Original Research

Efficacy End Points and Dose Analysis of Food and Drug Administration-Approved Novel Drugs in 2020

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ARTICLE INFO

ABSTRACT

Background: During 2020, the Food and Drug Administration approved 53 novel drugs.
Objective: Biomarkers, surrogate endpoints and dosing regimens used in early and pivotal clinical stages are evaluated.
Methods: Information on various efficacy end points of 2020 Food and Drug Administration approved novel drugs was gathered from the Drug Approvals and Databases page of the Food and Drug Administration website. Endpoint data from efficacy end points for the 2019 approved novel drugs by Tong and Wang are used as a comparison.
Results: Among the 53 drugs approved during 2020, 49 were for treatment of various diseases and 4 were for diagnostics. Twenty-five drug approvals (51%, relative to 49 drugs for treatment of diseases) were based on surrogate end points, consisting of 12 accelerated approvals and 13 regular approvals. There were 19 drug approvals for cancer treatments (39%, relative to 49 drugs for treatment of diseases). During 2019, there were 48 drugs approved. Forty-four were for treatment of various diseases and 4 were for diagnostics. Fourteen drug approvals (32%, relative to 44 drugs for treatment of diseases) were based on surrogate end points, consisting of 9 accelerated approvals and 5 regular approvals. There were 10 drug approvals for cancer treatments (23%, relative to 44 drugs for treatment of diseases).

The approved doses were usually much closer to the highest dose tested in clinical trials (about 2-fold lower) compared with the lower dose tested in clinical trials (about 11-fold higher). Large and variable distances between the starting low dose in humans and the final approved doses indicate that finding the optimal dose in clinical trials is still a time-consuming and costly process. Further dose analysis for cancer drugs approved during 2020 showed that the distances between the starting dose in human beings and the final approved doses of cancer drugs were still large and variable, similar to distances in noncancer drugs. Stratification of drugs approved in 2020 by molecular weights shows that small molecular weights (<1000 Daltons) appeared to be smaller and less variable than those for drugs with large molecules (>1000 Daltons). (*Curr Ther Res Clin Exp.* 2022; 83:XXX–XXX)
Conclusions: Surrogate end points with accelerated approval have been widely used for approvals, with an increasing trend from 2019 to 2020 (32% vs. 51%). The approved doses usually were much higher (10-fold) than the lowest tested dose in first-in-human trials, while much closer (2-fold lower) to the highest dose tested in clinical trials.

Introduction

Surrogate end points (SEs) are clinical indicators used during clinical trials that could reasonably forecast clinical benefit. SEs are used under circumstances where it is impractical or unethical to conduct clinical end point studies. For example, when developing a drug to treat stroke, it may take very large and time-consuming clinical trials to demonstrate clinical benefits. In this case, blood pressure can be used as an SE because a higher blood pressure could indicate a greater risk of stroke. The use of SEs is also widely adopted in oncology. Rather than measuring clinical end points, such as overall survival, surrogates such as tumor size or growth are used instead when conducting clinical trials. Between 2010 and 2012, the Food and Drug Administration (FDA) approved 45 percent of new drugs based on an SE.[1]

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Although SE studies consume less time and resources compared with clinical end point studies, there has been controversy over their effectiveness and clinical benefits.[2] Some argue that a drug could favorably affect a surrogate and may not have an overall clinical benefit.[3] For example, Gyawali et al[2] showed that SEs in the FDA list of SEs for cancer treatment—including pathological complete response rates, event-free survival, disease-free survival, objective response rates, and progression-free survival (PFS)—had weak or no correlation with anticancer efficacy measured by overall survival (OS). Weintraub et al[3] argued that some SEs for cardiovascular diseases may fail to predict cardiovascular events. For example, the SE, serum HDL cholesterol level, is believed to predict cardiovascular events. However, recent trials using niacin and cholesterol ester transfer protein blockers, which increased serum HDL cholesterol levels, did not show efficacy in reducing cardiovascular events; in some trials, a higher mortality was observed with increased HDL level.

