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White Paper

GLOBAL APPROACHES TO DRUG DEVELOPMENT: WHEN EX-US CLINICAL DATA CAN SUPPORT US DRUG APPROVALS

Understand factors that drive positive US FDA review

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EXECUTIVE SUMMARY

As drug discovery and development capabilities continue to expand globally, pharmaceutical companies are increasingly interested in understanding the most efficient way to bring drugs to the US market based on a global clinical development strategy. This trend is not limited to established multi-national corporations, as an increasing number of emerging biopharmaceutical companies are seeking a global presence to better address unmet medical needs and to maximize their commercial opportunity.

From a US regulatory perspective, the typical rule of thumb cited by experts is that *"at least 20% of the supporting clinical data should be from patients in the US."* To accommodate this assumption, clinical trial strategy must include the US as a key and potentially rate limited country, which can have significant implications in terms of higher trial costs, longer study timelines, delays for achieving approval, and ultimately impacts the probability of success of the drug development program.

However, the conventional wisdom of the "20% rule" is in contrast to stated US Food and Drug Administration (FDA) regulations related to foreign clinical data.

"An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if:

(1) the foreign data are applicable to the U.S. population and U.S. medical practice;

(2) the studies have been performed by clinical investigators of recognized competence; and

(3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means."

21 CFR 314.106

For example, since 2008, 21 CFR Part 312.120 has permitted FDA acceptance of foreign clinical studies not conducted under an investigational new drug application (IND) as support for an IND or a marketing application, provided that these studies are conducted under Good Clinical Practices (GCP). Moreover, under 21 CFR 314.106, FDA may grant marketing approval based solely on high quality foreign clinical data.

The question that therefore faces pharmaceutical companies seeking regulatory approval for a drug in the US is: "what proportion of my study population needs to be from the US?" According to a review done by the Department of Health and Human Services, Office of the Inspector General, in fiscal year 2008, the majority of subjects and sites in trials supporting NDA and BLA approvals that year were located outside the United States (Office of Inspector General, 2010). This paper takes a closer look at FDA's more recent track record with respect to approving drugs based on studies that were conducted with primarily non-US patient populations and examines the information FDA has accepted to demonstrate that foreign clinical data are applicable to the US patient population.

FDA'S TRACK RECORD OF ACCEPTING NON-US CLINICAL DATA TO SUPPORT MARKETING APPROVAL

METHODOLOGY

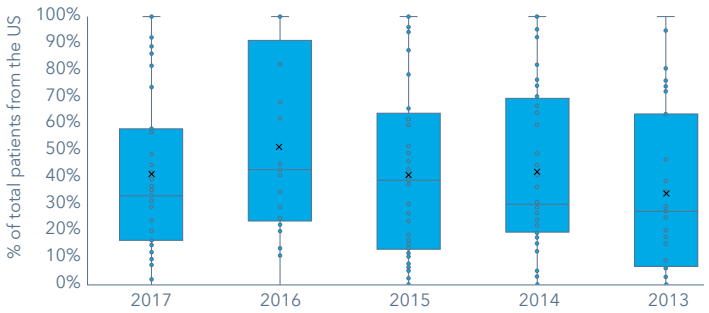
A comprehensive list of drugs and biological products approved by FDA between 2013 and 2017 was collected from the FDA website. The analysis included only new drug and biological product approvals, and not reformulations or 505(b)(2) products. For each new approval, we reviewed the statistical review memorandum published as part of the approval documentation.

Through this review process, we developed a dataset by recording key elements of the study design including: number of pivotal trials submitted for review, total number of participants completing each pivotal trial, and the geographic location of each trial participant. Lastly, internal IQVIA experts reviewed the database and coded each approval into a relevant therapeutic area grouping. Through this analysis, of the 181 new drug approvals from 2013 – 2017, the percent of all participants in pivotal trials from the United States was calculated for 176 new drugs and biological products. Five approvals were excluded from analysis given lack of reporting on specific geographic mix of trial participants.

RESULTS AND ANALYSIS

For the five-year period of 2013-2017, the 176 pivotal clinical studies that supported approval by FDA, had on average, 41% of study participants from the US. While this is significantly higher than the hypothesized 20% rule-of-thumb threshold, in each year there was significant variation from this mean – in every year from 2013 to 2017, some products were approved based on pivotal studies with 100% of participants from the US and others were approved based on studies with less than 10% of participants from the US. Figure 1 below summarizes the distribution of patients for each approved drug within the timeframe.

