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# Disagreements Within the US Food and Drug Administration Regarding Approval of Novel Therapeutic Agents, 2011-2015

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## Introduction

Thirty days after a novel therapeutic agent, a new molecular entity, or original biologic is approved, the US Food and Drug Administration (FDA) must publicly disclose its approval package, including scientific reviews completed by FDA disciplines (eg, pharmacology, statistical, and medical reviewers) and any available assessments by agency leadership.<sup>1</sup> Although reports of internal disagreement have surfaced,<sup>2</sup> it is unclear how often such disagreements occur. Disagreements document differing points of view or engaged discussion and may, thus, capture important scientific debates or signal challenging decisions within the agency. We sought to determine the frequency of disagreements within the FDA regarding approval of novel therapeutic agents.

Author affiliations and article information are listed at the end of this article.

## Methods

This cross-sectional study did not require institutional review board approval or patient informed consent because it was based on publicly available information and involved no patient records, in

Table 1. Novel Therapeutic Agents Approved 2011-2015

Year, agent		
2011 (n = 29)		
<ul style="list-style-type: none"> <li>• Afibercept<sup>a</sup></li> <li>• Asparaginase <i>erwinia chrysanthemi</i></li> <li>• Ruxolitinib phosphate</li> <li>• Clobazam</li> <li>• Deferiprone</li> <li>• Crizotinib</li> <li>• Icatibant acetate<sup>b,c</sup></li> <li>• Brentuximab vedotin</li> <li>• Vemurafenib</li> </ul>	<ul style="list-style-type: none"> <li>• Ticagrelor<sup>b</sup></li> <li>• Indacaterol maleate</li> <li>• Rivaroxaban</li> <li>• Belatacept</li> <li>• Ezogabine</li> <li>• Fidaxomicin</li> <li>• Telaprevir</li> <li>• Rilpivirine hydrochloride</li> <li>• Boceprevir</li> <li>• Linagliptin</li> </ul>	<ul style="list-style-type: none"> <li>• Abiraterone acetate</li> <li>• Gabapentin enacarbil</li> <li>• Vandetanib</li> <li>• Ipilimumab</li> <li>• Belimumab</li> <li>• Roflumilast</li> <li>• Azilsartan kamedoxomil<sup>a</sup></li> <li>• Vilazodone hydrochloride<sup>c</sup></li> <li>• Spinosad</li> </ul>
2012 (n = 36)		
<ul style="list-style-type: none"> <li>• Crofelemerb<sup>b</sup></li> <li>• Apixaban<sup>c</sup></li> <li>• Bedaquiline fumarate</li> <li>• Lomitapide mesylate</li> <li>• Teduglutide recombinant</li> <li>• Pasireotide diaspertate<sup>a</sup></li> <li>• Ponatinib hydrochloride</li> <li>• Raxibacumab</li> <li>• Cabozantinib s-malate</li> <li>• Tofacitinib citrate</li> <li>• Omacetaxine mepesuccinate<sup>c</sup></li> <li>• Perampanel<sup>c,d</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Ocriplasmin</li> <li>• Regorafenib</li> <li>• Teriflunomide<sup>a,c</sup></li> <li>• Bosutinib monohydrate<sup>a,c,d</sup></li> <li>• Enzalutamide</li> <li>• Linacotide<sup>a,c,d</sup></li> <li>• Tbo-filgrastim</li> <li>• Cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate</li> <li>• Ziv-aflibercept</li> <li>• Acridinium bromide</li> <li>• Carfilzomib</li> </ul>	<ul style="list-style-type: none"> <li>• Mirabegron</li> <li>• Lorcaserin hydrochloride</li> <li>• Pertuzumab<sup>b</sup></li> <li>• Taliglucerase alfa</li> <li>• Avanafil</li> <li>• Peginesatide acetate</li> <li>• Lucinactant</li> <li>• Tafuprost</li> <li>• Ivacaftor</li> <li>• Vismodegib<sup>c</sup></li> <li>• Axitinib</li> <li>• Ingenol mebutate</li> <li>• Glucarpidase</li> </ul>
2013 (n = 24)		
<ul style="list-style-type: none"> <li>• Umeclidinium bromide; vilanterol trifrenate</li> <li>• Sofosbuvir</li> <li>• Simeprevir sodium</li> <li>• Luliconazole</li> <li>• Ibrutinib</li> <li>• Eslicarbazepine acetate<sup>b</sup></li> <li>• Obinutuzumab</li> <li>• Macitentan</li> <li>• Riociguat<sup>a</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Bazedoxifene acetate; estrogens, conjugated</li> <li>• Vortioxetine hydrobromide</li> <li>• Dolutegravir sodium</li> <li>• Afatinib dimaleate</li> <li>• Idaracitinib mesylate</li> <li>• Trametinib dimethyl sulfoxide</li> <li>• Radium Ra-223 dichloride</li> </ul>	<ul style="list-style-type: none"> <li>• Fluticasone furoate; vilanterol trifrenate</li> <li>• Canagliflozin<sup>a,d</sup></li> <li>• Dimethyl fumarate<sup>b</sup></li> <li>• Ospemifene</li> <li>• Ado-trastuzumab emtansine</li> <li>• Pomalidomide</li> <li>• Mipomersen sodium</li> <li>• Alogliptin benzoate<sup>c</sup></li> </ul>

