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REVIEW

Exploring the Food and Drug Administration's review and approval of Entresto (sacubitril/valsartan)

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Abstract

Federal regulatory agencies such as the United States Food and Drug Administration review pharmacological evidence to ensure the safety and efficacy of new and repurposed pharmaceuticals prior to market approval. The discussions, disagreements and procedural decisions contained within such reviews offer unique insight into a pharmaceutical's strengths, weaknesses and opportunities, yet are often overlooked as a significant source of pharmacological information for research and development. To highlight the value of such resources, we present a case study on Entresto, a first-in-class angiotensin receptor-neprilysin inhibitor for the treatment of heart failure with reduced ejection fraction, and explore the regulatory rationale underlying its market approval. Using information extracted from Entresto's online approval package at Drugs@FDA, we explore some of the procedural complexities underlying market approval of new pharmaceuticals, discuss the broad pharmacological implications contained within regulatory agency grey literature, and highlight opportunities for future therapeutic development.

KEYWORDS
NT-proBNP, PARADIGM-HF, PARAGON-HF, pediatric heart failure, postmarketing requirements, sex differences

1 | INTRODUCTION

The discussions, processes, and procedural decisions documented in regulatory decisions can offer unique insight into a pharmaceutical's strengths, weaknesses, or residual knowledge gaps; yet these resources are often overlooked. From a research perspective, the disclosure of regulatory agency reviews, procedures and evidence holds significant value as the information contained within such documents is often more extensive than what is reported in the primary medical literature or continuing medical education.[1–5] As a result,

Abbreviations: ACE, angiotensin converting enzyme; ANP, atrial natriuretic peptide; ARB, angiotensin II receptor blockers; ARNi, angiotensin II receptor-neprilysin inhibitor; b.i.d., twice a day; BNP, B-type natriuretic peptide; CDER, Center for Drug Evaluation and Research; CMC, Chemistry Manufacturing and Controls; CTDL, Cross-Discipline Team Leader; DCaRP, Division of Cardiovascular and Renal Products; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention Analysis; FDA, Food and Drug Administration; FDAAA, Food and Drug Administration Amendments Act; FDCA, Federal Food, Drug, and Cosmetic Act; GDF15, Growth Differentiation Factor 15; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IND, Investigational New Drug; NDA, New Drug Application; NME, new molecular entity; NYHA, New York Heart Association; OCP, Office of Combination Products; ODE, Office of Drug Evaluation; OMEPRM, Office of Medication Error Prevention and Risk Management; OSE, Office of Surveillance and Epidemiology; PDUFA, Prescription Drug User Fee Act; PMC, postmarketing commitments; PMR, postmarketing requirements; PREA, Pediatric Research Equity Act; RAAS, renin-angiotensin-aldosterone system; sNDA, supplemental New Drug Application.

these traditional resources are often an incomplete reflection of all drug information, negative findings, or adverse events that could be of interest to researchers, prescribers, patients, and the general public.[6]

To highlight the importance of information available from regulatory agencies beyond the peer-reviewed literature, we examined the regulatory decision-making underlying the United States' Food and Drug Administration's (FDA) approval of Entresto (sacubitril-valsartan). Entresto is a celebrated first-in-class drug developed by Novartis Pharmaceuticals for the treatment of heart failure with reduced ejection fraction. Yet, Entresto's path to market approval reveals a complex path to market, characterized by an iterative process of regulatory review for quality, safety and efficacy. To date, Entresto remains the only market-approved drug of its class in the United States (or globally) and so presents an ideal case study to explore its approval. This case study also provides an opportunity to uncover factors that may have contributed to Entresto's failure to achieve efficacy in heart failure with preserved ejection fraction—a growing problem bereft of any clinically approved treatment—in a manner that could eventually lead to improved therapeutic strategies, more informed prescribing practices, and ultimately, better patient outcomes.

1.1 | Heart failure

A significant unmet need exists for therapeutics capable of improving patient outcomes in heart failure, particularly amongst women, aging populations and those with metabolic syndromes.[7] Heart failure is defined by an inability to pump sufficient blood to match metabolic demand, causing shortness of breath, exertional fatigue, end organ damage, and death. Heart failure is further categorized by its etiology as reduced ejection fraction (HFrEF)—impaired cardiac muscle contraction reducing blood volume ejection to <40%—or preserved ejection fraction (HFpEF)—impaired cardiac muscle relaxation impairing proper filling of the heart's chambers.[8] At present, no drugs have demonstrated a mortality benefit for HFpEF.[9]

1.2 | Pharmaceutical interventions

1.2.1 | Beta-blockers and RAAS inhibition

Beta-blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors are the predominant pharmaceutical interventions used in the treatment of heart failure.[10] Beta-adrenergic system antagonism reduces cardiac workload by decreasing heart rate and the overall demand for oxygenated blood. Inhibition of RAAS by angiotensin II receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, and chymase inhibitors reduces cardiac workload and peripheral hypertension that exacerbate heart failure progression. Despite the established efficacy of beta-blockers and RAAS inhibitors in heart failure, morbidity and mortality remain high, reinforcing the need for novel molecular targets.[11,12]

1.2.2 | Neprilysin inhibitors

The pharmacological inhibition of neprilysin was first developed as a therapeutic strategy in 1980 yet was not successful in garnering market approval until 2015.[13] Neprilysin is one of two major enzymes responsible for the inactivation and degradation of the vasodilator bradykinin and the natriuretic peptides: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) (Figure 1).[14] These hormones directly exert cardioprotective effects on cardiac muscle cells and reduce pathological fibrosis.[15] Additional benefit to the heart is conferred by their promotion of blood vessel relaxation—increasing the flow of oxygenated blood and reducing high blood pressure by natriuresis.[13] Bristol-Myers-Squibb's neprilysin inhibitor, omapatrilat, quickly emerged as a leading drug candidate for the treatment of heart failure in 2001 with the IMPRESS trial.[16] The IMPRESS trial showed a trend towards reduced mortality and heart failure morbidity in patients with reduced ejection fractions treated with omapatrilat (N = 573).[16] However, comparison of omapatrilat to enalapril in the Phase 3 OVERTURE heart failure trial (N = 2886) and in the OCTAVE hypertension trial (N = 12,668) revealed significantly higher incidence of angioedema with omapatrilat administration (2.2% and 5.5% amongst black patients with omapatrilat vs. 0.7% with enalapril).[17] Angioedema is the rapid onset of swelling due to the accumulation of fluid under the skin and can cause life-threatening asphyxiation. It was posited that omapatrilat's higher incidence of angioedema resulted from its additional inhibition of ACE—a second bradykinin-degrading enzyme—thus increasing vascular permeability and fluid extravasation.[17,18]