Recently there have been mixed messages from FDA on the use of SEs for approval of drugs. On June 7, 2021, despite the opposition from the FDA advisory committee, the FDA approved aducanumab for the treatment of Alzheimer disease (AD). The approval decision was subsequently surrounded by significant concerns and controversies. Among the major concerns is the use of amyloid β (Aβ) plaque as an SE for its accelerated approval. The accumulation of Aβ plaques is the hallmark of AD development. However, the medical community is divided on whether reducing of Aβ plaques has clinical benefits.[4] In contrast, the FDA recently denied approval of sintilimab, a PD-1 antibody for treatment of nonsquamous non–small cell lung cancer, although there was clinical data that indicated PFS—an accepted SE in the past—met the statistical significance. However, there is a reasonable explanation for the inconsistency. The approval of aducanumab was likely based on the serious unmet medical need for AD.[4] In the case of sintilimab, although PFS is an acceptable clinical end point, OS is the preferred end point. The FDA argues that there are multiple approved agents that demonstrated higher OS in clinical trials. Overall, these examples reflect that the availability of existing medications and severity of diseases governs FDA's position on the use of SE for new drug approval.[5]

To investigate the use of SE in the past, surveys on SE-based regulatory approvals have been carried out. Chen et al[6] showed that the FDA had used SE about 194 times for approving oncology drugs from 1992 to 2019; around 1 in 3 times, an oncology drug is approved based upon a new SE. During 2019, 14 drugs were approved based on SE.[7]

This work surveys SE for drugs approved by FDA during 2020. The original objective was to evaluate how doses were selected and approved (eg, determination of first dose in human beings and dose escalations in efficacy or safety clinical trials) based on the type of end point and pharmacodynamic and pharmacokinetic data. This objective was not fully achieved and is not included in this report. However, the data collected on doses for this objective was analyzed. A comparative analysis of doses tested during clinical trials and doses approved in FDA prescription labels was conducted with the objective of evaluating the process and difficulty in determining the dose levels for clinical trials and regulatory approval.

Methods

Data on biomarkers, surrogates, clinical end points, doses tested in clinical trials and approved by the FDA, and the approval types (accelerated or regular approval) was collected from the open-source FDA drug database website.[1] The available multidisciplinary reviews on the 53 drugs approved by the FDA in 2020 were examined and relevant data was extracted; most of the clinical data

were collected from the Clinical Pharmacology and Medical Review. SEs, defined and assigned by FDA on their website, were used to validate the data found in the reviews.[8] The use of biomarkers, SEs, and clinical end points was identified for early and pivotal stages of clinical trials.

For drugs approved during 2019, similar data on the use of surrogates compiled by Tong and Wang[7] were used as a comparison.

Limitations

Data on the doses tested in clinical trials might not be complete because the FDA reviews may not include all the tested doses or studies. For consistency, only data reported in the FDA reviews were evaluated.

Drugs with the following dosing scenarios were excluded from the dose analysis:

- Approved doses have complicated dose stratifications in clinical trials. For example, nifurtimox is a nitrofuran antiprotozoal, indicated in pediatric patients (birth to age <18 years and weighing at least 2.5 kg) for the treatment of Chagas disease. In Phase I studies, fixed doses (30 and 100 mg) were tested for evaluating pharmacokinetics and food effect. In Phase III study, a total daily dose of 10 to 20 mg/kg for patients with a body weight <40 kg and 8 to 10 mg/kg for patients with a body weight >40 kg. The approved doses are based on body weights, exactly following the doses investigated in the Phase III study. It is difficult to compare the doses with ranges and stratification of body weight. Zokinvy is a farnesyltransferase inhibitor indicated in patients aged 12 months and older with a body surface area of 0.39 m^2 and larger. Doses in clinical development for Zokinvy were administered by total doses in different populations (adults and pediatrics with different body weights). The final approved doses were defined by strict age and body surface requirements.

- The drug is administered in combination with other drugs. For example, inmazeb is a combination of *Zaire ebolavirus* glycoprotein-directed human monoclonal antibodies (eg, atoltivimab, maftivimab, and odesivimab) indicated for the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients. A range of doses were tested in early clinical trials by single agents. In Phase III, the combinations of 50 mg/kg for each of the 3 agents were tested. The approved doses followed the ones tested in Phase III. It is difficult for comparative analysis because 3 agents were involved.

- Dermal drugs, for which doses were tested and approved based on formulation strengths, percent total body surface area applied, application rate, and populations tested. Additionally, maximal usage trials for topically applied drugs are typically required by FDA. It is not meaningful to compare the approved dose with maximal usage doses, regardless of pharmacology or efficacy.

- Tracers for diagnostics. Typically, tracer doses are very low—micrograms or lower—and not governed by efficacy or safety issues. Therefore, it is not meaningful to compare the doses tested (typically 1 dose or very few) and approved.

Descriptive statistics such as mean, median, range, and percentile analysis were used for data analysis.

Results

Surrogate end point review

There were 53 drugs approved by FDA in 2020 (Table 1); 4 drugs were for diagnostics. A large percentage of the approved drugs for treatment of diseases were based on SE (25 drugs; 51%).