Figure 1: US Drug Approvals 2013-2017; % of Pivotal Clinical Trial Participants from the US



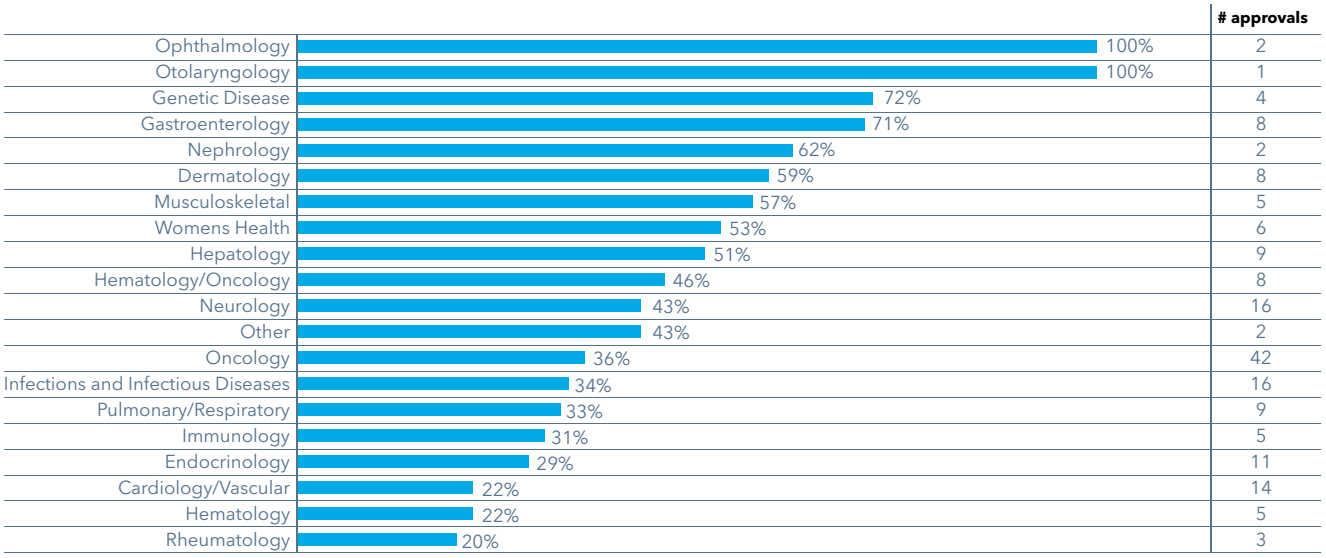
Source: IQVIA

Of the 176 new drug and biological product approvals included in our analysis, 30 were approved based on pivotal clinical trials with less than 10% of patients from the US and 55 were approved based on trials with less than 20% of patients from the US. This represents 17% and 31% of all approvals during this time period respectively. Each year, there was at least one approval based on pivotal clinical trial data with less than 10% of patients from the US, with the highest number seen in 2013 (9 out of 27 approvals or 33%). This demonstrates that new drugs and biological products are routinely and consistently approved by the US FDA based on clinical trials that were conducted primarily at sites outside of the US.

	2013	2014	2015	2016	2017	Total 2013 to 2017
Total number of drug and biological product approvals included in the analysis	27	40	45	21	43	176
Number of drugs approved based on pivotal clinical trial data with <10% US patients	9	6	7	1	7	30
Percent of approvals based on pivotal clinical trial data with <10% US patients	33%	15%	16%	5%	16%	17%
Number of drugs approved based on pivotal clinical trial data with <20% US patients	11	11	17	4	12	55
Percent of approvals based on pivotal clinical trial data with <20% US patients	41%	28%	38%	19%	28%	31%

While each year the average percentage of pivotal clinical trial participants from the US across all approvals is consistent at around 40%, there is significant variance across therapeutic areas. As highlighted in Figure 2, the two approvals in ophthalmology and one in otolaryngology were based on pivotal clinical trials in which 100% of participants were from the US, while the 14 approvals in cardiology were based on pivotal clinical trials in which ~20% of participants were from the US on average.