Neprilysin inhibitors were later explored for heart failure treatment by Novartis Pharmaceuticals with the development of Entresto, a first-in-class angiotensin II receptor-neprilysin inhibitor (ARNi). Entresto is a combination of the neprilysin inhibitor, sacubitril—a new molecular entity (NME)—and the ARB, valsartan (an FDA-approved monotherapy for the treatment of hypertension).[19] Similar to ACE inhibition, valsartan inhibits the pathological RAAS feedback mechanisms contributing to heart failure, however, it does not target the degradation of bradykinin. Instead, valsartan prevents angiotensin II peptide from binding to its receptor, AT_1R (Figure 1), thus decreasing the risk of angioedema, while still reducing heart rate, blood pressure, cardiac fibrosis, inflammation, oxidative stress, and cell death.[20]

On March 31st 2014, Novartis announced the completion of its landmark PARADIGM-HF trial (NCT01035255) comparing the safety and efficacy of Entresto to the ACE inhibitor enalapril in HFrEF.[21] The trial was terminated early, after a prespecified interim analysis revealed compelling efficacy of reduced risk of cardiac death and hospitalization with Entresto.[22] The trial involved 8442 participants with HFrEF (6595 males, 1847 females) across 1030 centers and was conducted as a randomized, double-blind, parallel

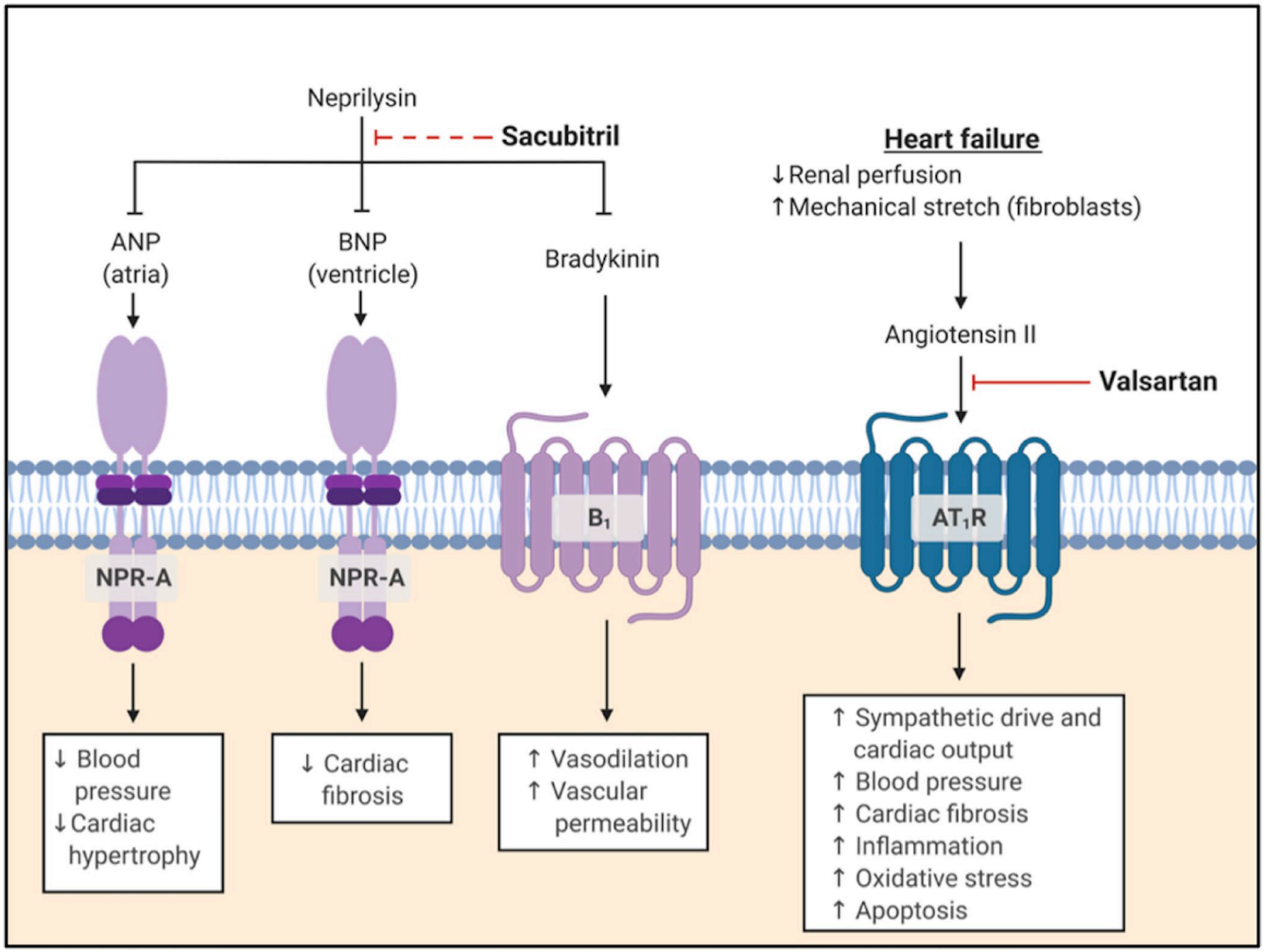

FIGURE 1 Entresto's mechanism of action. Entresto is a combination drug composed of sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin receptor blocker). Neprilysin is responsible for the degradation of natriuretic peptides ANP and BNP, as well as bradykinin. ANP reduces blood pressure and prevents cardiac hypertrophy, whereas BNP reduces cardiac fibrosis. Bradykinin regulates blood vessel dilation through smooth muscle relaxation. The binding of angiotensin II to the angiotensin II receptor type I increases cardiac workload from sympathetic drive and increased blood pressure, however chronic activation of the receptor can lead to increased cardiac fibrosis, inflammation, oxidative stress, and programmed cell death. Angiotensin II levels are increased in heart failure due to reductions in renal blood flow resulting from reduced cardiac output, as well as from the increased mechanical load placed on surviving cardiac cells. ANP, atrial natriuretic peptide; AT_1R, angiotensin II receptor type I; B_1, bradykinin receptor; BNP, B-type natriuretic peptide; NPR-A, natriuretic peptide receptor type A. Created with BioRender.com

group study.[21] On July 7th 2015, Novartis was granted FDA market approval for Entresto in HFrEF (New York Heart Association (NYHA) class II-IV severity).[23]

