of the drug characteristics and the need to maximize data to obtain necessary information in a data sparse setting. More non-orphan drugs had dedicated RI study compared with orphan drugs in the labeling. This may possibly be related to the characteristics of the non-orphan drugs included in this analysis and the general expectation to follow conventional study design in data rich settings.

With respect to PMRs and PMCs, there were no observed differences in the studies being established to determine the appropriate dosing recommendations for various RI stages for orphan and non-orphan drugs. PMRs were most commonly established for severe RI. These studies were driven by a lack of data at the time of drug approval and the need to identify the appropriate dosing recommendations for the subpopulation.

Hepatic impairment

The liver is an important organ involved in the clearance of drugs, and HI can alter the PKs of drugs eliminated by the liver.[35] Standalone PK studies in subjects with HI are typically used to derive dosing recommendations for this patient population, as they are often excluded from pivotal clinical trials.[35] Patients are most commonly enrolled into an HI study using the Child-Pugh score to classify the degree of HI into mild, moderate, and severe stages, however, in oncology, a growing number of studies utilizes the National Cancer Institute (NCI) organ impairment working group (ODWG) criteria. Similar to RI, different labeling recommendation may be needed for different HI stages based on the knowledge of the exposure response relationships. The FDA guidance provides recommendations on when a dedicated PK study in patients with impaired hepatic function is needed and when PopPK analysis may be useful.[17] The labeling expectations are similar for HI as described above for RI.[2,17,25,27] The expectations outlined here apply to the development and approval of both orphan and non-orphan drugs.

In this analysis, numerical difference in the availability of recommendations was observed in the HI subsection of section 8 between orphan and non-orphan drugs, although not statistically significant. As stated above in the RI discussion, both explicit and implicit recommendations were collected by pooling information from subsection 12.3 and section 8. When looking in both section 8 and subsection 12.3, no difference was observed between orphan and non-orphan drugs for mild HI. As the disease severity progressed, information became scarce for orphan drugs

when compared with non-orphan drugs. The biggest difference was observed for severe HI for orphan drugs when compared with non-orphan drugs. Similar to RI, this difference may be influenced by a number of factors. For example, patients with severe HI were often excluded from clinical trials and the labeling might be more conservative in the absence of data in the specific subpopulation.

When examining the type of studies conducted to support HI recommendations, based on the labeling language, orphan drugs more often relied on PopPK analyses than non-orphan drugs. This may be a result of specific drug characteristics distributed between orphan and non-orphan populations and the need to leverage sparse data to the maximum possible extent. Non-orphan drugs reported more dedicated HI studies when compared with orphan drugs in the labeling. This may possibly be related to non-orphan drug-specific characteristics included in this analysis and the general expectation to follow traditional study design when more data are available.

With respect to PMRs and PMCs, more orphan drugs had HI studies established than non-orphan drugs. All studies were established as PMRs. Whether orphan drug or non-orphan drug, when adequate information was unavailable at the time of the drug approval, postmarketing studies, and clinical trials are established to obtain more data to provide labeling recommendations for the corresponding HI stages.

QT assessment

Evaluation of QT interval prolongation and proarrhythmic risk for non-antiarrhythmic drugs must be conducted with rigorous study design to investigate any potential cardiac safety signals.[18] Different study designs can be used to study cardiac safety.[18] In general, the TQT study should be conducted early in clinical development to inform the design of the late phase clinical trials. This study is typically conducted in healthy volunteers. Alternatively, if there is a toxicity or tolerability concern, then it can be conducted in patients. When the TQT studies are not conducted, other studies (e.g., alternative study design and exposure-response analysis) may be used to infer QT/QTc interval prolongation.[18] Information related to QT prolongation can be presented in several sections of the labeling, including subsection 12.2 (*Pharmacodynamics*) that describes the specifics of the study.[27] The general recommendation is that the subsection 12.2 should include the subheading *Cardiac Electrophysiolog*y and describe the drug's effect on the QT interval for dose(s) studied or exposure range observed as well as any dose- or exposure-response relationships that are identified.[27] If there is no effect of the drug on

the QT interval, the subsection should state that, and if the information is unknown, the subheading may be omitted.[27] When there are potential clinically significant risks associated with QT prolongation, other sections of the labeling will include additional information.[25] The expectations outlined here apply to the development and approval of both orphan and non-orphan drugs.