(continued)

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Table 1. Novel Therapeutic Agents Approved 2011-2015 (continued)

Year, agent		
2014 (n = 38)		
<ul style="list-style-type: none"> <li>Nivolumab</li> <li>Ceftolozane sulfate; tazobactam sodium</li> <li>Dasabuvir sodium; ombitasvir; paritaprevir; ritonavir</li> <li>Olaparib<sup>a</sup></li> <li>Peramivir</li> <li>Finafloracin</li> <li>Blinatumomab</li> <li>Nintedanib esylate</li> <li>Pirfenidone</li> <li>Ledipasvir; sofosbuvir</li> <li>Netupitant; palonosetron hydrochloride</li> </ul>	<ul style="list-style-type: none"> <li>Dulaglutide<sup>a</sup></li> <li>Naloxegol oxalate</li> <li>Pembrolizumab</li> <li>Eliglustat tartrate</li> <li>Peginterferon beta-1a</li> <li>Suvorexant</li> <li>Oritavancin diphosphate</li> <li>Empagliflozin</li> <li>Olodaterol hydrochloride</li> <li>Idelalisib</li> <li>Tavorole</li> <li>Belinostat</li> <li>Tedizolid phosphate</li> <li>Dalbavancin hydrochloride<sup>a,b</sup></li> </ul>	<ul style="list-style-type: none"> <li>Vedolizumab<sup>d</sup></li> <li>Vorapaxar sulfate<sup>c</sup></li> <li>Ceritinib</li> <li>Siltuximab</li> <li>Ramucirumab<sup>c</sup></li> <li>Albiglutide</li> <li>Apremilast<sup>c</sup></li> <li>Miltefosine<sup>c</sup></li> <li>Metreleptin</li> <li>Droxidopa<sup>a,b</sup></li> <li>Elosulfase alfa</li> <li>Tasimelteon</li> <li>Dapagliflozin</li> </ul>
2015 (n = 48)		
<ul style="list-style-type: none"> <li>Lesinurad<sup>b,c</sup></li> <li>Selexipag<sup>c</sup></li> <li>Sugammadex sodium</li> <li>Alectinib hydrochloride</li> <li>Sebelipase alfa</li> <li>Elotuzumab</li> <li>Necitumumab</li> <li>Ixazomib citrate</li> <li>Daratumumab</li> <li>Osimertinib mesylate</li> <li>Cobimetinib fumarate</li> <li>Cobicistat; elvitegravir; emtricitabine; tenofovir alafenamide fumarate</li> <li>Mepolizumab<sup>c,d</sup></li> <li>Asfotase alfa</li> <li>Trabectedin</li> <li>Patiomer sorbitex calcium</li> </ul>	<ul style="list-style-type: none"> <li>Idarucizumab<sup>c</sup></li> <li>Aripiprazole lauroxil</li> <li>Insulin aspart; insulin degludec</li> <li>Insulin degludec</li> <li>Tipiracil hydrochloride; trifluridine</li> <li>Cariprazine hydrochloride</li> <li>Uridine triacetate</li> <li>Rolapitant hydrochloride</li> <li>Evolocumab</li> <li>Flibanserin<sup>b</sup></li> <li>Alirocumab<sup>c,d</sup></li> <li>Daclatasvir dihydrochloride</li> <li>Sonidegib phosphate</li> <li>Brexipiprazole</li> <li>Sacubitril; valsartan<sup>a</sup></li> <li>Ivacaftor; lumacaftor</li> </ul>	<ul style="list-style-type: none"> <li>Cangrelor<sup>a,b</sup></li> <li>Eluxadoline</li> <li>Olodaterol hydrochloride; tiotropium bromide</li> <li>Deoxycholic acid</li> <li>Ivabradine hydrochloride<sup>a,d</sup></li> <li>Cholic acid<sup>d</sup></li> <li>Dinutuximab</li> <li>Filgrastim-sndz</li> <li>Isavuconazonium sulfate</li> <li>Avibactam sodium; ceftazidime</li> <li>Panobinostat lactate<sup>b</sup></li> <li>Lenvatinib mesylate</li> <li>Palbociclib</li> <li>Parathyroid hormone</li> <li>Secukinumab<sup>a,c</sup></li> <li>Edoxaban tosylate<sup>d</sup></li> </ul>