1.3 | Learning opportunities for therapeutic improvement

Entresto is a breakthrough drug for the treatment of heart failure, yet questions about its risks and benefits remain unresolved in the primary literature. To date, sacubitril has only received market approval as a constituent part of Entresto; it has no stand-alone application (nor does any other neprilysin inhibitor as of yet). In PARADIGM-HF's study design, sacubitril was not evaluated independently from valsartan or as an add-on study to standard-of-care as might be expected to identify sacubitril's individual contributions or effects. It is also unclear exactly why Entresto was unable to meet primary outcome measures set forth in treating HFpEF (PARAGON-HF trial; NCT01920711) and what this could indicate for future clinical populations or off-label use. Comparisons between Entresto and valsartan in the PARAGON-HF trial showed no significant difference in cardiovascular mortality or hospitalization among patients with HFpEF.[24] HFpEF differs in many respects to that of HFrEF, yet the molecular mechanisms of Entresto are still expected to confer cardioprotection in both.

Here we provide a historical overview of the discussions, processes and procedural decisions associated with the FDA's market approval of Entresto. Should more ARNi-class drugs seek to join

Entresto in obtaining market approval, this case study may inform future studies of Entresto, patient education, physician prescribing practices, similar new entries, and the development of other drugs by debriefing evidence from the available regulatory documents and identifying concerns or considerations underlying the regulatory approval process by the FDA.

2 | MATERIALS AND METHODS

Regulatory documents pertaining to Entresto approval were retrieved from the Drugs@FDA database (Figure 2; https://www.accessdata.fda.gov/scripts/cder/daf/). Using the search term "Entresto", approval dates, letters, correspondences, labels, memorandums, and reviews linked to Entresto's original application documents were collected. Additional information pertaining to the approval of valsartan were also retrieved from the Drugs@FDA database. All regulatory documents pertaining to this study were read by a single author (ALE) and the information contained within was extracted by hand, with particular attention given to event dates, major approval milestones, regulatory disagreements, and postmarketing requirements. To provide a historical overview of Entresto's approval, major approval milestones were compiled from FDA documentation and concatenated in a timeline (Figure 3). Key clinical trials were listed in Table 1. As the location of information contained within the many FDA approval package documents is subject to changes in the agency's review framework and can vary based on a drug's year-of-approval, supplementary guidance for the navigation of FDA documentation over time can be found in Ladanie et al. 2018 for readers wishing to implement this methodology into future studies.[25]

3 | RESULTS

3.1 | Pre-NDA

Prior to submitting a New Drug Application (NDA)—the formal proposal made to the FDA for market approval of a new drug—sponsors undergo a series of preliminary regulatory agency meetings and assessments. On June 1st 2009, Novartis Pharmaceuticals submitted a request for special protocol assessment to the FDA for the Phase 3 PARADIGM-HF trial of LCZ696 (later named Entresto).[26,27] Special protocol assessments are requested by drug sponsors to determine whether the proposed design of a Phase 3 clinical trial meets the standards for FDA approval. The FDA's Division of Cardiovascular and Renal Products (DCaRP) responded with a No Agreement letter on July 16th 2009, citing that "*the trial would need to assess whether one of the components of the combination [drug] was sufficient for the entirety of the benefit*".[26] The Division further proposed an add-on study to valsartan in order to evaluate sacubitril's individual contribution to clinical benefit. Novartis did not resubmit a request for special protocol assessment.

The proposed dose of the active comparator (10 mg b.i.d. Enalapril) was also expressed as a point of concern since it was lower than the labelled recommendation for heart failure (titration to 40 mg·day^{-1} as tolerated).[26,28] Novartis proceeded to use the 10 mg b.i.d. dose in its Phase 3 PARADIGM-HF trial.[22] In an addendum within the FDA's Clinical Pharmacology and Biopharmaceutics Review(s), Novartis revealed that the proposed dose of the active comparator was selected because the same mean daily dose significantly reduced mortality in the SOLVD-T heart failure trial.[29] Further mathematical analysis by the Clinical Pharmacology and Biopharmaceutics reviewers concluded that the daily dose of Enalapril in PARADIGM-HF was not lower than the dose of Enalapril in the SOLVD-T trial.