Table 1

Compilation of drugs approved during 2020 with use of biomarkers (BIO), surrogate end points (SE), and clinical end points (CE) as approval basis.

Drugs	Use of BIO/SE/CE in early stage	Use of BIO/SE/CE in pivotal stage
Diagnostics		
Copper Cu 64 dotatate	Biodistribution	Sensitivity/specificity
Flortaucipir F18	None	Sensitivity/specificity
Fluoroestradiol F18	None	Sensitivity/specificity
PSMA-11 Gallium 68	Biodistribution	Sensitivity/specificity
Treatment of diseases		
AA based on SE		
Belantamab mafodotin-blmf	ORR	ORR
Capmatinib	DoR	ORR, DoR
Lurbinectedin	ORR	ORR, DoR
Naxitamab-gqgk	ORR, DoR	ORR, DoR
Pemigatinib	ORR	PFS, ORR
Pralsetinib	ORR, DoR	ORR, DoR
Sacituzumab	ORR, DoR	ORR, DoR
Selpercatinib	ORR, DoR	ORR, DoR
Tafasitamab-cxix	Physical exam/CT	ORR, DoR
Tazemetostat	ORR, DoR	OS, PFS
Nifurtimox	None	Serological response
Viltolarsen	mRNA and protein of dystrophin	mRNA and protein of dystrophin
RA based on SE		
Decitabine and Cedazuridine	ORR, DoR	CR, DoR
Avapritinib	ORR	ORR
Decitabine and Cedazuridine	ORR, DoR	CR, DoR
Isatuximab	PFS, ORR	PFS, ORR
Margetuximab	ORR, DoR	PFS, OS
Relugolix	LH/FSH	Testosterone
Ripretinib	ORR, DCR	PFS, ORR
Selumetinib	ORR, DoR	ORR, DoR
Tucatinib	PFS, DCR	PFS, ORR
Bempedoic acid	LDL-C	LDL-C
Fostemsavir	None	RNA load
lumasiran	Urinary oxalate	Urinary oxalate
Osilodrostat	Plasma/ urinary free cortisol	Urinary free cortisol
RA based on CE		
Abametapir	Lice free	Lice free
Amisulpride	Nausea/vomiting	Nausea/vomiting
Ansuvimab-zykl	None	Mortality
Artesunate	Parasite clearance	Mortality
Atoltivimab, maftivimab, odesivimab-ebgn	None	Mortality
Berotralstat	Kallikrein inhibition	Hereditary angioedema
Clascoterone	IGA	IGA
Eptinezumab	Migraine	Migraine
Inebilizumab-cdon	CD20 B Cells	Relapse
Lactitol	Bowel movements	Bowel movements
lonafarnib	None	Mortality
Oliceridine	None	SPID-48
Opicapone	COMT activity	Off-time
Ozanimod	Lymphocyte count	Relapse rate
Remdesivir	None	Time to recovery
Remimazolam	None	Sedation success
Rimegepant	Migraine	Migraine
Risdiplam	None	Sitting/motor functions
Satralizumab-mwge	IL-6R	Relapse
Setmelanotide	Energy expenditure	Body weight loss
Somapacitan-beco	IGF-1	Truncal fat
Teprotumumab	IGF-1	Proptosis/diplopia responder
Tirbanibulin	AK lesion	AK lesion
Triheptanoin	None	Source of calorie and fatty acid
Vibegron	Micturition's, UUI and urgency	Micturitions, UUI and urgency

Accel = accelerated approval; AK = actinic keratosis; COMT = catechol-O-methyltransferase; CR = complete response; DoR = duration of response; FSH = follicle-stimulating hormone; IGA = investigator's global assessment; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; ORR = overall response rate; PFS = progress-free survival; Reg = regular approval; SPID-48 = sum of the pain intensity difference over the 48 hour time period; UUI = urge urinary incontinence.

The SE based approvals consisted of 12 accelerated approvals (AA) and 13 regular approvals (RA). Thirty nine (39%) drugs were approved for cancer treatments (Table 2). In comparison, of the 48 approvals in 2019, 4 were for diagnostics, and 14 (32%) approvals for treatment of diseases were based on SE. The 2019 SE approvals consisted of 9 AAs and 5 RAs. Ten (23%) drugs were approved for cancer treatments (Table 2).

Overall, the use of SE for approval has increased from 2019 to 2020, mainly due to a greater number of cancer drug approvals.

Table 2

Comparison of drug approvals in use of surrogate end points between 2019 and 2020.