Figure 2: Average Percent of Participants from US by Therapeutic Area (Approvals 2013-2017)

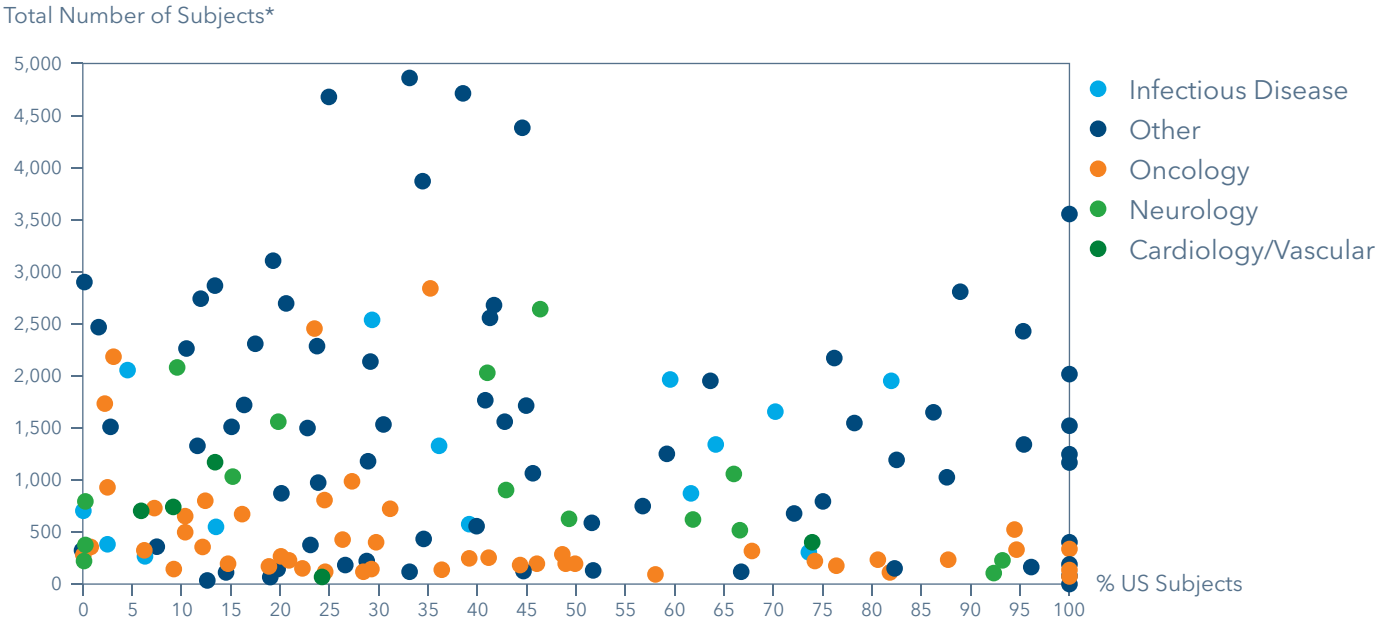


Source: IQVIA

Oncology saw the highest number of total approvals (42), 14 of which were based on pivotal clinical data with less than 20% of patients from the US. Among these 14 trials, the average percent of US patients was just 8%.

While the initial hypothesis might have presumed that the acceptance of non-US clincial trial data would be limited to smaller trials evaluating treatments for rare diseases that are not prevalent in the US, further analysis revealed that there is no correlation between the percent of participants from the US and the overall trial size, as seen in Figure 3.

Figure 3: Relationship Between Overall Trial Size and Percent of Participants from the US (Approvals 2013-2017)

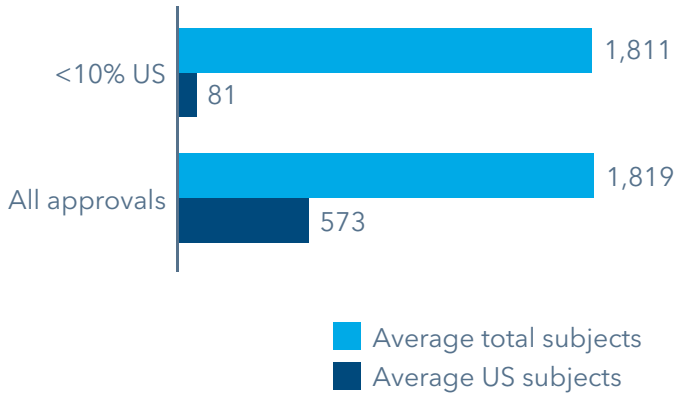


* Note: represents the total number of all subjects from all geographic regions across all pivotal trials; excluding 14 trials larger than 5,000 patients