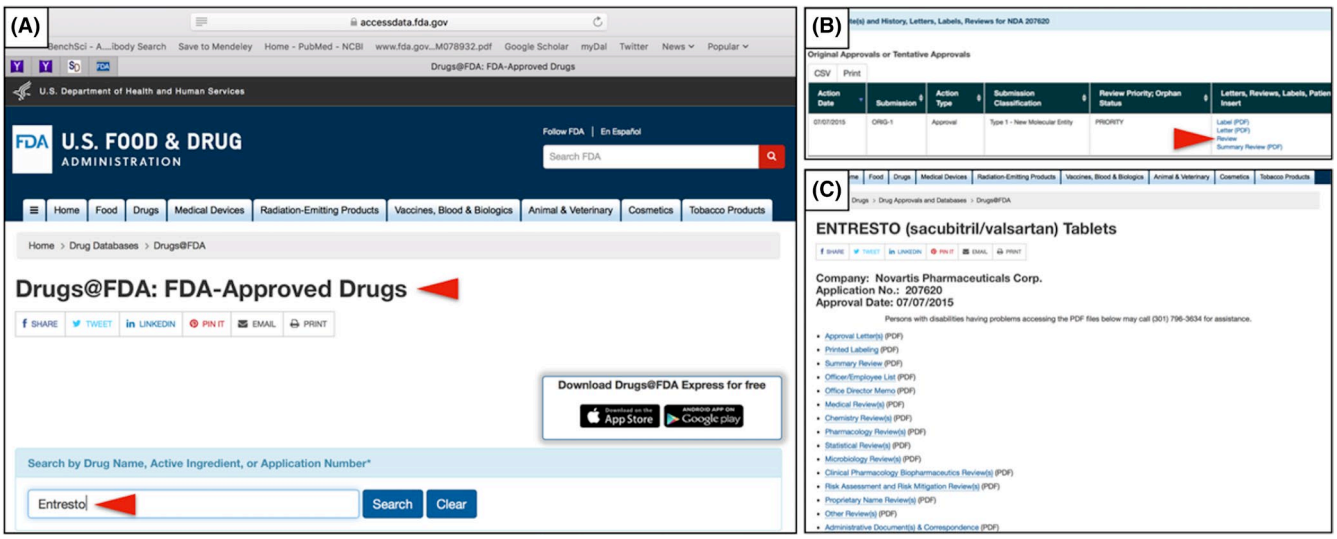

FIGURE 2 Retrieval of regulatory approval documents via the Drugs@FDA database. (A) Approval dates, letters, labels, and reviews were obtained from https://www.accessdata.fda.gov/scripts/cder/daf/ using the search term "Entresto". (B) Search results revealed links to Entresto's original application documents, (C) including approval letters, memorandums, reviews, and correspondences

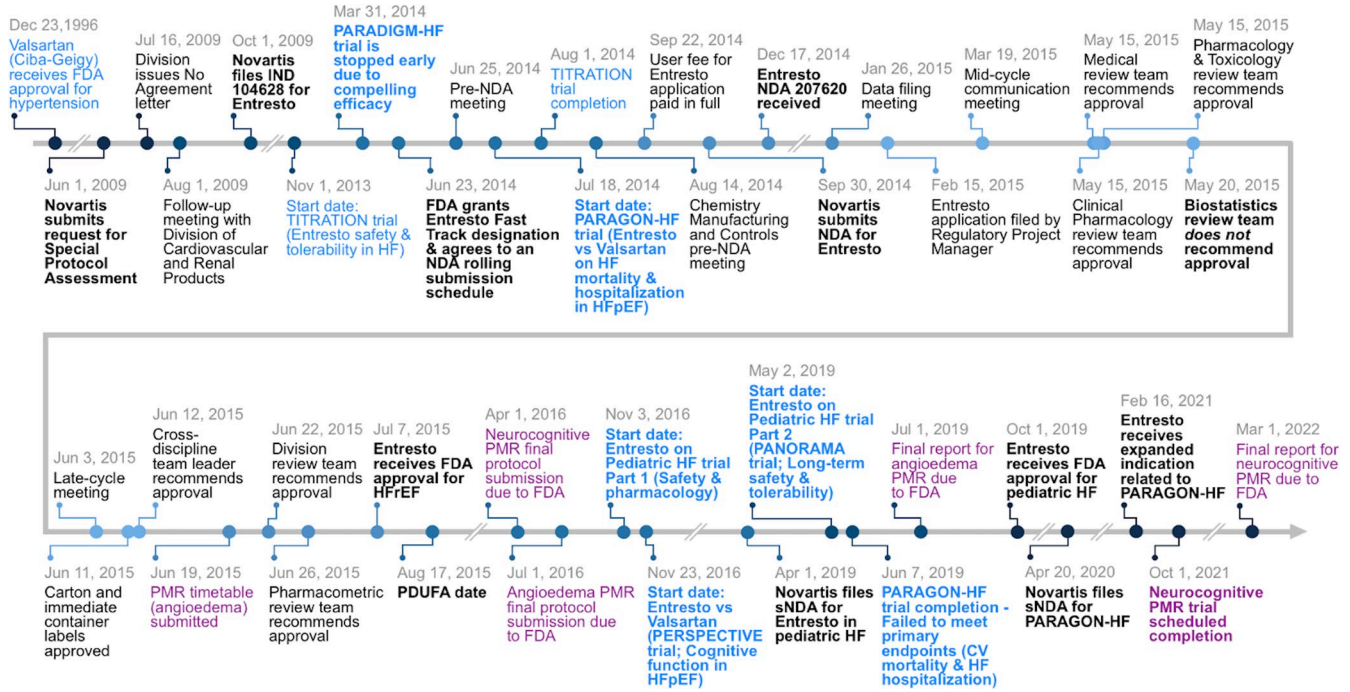

FIGURE 3 Timeline for the approval of Entresto (sacubitril/valsartan) compiled from FDA documentation. Major milestones are presented. Clinical trials and milestones relating to the FDA approval of Entresto (or valsartan) are highlighted in blue. Milestones relating to post-marketing requirements are highlighted in purple. CV, cardiovascular; FDA, Food and Drug Administration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IND, investigational new drug; NDA, new drug application; PDUFA, Prescription Drug User Fee Act; PMR, post-marketing requirements; RPM, Regulatory Project Manager; sNDA, supplemental new drug application. Created with Vizzlo

On August 1st 2009, a Type A meeting was held to discuss the concerns outlined in the Division's No Agreement letter.[26] Meetings between the FDA and drug sponsors are classified as Type A when they are immediately necessary to resolve clinical holds in a drug's development.[30] Here, the Division stated that "… *the issue of whether or not both components of LCZ696 contribute to the overall effect may or may not matter […] if Novartis showed an effect on nonreversible events, such as mortality, myocardial infarction, or strokes*".[26] According to the Summary Review document, Novartis asserted that a clinical study to evaluate sacubitril alone would be unethical given prior evidence indicating that neprilysin inhibitors alone are not effective. It is unclear whether Novartis was referring to evidence generated by the OVERTURE trial or to undisclosed data. The Division responded to Novartis by requesting the submission of data or literature to support its claim that sacubitril was not the sole contributing constituent of LCZ696. It was not clear what, or if, supporting evidence was provided by Novartis as it was not included in the FDA's regulatory approval records.