In this analysis, a majority of the drugs had information related to QT interval prolongation assessment in subsection 12.2 (Figure 1). Of those drugs, fewer orphan drugs had relied on TQT studies when compared with non-orphan drugs. The orphan drugs relied more on other studies (e.g., alternative study designs and/or concentration QT analysis) to provide labeling recommendations. Of note, all TQT studies were conducted for the assessment of small molecule orphan and non-orphan drugs. All of the biologics with information in subsection 12.2 utilized other study design (e.g., alternative study designs and/or concentration QT analysis) to determine the potential for QT prolongation. These results indicate that the needs of the drug development program (e.g., based on drug properties and clinical context) rather than designation (orphan vs. non-orphan) determines what studies are conducted. This finding is similar to a recent survey of oncology drugs approvals concluding that submissions for monoclonal antibodies were more likely to rely on model-based approaches in place of dedicated clinical studies for evaluation of potential QT prolongation.[36]

Orphan drugs had slightly higher number of PMRs established compared with non-orphan drugs. Whether orphan drug or not, when information on QT was limited or lacking (e.g., insufficient data available to rule out any safety concerns, and the study submitted for QT assessment did not meet the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use [ICH] E14 and ICH E14 Q&A guidelines to exclude small effects), a PMR was established to gather additional information.

Human radiolabeled mass balance study

For NMEs, it is essential to characterize their ADME during drug development.[19] A human radiolabeled MB study is one of the most informative studies to collect information on identity and quantity of circulating parent compound and metabolites, and to understand the elimination pathways of the drug.[37] In general, MB studies are conducted for small molecule drugs in order to help inform the subsequent drug development program (e.g., design of a DDI study and the need for HI and/or RI studies). However, when metabolism and elimination pathways are known (e.g., monoclonal antibodies, hormones,

peptides, and oligos) or a majority of dose is recovered in urine as unchanged parent, or if the systemic exposure is negligible, a study may not be needed.

In our analysis, information availability was not significantly different between orphan and non-orphan drugs, with numerically higher non-orphan drugs conducting human radiolabeled MB study. There was one PMR established for an orphan drug to address the knowledge gap related to routes and rates of excretion and to identify the presence of circulating metabolites.

Postmarketing studies and clinical trials

PMRs and PMCs remain a useful tool for the FDA to ensure that the approved drugs are safe and effective.[38] These studies can be established at the time of approval or even after drug approval, based on emerging needs. PMRs and PMCs are clinical studies and trials that a drug developer conducts after the approval of a drug to gather additional information about a product's safety, efficacy, or optimal use.[39] PMRs include studies that drug developers are required to conduct under one or more statutes or regulations whereas PMCs are studies that drug developers have agreed to conduct, but that are not required by a statute or regulation.[38]

Numerically higher PMRs and PMCs were established for orphan drugs when compared with non-orphan drugs at the time of approval (Figure 2). However, PMRs and PMCs are established irrespective of whether a drug is orphan or not when pertinent information is unavailable to help characterize benefit–risk assessments in general or specific populations. The goal is to gather additional information that will promote therapeutic optimization and individualization for all patient subgroups who will eventually receive the drug upon its approval.

Limitations

In this analysis, we did not evaluate if the therapeutic area of the orphan and non-orphan drugs had an impact on either the availability of labeling recommendation and information or the establishment of PMRs and PMCs. Additionally, clinical pharmacology covers a broad spectrum of studies. This analysis only examined select studies with recommendations and information that are available in the labeling and other regulatory documents (e.g., approval letters and clinical pharmacology reviews). In this analysis, we did not include other clinical pharmacology studies, such as dose finding, bioavailability, bioequivalence, etc. Additionally, only NMEs approved between 2017 and

2019 were included in this analysis. Therefore, these results may not be generalizable to all orphan and non-orphan drug approvals.

CONCLUSION

In this analysis, overall, there were no major differences in the availability of clinical pharmacology recommendations and information related to FE, DDI, RI, HI, QT assessment, and human radiolabeled MB studies in the product labeling for orphan and non-orphan NMEs. A trend for increased availability of labeling recommendations and information for non-orphan drugs was observed. PopPK approaches were more often invoked for orphan drugs to characterize the impact of renal and hepatic impairment. Some knowledge gaps existed at the time of initial approval for both orphan and non-orphan drugs, and this was more pronounced for orphan drugs leading to more postmarketing studies and clinical trials being established, particularly for DDI, HI, and QT assessments.

Development and regulatory evaluation of drugs for both common and rare diseases have several challenges and opportunities for both drug developers and regulators. For example, whether a drug has orphan designation or not, when relevant clinical pharmacology information was lacking, it can lead to incomplete benefit/risk assessment resulting in certain knowledge gaps at the time of drug approval, such as a lack of therapeutic optimization for some subpopulations. Leveraging clinical pharmacology principles during drug development and evaluation can fulfill knowledge gaps and help the right patient receive the right drug, at the right dose, and at the right time.

PREVIOUS REPORT

Parts of the results were presented at the 2021 American Society for Clinical Pharmacology and Therapeutics Annual Meeting.

DISCLAIMER

The article reflects the views of the authors and should not be construed to represent the FDA's views or policies.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.