Source: FDA Novel Drug Approvals; IQVIA Analysis

Further, across the 5 years examined there were 30 approvals that included less than 10% of pivotal clinical trial participants from the US. These studies included, on average, 1,811 total patients across the series of pivotal trials that formed the basis for approval of the drug. We found that the total number of patients enrolled for these trials was similar to that of all approvals (1,819 total patients studied).

Figure 4: Average Total Pivotal Trial Participants; all approvals vs. approvals with <10% of US participants



Source: FDA Novel Drug Approvals; IQVIA Analysis

Next, we examined whether approvals based on clinical trials with a lower percentage of US patients are more common within any one therapeutic area. We selected the four therapeutic areas with the highest number of new product approvals in the timeframe examined: oncology, infectious disease, neurology, and cardiology (Table 1). By comparing the distribution of all drug approvals to the distribution of approvals based on a low percentage of US patients, we saw that infectious disease and neurology had a disproportionately large percentage of drug approvals based on a less than 10% US participants.

Table 1: Most Common Therapeutic Areas for All Approvals and for Approvals with <10% of Patients from the US

Therapeutic Area	% of all approvals (n=176)	% of approvals with <10% US subjects (n=30)
Oncology	23%	27%
Infectious Disease	10%	20%
Neurology	9%	17%
Cardiovascular	8%	13%
Other	50%	23%

In summary, while the 20% rule of thumb has some basis, it is an over-simplification as every year there are cases where data from studies that were conducted entirely outside the US are found to be sufficient to support approval in the US. A drug development program would be better served by evaluating all non-US pivotal clinical trial data with respect to the underlying factors that determine whether the data will be acceptable to support marketing approval in the US.

Importantly, one must consider FDA's specific guidance on the use of data from non-US populations. FDA's guidance on this topic generally falls into two discrete areas:

- Demonstrating that standards for study quality, data quality and ethics are met, regardless of where study was located
- Establishing that foreign clinical data can be extrapolated to the US population

I) STANDARDS FOR STUDY QUALITY, DATA QUALITY AND ETHICS

All clinical studies that will be used to support either an Investigational New Drug (IND) application or a marketing application in the US must meet the same or equivalent standards for study quality, data quality and ethics regardless of where the study was conducted. This can be challenging when clinical studies are designed based on regional standards without prior consideration of US requirements for a well-designed and well-conducted study. Additionally, companies must keep in mind FDA must be able to validate the data from a clinical trial submitted to the agency under Part 312.120 through on-site inspection.

One option for companies that anticipate bringing their product to the US market is to submit an IND application to the FDA for their OUS study even though it is not a requirement to do so. This provides an opportunity to receive early FDA feedback on critical factors including the study design, the adequacy and completeness of the pre-clinical data and the manufacturing process.

However, a majority of foreign clinical studies are not conducted under a US IND. In those cases, the information described in 21 CFR 312.120 must be submitted as part of the application (Table 2). FDA's guidance document titled "FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND — Frequently Asked Questions" is a useful reference that explains in detail how to meet these requirements.

Table 2: Summary of information required for foreign clinical trials not conducted under a US IND

Requirement	21 CFR Part:
The study was conducted under Good Clinical Practices	312.120(a)
Documentation of investigator qualifications	312.120(b)(1)
Description of the Research Facilities	312.120(b)(2)
Detailed summary of the protocol and study results and, if requested, case records or additional background data	312.120(b)(3)
Description of the drug substance and drug product, including the components, formulation, specifications, and, if available, the bioavailability of the drug product	312.120(b)(4)
Information showing that the effectiveness study is adequate and well controlled under 21 CFR 314.126	312.120(b)(5)
The name and address of the independent ethics committee (IEC) that reviewed the study and a statement that the IEC meets the definition in 21 CFR 312.3(b). **The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;**	312.120(b)(6)
Summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion	312.120(b)(7)
Description of how informed consent was obtained	312.120(b)(8)
Description of what incentives, if any, were provided to subjects to participate	312.120(b)(9)
Description of how the sponsor monitored the study and ensured that the study was carried out consistently with the study protocol	312.120(b)(10)
Description of how investigators were trained to comply with GCP and to conduct the study in accordance with the study protocol, and written commitments by investigators to comply with GCP and the protocol	312.120(b)(11)

Companies planning to submit foreign clinical study data should consider how they will clearly identify for FDA where the required information is located in a submission, to avoid delays in review.