On October 1st 2009, LCZ696 was granted status as an Investigational New Drug (an experimental drug that shows promise in clinical testing; IND 104628), and in December 2009, Novartis launched its landmark PARADIGM-HF trial.[26] Novartis notified the FDA of the trial's early termination on April 1st 2014 and in June, submitted the proposed name for the then-experimental drug, Entresto, which was subsequently sanctioned by the FDA on November 1st.[27]

To facilitate the treatment of serious conditions and unmet medical needs, a drug may be granted designations meant to expedite the FDA review process.[31] Due to the high incidence of mortality associated with heart failure, the FDA granted Entresto Fast Track designation on June 23rd 2014.[27,32] As a result, Entresto's NDA was reviewed on a rolling basis, enabling the application to be submitted and reviewed in sections as completed.[16,22] To further accelerate the NDA review process, Entresto was granted a Priority Review classification with a review completion goal of 6 months; by comparison, a standard review will set an expectation for completion of 10 months.[27,32] An application is considered for Priority Review if: (1) a response to a pediatric written request under the Best Pharmaceuticals for Children Act is included (automatic Priority Review), (2) submitted in response to Pediatric Research Equity Act (PREA) requirements, or (3) the product qualifies as a tropical or infectious disease drug.[32] Novartis had requested—and was granted—a full waiver by the FDA's pediatrics committee as "*the causes and mechanisms of heart failure in children in adults are different*" and recruiting enough pediatric patients in a heart failure study would be impractical.[33]

On June 25th 2014, a Type B pre-NDA meeting was held between Novartis and the FDA to discuss the form and content of Novartis' NDA submission.[34] At the suggestion of the FDA, Novartis scheduled a separate pre-NDA Chemistry Manufacturing and Controls (CMC) meeting on August 14th 2014, however, the subject of this meeting was not disclosed in the FDA's Administrative and Correspondence

TABLE 1 Overview of key clinical trials

Clinical trial	Condition	Intervention/treatment	Phase	Sponsor	ClinicalTrials.gov identifier
IMPRESS	HFrEF (exercise capacity)	• Omapatrilat • Lisinopril	2	Bristol-Myers Squibb	Not registered
OCTAVE	Hypertension	• Omapatrilat • Enalapril	3	Bristol-Myers Squibb	Not registered
OVERTURE	HFrEF	• Omapatrilat • Enalapril	3	Bristol-Myers Squibb	Not registered
PANORAMA (part I)	Pediatric Heart Failure	• LCZ696	2	Novartis	NCT02678312
PANORAMA (part II)	Pediatric Heart Failure	• LCZ696	3	Novartis	NCT03785405
PARADIGM-HF	HFrEF	• LCZ696 • Enalapril	3	Novartis	NCT01035255
PARAGON-HF	HFpEF	• LCZ696 • Valsartan	3	Novartis	NCT01920711
PARALLAX-HF	HFpEF	• LCZ696 • Enalapril • Valsartan • Placebos to match	3	Novartis	NCT03066804
PARAMOUNT-HF	HFpEF (NT-proBNP)	• LCZ696 • Valsartan • Placebos to match	2	Novartis	NCT00887588
PERSPECTIVE	HFpEF (cognitive function)	• LCZ696 • Valsartan • Placebos to match	3	Novartis	NCT02884206
SOLVD-T	HFrEF	• Enalapril • Placebo to match enalapril	3	National Heart, Lung, and Blood Institute (NHLBI)	NCT00000516

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BNP, B-type natriuretic peptide.

documents.[34] A Top-Line Results Type C meeting was held between Novartis and the FDA on September 22nd 2014 to discuss the results of the PARADIGM-HF trial. The user fee for Entresto's NDA was paid in full and Novartis was subsequently given a Prescription Drug User Fee Act-V (PDUFA-V) date of August 17th 2015.[27,34]

3.2 | NDA 207620 approval process

On September 30th 2014, Novartis submitted the NDA for Entresto under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA).[27] The NDA was received by the FDA's Center for Drug Evaluation and Research's (CDER) DCaRP on December 17th 2014.[13,24] A data filing meeting was held on January 26th 2015 and the NDA was filed by the Division's Regulatory Project Manager on February 15th 2015.[35] Novartis and the Division met for a Mid-Cycle Meeting on March 19th 2015 to discuss topics of concern identified within the NDA.[34] The Division identified major concerns regarding the high incidence of angioedema reported in African-American patients and suggested that Novartis explore how it might evaluate the risk of angioedema in a post-market setting. It was not addressed whether the high incidence of angioedema is linked to an unidentified (epi)genetic difference in this population or to social determinants of health.

A critical consideration when evaluating a new drug relates to whether or not it affects cardiac rhythm. Abnormally long heart rhythm intervals, such as the prolongation of electrical QT waves, can lead to sudden cardiac death from improper timing of the heart's contractions.[36,37] CDER's interdisciplinary review team was consulted to assess the effects of Entresto on QT prolongation and Entresto's pharmacokinetics.[27,36] Novartis' Thorough QT/pharmacokinetics clinical study was conducted in 81 healthy male volunteers administered a single dose of either Entresto (at 1X or 3X the proposed therapeutic dose), placebo, or moxifloxacin (a QT interval-prolonging control).[27] No significant QT prolongation or other arrhythmic effects were detected with Entresto in healthy male volunteers. The absence of female inclusion in the Thorough QT/pharmacokinetics study was not addressed by CDER's interdisciplinary review team.

The NDA for Entresto was recommended for approval by six out of seven review team leaders.[27] The Medical, Clinical Pharmacology, Pharmacology and Toxicology, Pharmacometrics, and Tertiary Pharmacology review teams, in addition to the Cross-Discipline Team Leader and the Office of Drug Evaluation (ODE) all recommended NDA approval. However, the lead Biostatistics reviewer did not believe that Novartis had adequately addressed the FDA's combination policy—citing insufficient evidence that both sacubitril and valsartan contribute to the effects of Entresto in PARADIGM-HF—and thus

did not recommend approval.[26] The reviewer did not specify which combination policy was being referenced, however, the Office of Combination Products (OCP) provides nonbinding recommendations when considering the development of combination drugs containing NMEs.[38] The OCP's Guidance for Industry and FDA Staff in the Early Development Considerations for Innovative Combination Products states:

> "[…] it is critical to consider what information is necessary to characterize the safety and effectiveness of the NME when used in the combination product. Generally, this begins with a consideration of the NME alone; e.g., the preclinical information necessary to begin the initial studies in human subjects of the NME and the information needed for combination of the NME and the device constituent. For example, certain conventional pharmacology and toxicology studies may be necessary to establish the safety profile of the NME alone (e.g., genotoxicity, mutagenicity, immunotoxicity, and local tolerance) before beginning clinical investigation of the combination product".[38]