Variable	2019	2020
Drugs for treatment of diseases/diagnostics	44/4	49/4
Cancer drugs	10 (23)*	19 (39)*
Surrogate end points for approval	14 (32)*	25 (51)*
Accelerated approval	9	12
Regular approval	5	13

* Values are presented as n (%). Percentages were calculated based on drug approvals for treatment of diseases (ie, exclusion of diagnostics).

All 19 cancer drugs approved in 2020 were based on SEs—10 via AA and 9 via RA. This reflects that cancer diseases still represent a field with serious unmet medical need, for which SEs tends to be commonly used and accepted by FDA.

The other 2 AA-based SEs include:

• nifurtimox. The approval was based on the serological response (immunoglobulin G antibody negative) to infection of parasite *Trypanosoma cruzi*. Nifurtimox was the only treatment of Chagas disease in children up to age 18 years; and

• viltolarsen. The approval was based on an increase of dystrophin for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. The availability of therapeutics, as well as their effectiveness, for the treatment of DMD was extremely limited, representing a serious unmet medical need.

There are 9 cancer drugs that underwent regular approvals based on SEs, presumably because of the availability of existing therapeutics. However, all these 9 cancer drugs used SEs. This reflects the difficulty of conducting outcome studies for cancer drugs (usually having overall survival as the clinical end point) due to limited availability of patients, time constriction, and cost.

The SE used for noncancer drug approvals include:

- RNA load for fostemsavir treatment of HIV/AIDS;
- LDL-C for bempedoic acid treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease;
- urinary oxalate for lumasiran treatment of primary hyperoxaluria type 1; and
- urinary free cortisol for osilodrostat treatment of Cushing disease where pituitary surgery is not an option or has not been curative.

All these SEs are pharmacological effects from target engagement of corresponding drugs. These effects (eg, RNA load, LDL-C level, and urinary chemistry) are considered to be predictive of clinical benefits.

The 25 drugs approved via RA and based on clinical end points have clinical benefits/outcomes and feasibility of measurement of clinical benefits/outcomes, such as lice free by the treatment of abametapir, reduction of nausea/vomiting by amisulpride, and urinary urgency by vibegron.

Dose analysis

For each drug, the geometric mean of the approved doses (GMAD) was compared with the lowest and highest doses that were tested in clinical trials for each drug. The ratios of the highest dose versus GMAD and GMAD versus the lowest dose were calculated. These 2 ratios reflect the amount of effort expended during clinical trials to determine the optimal dose for approval—a larger ratio suggests that there was an extensive effort to incrementally find the right dose.

For example, for margetuximab, the ratio of the GMAD (15 mg) and the lowest dose tested (0.1 mg, which was the initial dose) was 150, indicating that numerous doses were tested before finding a dose with the optimal efficacy and safety profile. The highest dose tested is the same as the approved dose, suggesting that the approved dose be capped by adverse effects or safety concerns.

Of the 53 approved drugs during 2020, 40 were included in the dose analysis (see Methods). For these 40 drugs, the geometric mean of the ratios of the GMAD divided by the lowest dose tested is 11.2 with 75% percentile being 34.4 and 95% percentile being 150.5; the geometric mean of the ratios of the highest dose tested divided by the GMAD is about 2.3 with the 75% percentile being 3.3 and 95% percentile being 8.0 (Figure 1). Therefore, the approved doses were generally close to the highest investigated
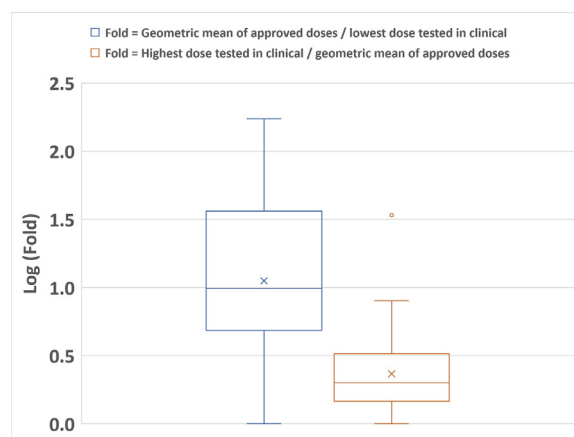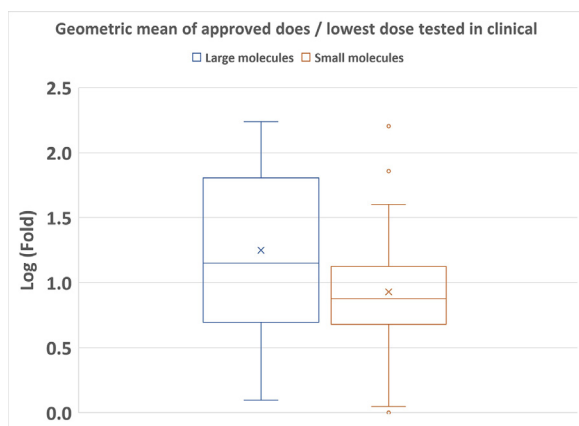