<sup>a</sup> Denotes approval packages containing 1 or more disagreements pertaining to some other form of disagreement not mentioned in the subsequent footnotes.

<sup>b</sup> Denotes approval packages containing 1 or more disagreements regarding approval.

<sup>c</sup> Denotes approval packages containing 1 or more disagreements pertaining to parameters of approval.

<sup>d</sup> Denotes approval packages containing 1 or more disagreements pertaining to population or indication.

Table 2. US Food and Drug Administration Disagreements Over New Drug Approvals, Populations Indicated, and the Parameters of Approval by Subject, Leadership, and Discipline (Total Instances)<sup>a</sup>

Variable	Approvals (dissents), No. <sup>b</sup>	Population or indication, No.	Approval parameters, No.	Other, No.	Total by discipline, No. (%) (n = 155)
Agency leadership					
Division director	9 (1)	8	10	6	33 (21.3)
Office director	5 (0)	2	8	4	19 (12.3)
Cross-disciplinary team leader	8 (4)	5	6	4	23 (14.8)
Agency disciplines					
Medical	6 (5)	6	8	7	27 (17.4)
Clinical pharmacology	2 (1)	2	3	5	12 (7.7)
Statistics	4 (3)	4	1	3	12 (7.7)
Safety	1 (1)	5	5	1	12 (7.7)
Pediatric	0 (0)	1	3	1	5 (3.2)
Chemistry	4 (1)	0	0	0	4 (2.6)
Nonclinical pharmacology	1 (0)	0	2	1	4 (2.6)
Office of Scientific Investigations and other reviewers of regulatory issues	1 (0)	0	1	0	2 (1.3)
Division of Risk Management and other reviewers of the Risk Evaluation and Mitigation Strategy	0 (0)	0	2	0	2 (1.3)
Microbiology	0 (0)	0	0	0	0 (0.0)
Total by subject (n = 155)	41	33	49	32	

<sup>a</sup> In 8 cases, the other party disagreeing with the disciplines listed here was not a member of 1 of the standard disciplines or leadership that are listed here. For example, in the case of the novel therapeutic agent sacubitril-valsartan (Entresto), a reviewer filed a nonstandard unsolicited review containing conclusions with which members of the standard disciplines disagreed.