Additionally, companies should evaluate prospectively whether they have the ability to fulfill each of the requirements under 312.120.

There are a number of challenges that companies often face when preparing foreign clinical data for FDA review. For example, in some countries and regions, obtaining and providing the names and qualifications of the Independent Ethics Committee members to FDA upon request presents a privacy challenge. Companies should consider how they will obtain such information or alternatively, whether a request for a waiver of this FDA requirement may be warranted. Secondly, relevant medical records that were stored at clinical study sites or other facilities are not always retained after a study is complete, especially after several years have elapsed. These records are often lost in the course of doing business, such as when a clinical site re-locates to a new facility or when investigators move on to other positions. Another common issue arises when companies fail to consent patients to allow the FDA to review their relevant medical records. Companies should ensure that consent forms make clear that FDA is among the regulatory authorities that may review subject records, to avoid delays in inspection should FDA determine such inspection is warranted.

When a company is unable to fulfill all of the requirements under 312.120, one option is to submit a request to FDA for a waiver of that requirement. Requests for waivers must contain an explanation why compliance with the requirement is unnecessary or cannot be achieved, the proposed alternative course of action and any other information that justifies the waiver.

II) ESTABLISHING THAT FOREIGN DATA CAN BE EXTRAPOLATED TO THE US

The other major requirement is to demonstrate that foreign clinical trial data are applicable to the US patient population and to US medical practice. Differences in regional medical practices and demographics may lead to differences in a drug's safety and efficacy profile and also may impact the dose and dosing regimen. Many companies have struggled to address this concern and it is the basis for the widely used "20% rule" mentioned above.

In determining whether foreign data can be extrapolated to US population, companies need to consider both extrinsic and intrinsic ethnic factors.

Extrinsic Ethnic Factors:
Extrinsic ethnic factors are factors associated with the environment and culture in which a person resides. Extrinsic factors tend to be less genetically and more culturally and behaviorally determined. Examples of extrinsic factors include the social and cultural aspects of a region such as medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, socio-economic status, compliance with prescribed medications, and, particularly important to the reliance on studies from a different region, practices in clinical trial design and conduct.

Intrinsic Ethnic Factors:
Intrinsic ethnic factors are factors that help to define and identify a subpopulation and may influence the ability to extrapolate clinical data between regions. Examples of intrinsic factors include genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction.

ICH Harmonised Tripartite Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1)

ICH Harmonised Tripartite Guideline: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1) is the primary resource for understanding the FDA's thinking in this area. This ICH guideline provides a framework for performing a systematic evaluation of intrinsic ethnic

factors and extrinsic ethnic factors that may impact a drug's safety and efficacy profile and dosing regimen. The results of this evaluation are then used to identify the key areas of concern and determine the extent and type of bridging information needed to support a marketing application.

The importance of evaluating intrinsic ethnic factors was further elevated by the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law in 2012, which directed FDA to investigate how well demographic information (sex, age, race and ethnicity) is captured in clinical trials and whether drugs are analyzed for safety and effectiveness by demographic subgroups. Historically, the elderly, women (in some therapeutic areas) and racial minorities within the US population have been underrepresented in clinical trials. One outcome of the FDASIA Section 907 mandate is the annual publication of drug trial snapshots on the FDA website that provide information about the demographics of participants in clinical trials that supported new drug approvals in the US (Drug Trials Snapshots, 2018).

This is an important consideration as there are drugs that do not have uniform safety, efficacy and dosing parameters across different ethnic groups. One study examining US drug approvals between 2008 and 2013 found that about one out of five drugs demonstrated differences in exposure or response across diverse patient populations resulting in population-specific prescribing recommendations (A Ramamoorthy, 2014). Notable examples are Crestor and Warfarin where a dedicated section within the Dosage and Administration section of the label provides separate information for dosage in Asian patients.