The Biostatistics reviewer believed that a case could nonetheless be made for the approval of sacubitril as a monotherapy in heart failure.[26]

In the Cross-Discipline Team Leader (CDTL) Review dated 12 June 2015, the Division's CDTL did not agree with the Biostatistics reviewer's decision to deny Entresto approval for not meeting the FDA's combination policy.[27] The CTDL highlighted that Entresto provided a mortality benefit to patients against an active comparator and did not present serious safety concerns that would require the contribution of each constituent part to be determined.[27] The CTDL stated that it would be unethical to evaluate sacubitril alone as ARBs, such as valsartan, are standard of care.[10,27]

On June 3rd 2015, Novartis and the Division convened a Late-Cycle Meeting to discuss the ongoing review of proposed postmarketing requirements/postmarketing commitments (PMR/PMC) and labeling.[34] On June 11th 2015, DCaRP, the Division of Medication Error Prevention Analysis (DMEPA), the Office of Medication Error Prevention and Risk Management (OMEPRM), and the Office of Surveillance and Epidemiology (OSE) approved Entresto's final printed carton and container labels.[27] Container labels included warnings and precautions for potential fetal toxicity, angioedema, hypotension, impaired renal function, and hyperkalemia. On June 22nd 2015, the DCaRP Review Team recommended NDA approval and on July 7th 2015, Novartis was granted market approval for Entresto in HFrEF.[23]

3.3 | Postmarketing requirements

Under section 505(o) of the Federal Food, Drug, and Cosmetic Act, the FDA is authorized to require postmarketing studies and clinical trials to assess/identify known or potential serious risks associated with the use of a prescription drug.[39,40] Prior to Entresto's market approval, the Division's Medical Review and Pharmacology and Toxicology Review teams highlighted safety concerns that warranted the development of two PMRs.[27,41] The first PMR sought to evaluate the incidence of angioedema in African-American patients in a postmarket setting.[39] The concern of Entresto increasing the risk of angioedema was amplified by the results of the OCTAVE trial where 2.2%–5.4% of patients administered the neprilysin inhibitor, omapatrilat, developed angioedema compared to 0.7% of patients administered enalapril.[42] The FDA thus required Novartis to conduct an observational pharmacoepidemiologic safety study using claims or electronic health records to determine the incidence of angioedema in African-American patients with heart failure treated with Entresto compared to control.[39]

The Division's Director did not agree with the Pharmacology and Toxicology Review team's angioedema PMR recommendation as the risk for angioedema was well-known and the Director believed the FDA's pharmacovigilance tools were superior to Novartis'.[27] The Cross-Discipline Team Leader conveyed concern that " … *in the absence of a reliable estimate of the risk, isolated reports of serious cases of angioedema in black patients may inappropriately discourage use of a drug that provides a mortality benefit*".[26] The ODE and the Division of Epidemiology (DEPI) agreed with the PMR in regards to angioedema and a draft study protocol was submitted by Novartis in December 2015.[26,27] A final study protocol was submitted by Novartis in July 2016 and interim study reports were due in July 2017 and July 2018.[26] A final report was due by July 1st 2019 although Novartis has reported the study as "*delayed*" in an internal report dated July 2020.[26,43]

The second PMR sought to evaluate the effects of Entresto on cognitive function compared to valsartan.[39] Neprilysin serves a critical role in the degradation of beta-amyloid, the principal component of amyloid plaques accumulating in the brains of patients with Alzheimer's disease. Thus, inhibition of neprilysin via Entresto could, theoretically, lead to beta-amyloid-mediated neurocognitive impairment. To assess this risk, Novartis measured the concentration of beta-amyloid in monkeys administered either a clinically relevant dose of Entresto for 2 weeks (50 $mg \cdot kg^{-1} \cdot day^{-1}$) or approximately 2× the maximum recommended human dose for 39 weeks (300 $mg \cdot kg^{-1} \cdot day^{-1}$).[41] Both doses were reportedly associated with elevated beta-amyloid levels in the cerebral spinal fluid and plasma, but no beta-amyloid accumulation was observed in the brain. There is no certainty as to the threshold of brain beta-amyloid accumulation required to initiate dementia symptoms in patients with Alzheimer's, or whether beta-amyloid accumulation is truly an incipient cause of Alzheimer's rather than an associated or consequential feature.[44–46]

Whether Entresto's hypothetical safety concern met the threshold for a PMR was the topic of internal discussion within the division.[27] Both the CTDL and Clinical Reviewer did not recommend a PMR for cognitive function as it could discourage the use of Entresto based on a theoretical risk of slow-onset disease in a patient population associated with a shortened life expectancy.[26,27] The ODE

Director responded that, under the FDA Amendments Act (FDAAA), postmarketing studies and clinical trials may be required "*to identify unexpected serious risks when available data indicates the potential for a serious risk […]*" such as that of Entresto.[26] Thus, the FDA required Novartis to conduct a multi-center, randomized, double-blind clinical trial to evaluate the effects of Entresto on cognitive function compared to valsartan alone.[39] Novartis and the FDA agreed that cognitive function would be assessed by comprehensive neurocognitive battery testing and positron emission tomography (PET-scan).[39] However, Novartis indicated that it was planning to conduct the clinical trial in patients with HFpEF instead of patients with HFrEF—the indication for which Entresto's NDA had been filed.[39] The FDA accepted Novartis' modification to the clinical trial and on November 23rd 2016, Novartis initiated the PERSPECTIVE trial (NCT02884206) to evaluate the effect of Entresto on cognitive function in HFpEF.[47] The trial is ongoing with a final report submission due March 2022.[39] The rationale for switching to HFpEF was not overtly stated but would reasonably add to the evidence base for this category of heart failure.