<sup>b</sup> The number in parentheses reflects the number of disagreements in which the discipline (or leadership) was the party recommending against approval. These numbers do not include within-discipline dissents, in which 1 reviewer recommended against approval but the discipline as a whole ultimately supported approval.

accordance with 45 CFR §46. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

Between May and September 2019, we identified all approval packages for novel therapeutic agents approved by the FDA from January 2011 to December 2015 using the Drugs@FDA database. Disagreements were defined as instances where multiple reviewers and/or leadership (whether part of the same discipline or not) disagreed about approving a drug, the indicated patient population (eg, patient age), and/or the parameters of the drug's approval (eg, postmarketing requirements). We searched for disagreements in 2 ways. First, we reviewed the Summary Review, the Office Director Memo, the Cross-Disciplinary Review, and the Medical Review, which tend to describe the recommendations and disagreements. Second, we used key word searches to identify disagreements located elsewhere in the package. The data were extracted by 1 author (A.M.); uncertain cases were resolved through discussion with 2 or 3 other authors (M.H., J.D.W., and A.D.Z.). The frequency of disagreements within and between different disciplines and/or FDA leadership (eg, Division Director) was recorded and tabulated using Excel software version 16.31 (Microsoft Corp). Data analysis was performed from June to November 2019.

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## Results

From 2011 through 2015, the FDA published 174 approval packages for novel therapeutic agents (**Table 1**). The most common therapeutic areas were cancer (46 agents [26.4%]) and infectious diseases (27 agents [15.5%]); 72 agents (41.4%) were first in class, and the FDA was the first major regulatory agency to approve the drug for 118 agents (67.8%).

Forty-two (24.1%) approval packages contained at least 1 disagreement: 12 (6.9%) included a disagreement about whether to approve a drug, 10 (5.7%) disagreed over the patient population for which the drug was indicated, and 35 (20.1%) disagreed regarding the parameters of approval, including 20 about postmarketing requirements, safety warnings, or risk evaluation and management strategies, and 15 about other issues, such as drug label phrasing.

Of 155 instances of disagreement, 18 (11.6%) were among reviewers within the same discipline, whereas 137 (88.4%) occurred between different disciplines and/or leadership. The most frequently involved parties were medical reviewers (27 cases [17.4%]), members of agency leadership (eg, the Division Director; 33 cases [21.3%]), the Cross-Discipline Team Lead (23 cases [14.8%]), and the Office Director (19 cases [12.3%]) (**Table 2**). Among the 12 disagreements regarding approval, 11 were approved with a postmarketing requirement or risk evaluation and management strategy.

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## Discussion

Among all approval packages for novel therapeutics approved by the FDA from 2011 to 2015, disagreements were common over new drug approvals, populations indicated, and the specific parameters of the approval. Given the complexity of determining drug safety and efficacy and the challenge of extrapolating to broad populations from a limited number of small, narrowly defined clinical trials,<sup>3</sup> disagreements within the FDA are not surprising and likely represent differing points of view that may inform pharmacovigilance efforts, as well as public discourse.<sup>4</sup>

Our study was limited to disagreements recorded within approval packages. Where disagreements may be unrecorded, our analysis may underestimate their prevalence. We also did not assess whether disagreements were discussed by advisory committees or associated with particular outcomes (eg, safety warnings discovered after approval).

Nevertheless, our findings have important implications for the FDA's recent move to publish only integrated reviews in lieu of reviews by each discipline and agency leadership.<sup>5</sup> It raises questions about whether disagreements within the agency will continue to be published in compliance with the law.<sup>1,6</sup>

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**Author Contributions:** Ms MacGregor and Mr Herder had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* MacGregor, Zhang, Wallach, Herder.

*Acquisition, analysis, or interpretation of data:* All authors.

*Drafting of the manuscript:* MacGregor, Wallach, Herder.

*Critical revision of the manuscript for important intellectual content:* All authors.

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