TWO DRUG APPROVALS USING A LOW PERCENTAGE OF US DATA

Determing the proportion of study population from US required for FDA approval requires careful consideration on the study quality, data quality, ethics and ethnic considerations of foreign trial data. Finally, we wondered how sponsors have addressed these challenges and successfully leveraged pivotal clinical data from primarily non-US patients. We examined two recent drug approvals that were based on a low percentage of US data: Radicava (edaravone) and Entresto (sacubitril/valsartan).

RADICAVA (EDARAVONE) TO TREAT PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

For 20 years the only FDA approved treatment for the fatal neurodegenerative disease amyotrophic lateral sclerosis (ALS) was Riluzole (Rilutek, FDA approved in 1995). Riluzole provides limited benefit to patients, and there remained an acute need for more effective treatments for this devastating disease.

A promising new ALS treatment emerged in 2015 when Mitsubishi Tanabe found that edaravone, a free radical scavenger previously approved for the treatment of cerebral ischemia in Japan, slowed the decline of physical function in moderate ALS patients by approximately 33% (FDA approves drug to treat ALS, 2017).

As ALS patients from around the world began travelling to Japan to gain access to the drug, Mitsubishi Tanabe sought the most efficient path to make edaravone widely available to patients in the US. After a series of discussions with the US FDA, Mitsubishi Tanabe applied for marketing approval based solely on the clinical trial and post-market surveillance data that they had already collected in Asia.

As documented in the Summary Review Memorandum (New Drug Application (NDA): 209176, 2017), they faced several challenges related to both demonstrating study, data, and ethic quality standards and the requirements for extrapolation to US population:

Challenges with demonstrating that standards for study quality, data quality and ethics are met

Challenge: The US FDA generally requires safety and efficacy data from two pivotal trials to support a marketing application. Although Mitsubishi Tanabe conducted two multi-center, 24-week double-blind and placebo-controlled pivotal clinical trials evaluating edaravone for the treatment of ALS, only one of those studies had positive results.

- When their initial study with broader enrollment criteria yielded negative results, Mitsubishi Tanabe performed a post-hoc analysis and found that a subgroup of patients with a more recent diagnosis and less severe symptoms may be responsive to the treatment. Mitsubishi Tanabe then designed a second pivotal study, titled Study 19, based on the post-hoc analysis selection criteria that ultimately formed the basis for edaravone's approval.

How it was addressed: Mitsubishi Tanabe presented the results of Study 19 as sufficient to meet the standard of substantial evidence of effectiveness based on several factors. First, the 2.5 point difference between the edaravone group and the placebo group in the primary endpoint, change in ALS Functional Rating Scale-Revised (ALSFRS-R) between baseline and week 24, was highly statistically significant (p=0.0013). Second, a 2.5 point change in ALSFRS-R is regarded as clinically meaningful because it represents a change in the level of physical function. Third, an analysis of the change in ALSFRS-R scores over time revealed that the edaravone group were relatively more stable over the course of the study. Finally, although the study was not statistically controlled for multiple comparisons, the results for the secondary endpoints were supportive of the results seen for the primary endpoint showing consistency in the activity of the drug.

Challenge: Mitsubishi Tanabe had not performed a dose-finding study and the unusual dosing regimen studied in Study 19 lacked a clear scientific basis.

The Study 19 dosing regimen involved a series of treatment cycles as follows:

- CYCLE 1: 14 days of treatment followed by 14 days with no treatment
- SUBSEQUENT CYCLES: treatment on 10 out of 14 days followed by 14 days with no treatment

How it was addressed: The FDA allowed this dosing regimen to be recommended in edaravone's labeling on an empirical basis and required that a dose finding study be conducted as a post-market study commitment.

Challenge: Edaravone was developed in Japan without the specific intention of bringing the drug to the US market. As a result, two pre-clinical studies that are required in the US were not conducted prior to the submission of the marketing application: (1) a thorough TQT study and (2) carcinogenicity studies in rat and mouse.

How it was addressed: Taking into consideration the high degree of clinical unmet need in ALS and the positive safety profile for edaravone, the FDA review team agreed to allow these studies to be performed post-approval.

Challenges with establishing that foreign data can be extrapolated to the US

Challenge: The pivotal clinical study was conducted in a population that was entirely of Japanese ethnic origin at clinical study sites located in Japan.