3.4 | sNDA for pediatric use

Supplemental NDAs (sNDA) are submitted to the FDA when sponsors wish to make changes to the packaging, labeling, dosages, manufacturing or therapeutic indications of an already-approved NDA. On April 1st 2019, Novartis filed an sNDA under FDCA section 505(b) for Entresto use in pediatric heart failure patients—an underserved special population—following Part 1 of a 2-part clinical trial (NCT02678312).[48,49] Novartis initiated Part 1 of the clinical trial on November 3rd 2016 and subsequently initiated Part 2 on May 2nd 2019 to evaluate the safety and tolerability of Entresto (PANORAMA trial; NCT03785405).[48–50] Although both trials and previous PMRs remain active and unreported, Entresto was granted approval for the treatment of symptomatic, left ventricular dysfunction heart failure (HFrEF) in pediatric patients ≥1 year old on October 1st 2019.[48]

3.5 | sNDA for use in HFpEF with below normal ejection fractions

On April 20th 2020, Novartis submitted an sNDA related to the completion of its PARAGON-HF trial (NCT01920711) on June 7th 2019.[51] PARAGON-HF compared the efficacy of Entresto to valsartan in reducing the rate of a composite endpoint of cardiovascular death and heart failure hospitalizations in patients with HFpEF (ejection fraction ≥45%). Although Entresto did not achieve statistical significance in PARAGON-HF's primary outcome measures (composite endpoint *p*-value = .06, 95% confidence interval; cardiovascular death hazard ratio = 0.95; total heart failure hospitalizations rate ratio = 0.85), Entresto was granted approval for modification of its indication in adult heart failure on February 16th 2021.[51,52] According to its new FDA-approved label, Entresto is not explicitly indicated for the treatment of all patients with HFpEF, but was granted a broader indication to include certain HFpEF patients with reduced ejection fractions.[52] Originally, Entresto was indicated for use in "*patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction*".[53] Entresto use is now indicated in "*patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal*", although 'normal' is not clearly defined.[52]

4 | DISCUSSION

4.1 | Contributions of sacubitril

Understanding the component contributions of a combination drug—especially when composed of a first-in-class NME—is important to improving the pharmacological comprehension of a drug's mechanisms and therefore its limitations or risks. This understanding is particularly important to tailoring treatments to patients, whose unique combinations of comorbidity, medications, demographics, and underlying genetic variability add complexity to drug interventions. Comprehension of a drug's pharmacology, by individual components and in combination, strengthens our ability to treat all patients effectively, to predict and prevent adverse side effects, and to identify therapeutic limitations.

The individual contributions of sacubitril to Entresto's effects in PARADIGM-HF are unclear from the data disclosed by the FDA. This gap in knowledge was clearly a topic of internal debate within CDER in regard to the FDA's Combination Policy. Ultimately, an ethical argument favors Entresto's market approval due to the drug's beneficial effects on mortality and hospitalization. However, a limited mechanistic understanding of Entresto's components could stunt future studies and make it more difficult to predict when Entresto and similar therapeutics will be ineffective or lack benefit.

4.2 | Expanding Entresto

Understanding when Entresto might not be effective appears to be a challenge Novartis is currently facing whilst seeking to expand the utility of Entresto to HFpEF following its initial market approval in HFrEF. In a multicenter, randomized, double-blind study, Novartis' PARAGON-HF trial sought to evaluate Entresto's safety and efficacy in reducing cardiovascular death and heart failure hospitalizations in HFpEF compared to valsartan alone (unlike in PARADIGM-HF where enalapril was used as the comparator).[24,54] Despite the dose of Entresto being identical to PARADIGM-HF and both trials possessing similar criteria for exclusion, Entresto still failed to meet the primary outcomes outlined in PARAGON-HF (a reduction in the rate of composite cardiovascular death and heart failure hospitalizations).[55] Novartis has since begun conducting a new Phase 3 trial—PARALLAX-HF (NCT03066804)—aimed at evaluating whether the difference in active comparators factored into Entresto's results

in PARAGON-HF. With valsartan as the active comparator or not, Entresto's inhibition of neprilysin did not add significant benefit to meet primary outcomes in PARAGON-HF, despite demonstrating a numerical reduction in the rate of the composite endpoint.[52,55] Although Entresto was granted an expanded indication to include certain HFpEF patients with reduced ejection fractions, this was not the breakthrough that many had hoped for in treatment. Information contained within the FDA's regulatory approval documents may provide insight into opportunities for Entresto improvement and future ARNi development for this patient population.

4.3 | Sex differences in heart failure etiologies

The clinical pharmacological studies included in the FDA's review of Entresto provide important insight into factors that could have contributed to Entresto's initial failure to meet primary outcomes in PARAGON-HF (HFpEF). In contrast to reduced ejection fraction, the incidence of HFpEF is higher in females.[56,57] Although a higher proportion of females was included in the PARAGON-HF trial (HFpEF; 2479 females: 2317 males) compared to PARADIGM-HF (HFrEF; 1847 females: 6595 males), the pharmacokinetic studies cited within the FDA's original Entresto review were largely conducted in males.[42] For example, Novartis' Thorough QT study—an FDA-required study evaluating the risk of a life-threatening event occurring with equal incidence across both sexes—was solely conducted in healthy males.[27,58] In a peer-reviewed pharmacokinetic summary of its pooled pre-PARADIGM-HF Phase 2 data (whose graphs are included in Entresto's FDA-approved prescribing information), Novartis concluded that there was no difference in Entresto pharmacokinetics between males and females.[59,60] However, further investigation into the summary's constituent studies (in which the impact of drug-drug and food interactions were not the focus) indicated a disproportionate ratio of males:females. In one constituent study, the pharmacokinetics of Entresto following single ascending doses were only measured in healthy males (40 males enrolled).[61] In another constituent study, 29 males and 25 females were included, however sex-dependent analysis was conducted by pooling both young (18–45 years old) and elderly (≥65 years old) volunteers together, which could be confounded by menopause status (pre-, peri- & post-).[62] Sex-independent data within the same study demonstrated that Entresto clearance was significantly reduced with age. Pooling such distinct age categories of males and females can mask sex-specific differences in pharmacokinetics behind age-and-sex-dependent differences.[63] In a third constituent two-part study, strict female inclusion criteria resulted in the inclusion of only 1 female and 48 males.[64] In this particular study, criteria for inclusion were stated as following: "*Both studies enrolled healthy male and female volunteers aged 18 to 55 years, of at least 50 kg in weight, and with a body mass index (BMI) of 18 to 30 kg/m2. Female volunteers had to be postmenopausal (no hormone replacement therapy in the past 6 months) or had to have undergone ovarectomy (with or with-out hysterectomy) for inclusion*".[64] Neither hormone therapy (e.g. testosterone) nor gonadectomy were listed as criteria for male inclusion/exclusion. Female inclusion in Novartis' Thorough QT or pharmacological studies was not addressed within the FDA documentation aside from the potential impact of Entresto on pregnancy and the reduced clearance of Entresto metabolites in female mice.[59]