Figure 1. Comparison of doses approved (in geometric means) versus doses (the lowest and highest) studied in clinical trials.
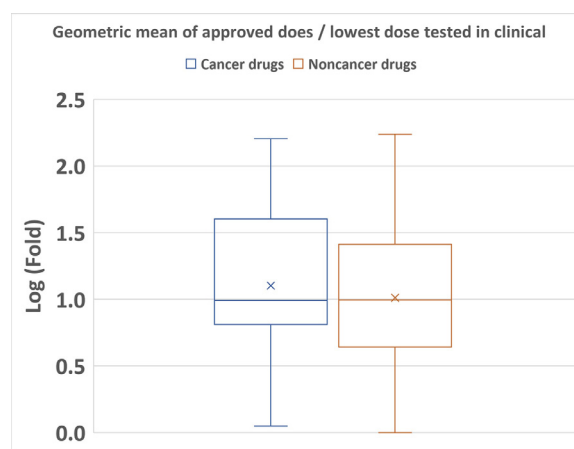
Figure 2. Comparison of doses of approved (in geometric means) versus doses (the lowest and highest) studied in clinical trials by drugs for cancer treatment versus other diseases.

doses tested with relatively small variations. A likely explanation for this observation is that the clinical trials were conducted to find the boundary where the efficacy is maximized, and patient safety/tolerability is maintained. After reaching the highest dose where adverse effects or safety risks manifest, stepping back a few folds could ensure certain safety measures while maintaining optimal efficacy. In contrast, the starting dose (which is usually the lowest dose) for different drugs could vary wildly due to numerous factors, such as mechanisms of action, safety profiles in nonclinical species, rationales of determining the initiating starting doses (by safety guidance or target engagement), potential negotiations between sponsors and FDA and prior experience with similar classes of drugs. This could explain the large ratios of GMAD to the lowest dose and substantial variation of the ratios.

The distances between the lowest dose tested and the approved doses were further analyzed by stratifications of therapeutic indications (cancer vs noncancer) and by molecular weights (small vs large). Cancer drugs normally have narrower therapeutic windows, and oftentimes the first-in-human trials directly start in patients. This might entail that the initial starting low dose would be close to the therapeutic dose for cancer drugs. However, this was not the case in this analysis. The cancer and noncancer drugs had similar geometric mean of the ratios between the GMAD and the initial low dose (noncancer drug = 11.2-fold vs cancer drug = 10-fold) and a similar ratio distribution (Figure 2).

Figure 3. Comparison of doses of approved (in geometric means) versus doses (the lowest and highest) studied in clinical trials by drugs of small molecules versus large molecules (peptides, proteins, and RNAs).

Dose analysis was also conducted for the comparison between small molecules (chemicals with molecular weight less than 1000 Daltons) and large molecules (such as RNA, peptide, and antibodies). The analysis showed that large molecules had a larger ratio between the initial starting dose and the GMAD compared with the smaller molecules. For large molecules, the ratio of the GMAD divided by the lowest dose tested was about 17.8 with 75% percentile being 35.3 and 95% percentile being 157.0; for small molecules, the corresponding ratio was about 8.5 with 75% percentile at 13.3 and 95% percentile at 65.6 (Figure 3).

Conclusions

SEs have been widely used for regulatory new drug approvals, with an increasing trend from 2019 to 2020 (from 32% to 51%). AA slightly increased from 20% (9 out of 44) in 2019 to 24% (12 out of 49) during 2020. The approved doses were usually much closer to the highest dose tested in clinical trials (about 2-fold lower) compared with the lower dose tested in clinical trials (about 11-fold higher). Large and variable distances between the starting low dose in human beings and the final approved doses indicate that finding the optimal dose in clinical trials remains a time-consuming and costly process. Cancer drugs are commonly assumed to have narrower therapeutic windows compared with other drugs, and cancer drugs are often tested directly in patients at doses that potentially offer therapeutic effects. However, dose analysis for cancer drugs approved during 2020 showed that the distances between the starting dose in human beings and the final approved doses of cancer drugs were still large and variable. Stratification of drugs approved in 2020 by molecular weights shows that large molecules appear to have larger and more variable distances compared with smaller molecules.

Acknowledgments

Conflicts of Interest

The author has indicated that he has no conflicts of interest regarding the content of this article.

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