How it was addressed: In accordance with the guidelines provided in ICH E5 R1, Mitsubishi Tanabe performed an analysis of the intrinsic and extrinsic ethnic factors that have the potential to impact the extrapolation of their edaravone study data to the US ALS population.

They identified four key areas of concern: diagnosis of ALS, medical practice as it relates to ALS, disease progression in Japanese and US ALS patients and drug pharmacokinetics. They addressed these key areas through a well-constructed ethnic bridging information package that was included as part of their Complete Clinical Data Package (summarized below).

Table 3: Outline of edaravone's ethnic bridging information package as summarized in the FDA approval documentation:

Factors	Information Submitted in Radicava's Complete Clinical Data Package
Diagnosis of ALS	• In the US, the ALS diagnostic cross-section is comparable among White, Black and Asian populations • The prevalence of Sporadic vs Familial ALS is the same in the two regions
Practice of medicine, as it relates to ALS	• Comparison of the primary treatment guidelines used in the two regions demonstrated consensus in diagnostic criteria and similar recognition of symptoms and their progression • Same first line treatment (Riluzole) in the two regions • Only modest differences were noted in the medications prescribed for secondary complications and symptomatic relief • The regional guidelines provided strongly consistent advice regarding the timing and type of other interventions • Differences in the terminal choice of discontinuation of ventilator support were not expected to impact the interpretation of data from the Radicava study which evaluated early stage ALS patients
Natural History of ALS	• The progression of ALS is similar in the two regions as determined by the change in ALSFRS-R score over time and the change in ALS biomarkers over time
Drug Pharmacokinetics	• Population PK analysis supported an absence of racial differences. • Gender, weight and age did not affect PK model parameters. Race affected peripheral volume of distribution 2 (V2) but was not detected as a covariate for any other parameter. The difference in V2 by race was small and would not result in accumulation or a change in drug concentration. • Ethnic differences were also evaluated with Population PK simulations using virtual ALS populations. Assumptions were based on data from edaravone studies for Japanese and literature for ALS studies for non-Japanese. The simulations demonstrated no differences between the two populations.

ENTRESTO (SACUBITRIL/VALSARTAN) FOR HEART FAILURE

On the other end of the spectrum from Radicava, which was evaluated in just one country, heart failure drug Entresto was approved by the US FDA based on data from an international clinical trial that spanned 984 sites across 47 countries. This pivotal clinical trial was the largest that had been conducted in heart failure patients although only 5% of the patients were randomized in the US.

An analysis of the Summary Review Memorandum revealed the following challenges that were overcome (New Drug Application (NDA): 207620, 2015):

Challenges with establishing that foreign data can be extrapolated to the US

Challenge: Trial sites were located across Europe, Asia and Latin America – with very little representation from the US.

How it was addressed: Novartis ensured that the overall trial population was generally representative of the US heart failure population. This was determined by comparing the trial population demographics to patient demographics in the US cohort and in a large US registry of heart failure patients.

Challenge: Given the prevalence of heart failure in the US black population, black patients were under-represented in the Entresto pivotal trial. This was particularly concerning because the incidence of angioedema was higher in black patients treated with Entresto than in black patients receiving the active control drug, and it is known in the field that black patients are more susceptible to angioedema induced by some heart failure drugs.

How it was addressed: Considering Entresto's strong overall risk/benefit profile, the FDA allowed this issue to be addressed through a post-marketing requirement for an observational study to better characterize the risk of serious angioedema to black patients treated with Entresto.

Challenge: Due to differences in medical practices among regions, the use of Implantable Cardioverter Defibrillators (ICDs) in the trial population was much lower than that of subjects in the US or in the US heart failure registry.

How it was addressed: The possible impact of ICD use on the risk/benefit profile of Entresto was considered, and the FDA determined that ICD patients could be expected to derive the same benefits from the drug as patients who had not received that intervention. Therefore, regional differences in ICD use were determined to have no impact on the interpretation of the study results.

CONCLUSION

Although the "20% rule" is commonly relied upon, it is an over-simplification that could lead drug developers to perform unnecessary clinical trials that delay bringing their therapies to US patients. The FDA has a long and well-established track record of approving drugs and biological products based on pivotal clinical data with a low percentage of US participants when the data fulfills FDA's requirements related to the strength of the evidence, study quality, data quality and ethics as well as the impact of ethnic factors.