The lack of female inclusion within Entresto's fundamental pharmacological studies could explain the drug's failure to meet primary outcomes in PARAGON-HF and highlights opportunities for further sex-dependent research. Females have historically been excluded from clinical studies due to unconscious bias or a perpetuated false assumption of data variability and added complexity mediated by hormonal fluctuation and reproductive cycles, yet, more recent evidence indicates that males experience similar cycles of hormonal fluctuation.[65–68] Biological sex can alter drug responses by differentially affecting the rate of drug absorption, metabolism, distribution, and excretion.[69,70] These differential effects can further be compounded by repetitive dosing (as in heart failure), thus creating disparities in effectiveness when drug pharmacology is measured more prominently in one sex. Thus, incorporation of sex-based analyses into all stages of drug development—from early pharmacokinetic studies to clinical trials—is warranted. An approach to date might seek to collect additional market data from female patients currently or newly prescribed Entresto.

4.4 | Postmarketing requirements and implications

In clinical studies such as PARADIGM-HF where the duration of the Phase 3 trial was shortened, PMR compliance is integral to understanding the drug's safety profile in real-world settings and across different populations. However, the regulatory history of Entresto's original NDA, its associated PMRs, and the approval of its sNDA in pediatric patients (Figure 3) raises questions about the purpose that PMRs are intended to serve. If the FDA's concerns about angioedema and cognitive impairment meet the requirements to warrant PMRs (including their associated costs), why was approval for Entresto use granted in pediatric patients prior to their completion? Both the CTDL and Clinical Reviewer for Entresto's original NDA perceived a reduction in risk of aged patients developing Alzheimer's due to the disease's slow-onset nature coupled with the shortened expected lifespans of heart failure patients.[16,17] This risk could therefore be increased with the long-term use of Entresto expected in pediatric heart failure patients and—once granted market approval—withdrawal is unlikely.[71,72]

It should also be noted that the sNDA for Entresto in pediatric patients was submitted subsequent to the original pre-NDA request asking to waive the requirement for PREA assessments based on the underlying differences in heart failure etiologies between children and adults.[33] Waiving initial PREA assessments contributed to the NDA's consideration for Priority Review, effectively reducing Entresto's time to market approval. Although the review of drugs for unmet needs, such as Entresto, should be expedited, this highlights Priority Review's potential risk in creating incentives

for faster review times at the expense of pediatric patients' access to new medicines. As an underserved special population, pediatric patients require greater incentives for the development of better therapeutics tailored to their needs but also represent a vulnerable population who require extra care during the regulatory review process.

The timing of Entresto's sNDA approval prior to the completion of PARAGON-HF also raises questions about evidence-based efficacy (Figure 3). Under the 1962 Kefauver-Harris Amendments to the FDCA, drug manufacturers are required to provide substantial evidence of drug product effectiveness prior to market approval.[73] In the decades since these legal reforms, the FDA's interpretation of that standard has evolved, with today's smaller, single-site, randomized controlled trials more often regarded as sufficient despite the agency's guidance to the contrary and an increasing reliance upon surrogate markers of efficacy as illustrated in the case of Entresto.[74,75] In the pediatric PANORAMA-HF trial, reduction in circulating NT-proBNP (a peptide biomarker) was used as an endpoint to measure Entresto efficacy because Entresto reduced NT-proBNP in adult heart failure and improved outcomes.[76] Entresto was also found to reduce NT-proBNP in PARAMOUNT-HF—the Phase 2 predecessor trial to PARAGON-HF.[77] The results of Novartis's PARAGON-HF trial—including Entresto's effect on NT-proBNP in a larger Phase 3 study—have yet to be completely released. However, if NT-proBNP reductions are consistent with the Phase 2 study then NT-proBNP may not represent an effective biomarker to predict improved mortality benefits and reduced heart failure hospitalization in pediatric patients as previously thought, particularly given the biochemical relationship between NT-proBNP and neprilysin inhibition. NT-proBNP is a precursor to the natriuretic peptide BNP. The degradation of BNP is regulated by neprilysin—the molecular target of sacubitril (Figure 1). Therefore, reliance on NT-proBNP—a precursor to one of Entresto's downstream molecular targets—may not be the most suitable biomarker to measure Entresto's effectiveness. Shortness of breath, exercise tolerance or additional biomarkers of note (i.e. GDF15) could aid in facilitating clinical translation over to this categorical application.

4.5 | Regulatory data and future research

Publication of the FDA's regulatory reviews—including conflicting interpretations of evidence within the agency—offers insights into the complexity of pharmaceutical regulation and decision-making.[78] In other regulatory jurisdictions, bodies such as Health Canada and the European Medicines Agency have recently followed the FDA's shift toward greater transparency through the publication of drugs' clinical data but have yet to publish their own interpretations of pharmacological evidence. Each of these sources of regulatory data are valuable, however, there exists a need to improve content incorporation into systematic reviews and meta-analyses.[79] Publication of research that avails of regulatory data, such as the present study, can thus increase awareness of these regulatory resources and the emerging methods utilizing them in secondary studies.[25]

5 | CONCLUSION

The discussions, processes, and procedural decisions documented in regulatory approval packages are a valuable, yet often overlooked, source of pharmacological information. This information holds important implications for the improved development of novel therapeutics, pre-clinical study and clinical trial design, informed prescribing via inclusion/translation in systematic reviews, and ultimately for the improvement of patient outcomes. Collectively, this study highlights the importance of pharmaceutical information contained within FDA reviews and showcases how these resources may be used to identify opportunities for evidence synthesis.

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DISCLOSURES

Mr. Herder reported being a member of the Patented Medicine Prices Review Board, Canada's national drug price regulator, and receiving honoraria from the Board for his service.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[80] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[81]

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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