Looking at the case of Entresto, we see that sponsors of international trials may be able to achieve baseline demographics that are similar to the US population by selecting sites that span the major global regions. We also saw that post-market studies may be leveraged to better characterize the risk of serious adverse events in underrepresented ethnic groups when the overall risk/benefit profile of the therapy is positive. Further, variation among regions in the use of other interventions in the treatment of the disease or condition, such as surgical interventions and the use of medical devices, can be acceptable if those interventions are not expected to impact the study results.

FDA's May 2017 approval of Radicava (edaravone), demonstrated that a thorough ethnic bridging information packet can be sufficient to allow for the use of high quality foreign studies conducted in a single region in an ethnically homogenous population to support approval of the drug in the US. In some cases, a single pivotal clinical study can be sufficient to support FDA approval of a drug. A single pivotal study is more likely to be accepted if it is a robustly positive and multicentered study and if the secondary endpoints are supportive of the study results.

When studies are conducted in the absence of FDA input, important questions are often left unanswered. The FDA has the latitude to exercise flexibility and allow such gaps to be addressed through post-market study requirements. In general, the FDA is more likely to exercise flexibility in drug approvals when there is a robust set of safety data for the subject drug and when it addresses an area of high unmet clinical needs.

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Ms. Meeker-O'Connell has more than 20 years of clinical and biomedical research experience, including Quality Assurance leadership roles at the U.S. Food & Drug Administration as the Director of the Division of Good Clinical Practice Compliance, as well as at Johnson & Johnson, Amgen and Pfizer. She is a recognized industry thought leader for clinical quality, having developed key FDA guidance related to trial oversight and led cross-industry innovation initiatives on clinical Quality by Design and Clinical Quality Management Systems. Ms. Meeker-O'Connell also serves on the Board of Directors for the Association for the Accreditation of Human Research Protection Programs.

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In his more than 20 years in the biotechnology and CRO sector, Dr. Abruzzini has held positions of increasing responsibility. He holds positions as lecturer for several university and training courses in clinical research and regulatory affairs. He also served as the sponsor's authorized representative to the US FDA for US and non-US pharmaceutical companies.

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IQVIA Cell and Gene Therapy Center

Dr. Caitilin Hamill is the head of regulatory affairs for IQVIA's Cell and Gene Therapy Center, where she advises companies on integrated planning, regulatory, and clinical development strategy.

Prior to joining IQVIA, Dr. Hamill spent seven years at the US Food and Drug Administration (FDA) where she served as a reviewer in the Center for Biologics Evaluation and Research (CBER) Office of Tissues and Advanced Therapies (OTAT, formerly OCTGT) and later in the Office of the Director for CBER. Dr. Hamill reviewed and recommended action on Investigational New Drug (IND) applications for cell therapies and Pre-Market Notifications [510(k)s] for devices used in the collection, processing, testing and administration of cell and tissue-based therapies. Dr. Hamill also evaluated performance data for Biologic License Applications for in vitro diagnostic devices used for donor screening. She played an active role in cell and gene therapy policy development contributing to more than 30 guidance documents and regulations. Subsequently, in her position in CBER's Office of the Director, she was responsible for Center-level management of CBER's review programs where she identified and assessed emerging complex issues, often resulting from implementation of new legislation, and formulated appropriate programmatic review actions.

Dr. Hamill earned her PhD in Neuroscience from Northwestern University and received her postdoctoral education in human embryonic stem cell biology under Professor Matthias Hebrok at the University of California San Francisco. Dr. Hamill earned an MBA in finance from The Wharton School, University of Pennsylvania.

JESSICA ZAKAR
Associate Principal,
Consulting Services, IQVIA

Ms. Zakar is an experienced leader responsible for overseeing complex client engagements. With more than 7 years of strategic consulting experience, Jessica oversees consulting engagements across a wide spectrum of solutions with a primary focus on due diligence and asset evaluations, therapeutic landscape assessments, and portfolio strategy work. She also has significant experience overseeing commercial assessments and indication prioritization for early-stage clinical assets.

Ms. Zakar holds a BA in public policy from the University of Michigan, Ann Arbor.

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