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2 **Assessing the potential clinical impact of reciprocal drug approval legislation on access to**
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4 **novel therapeutics in the U.S.**
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ABSTRACT

OBJECTIVE: To quantify the potential impact of reciprocal approval legislation on access to novel therapeutics in the U.S.

DESIGN: Cohort study.

SETTING: New therapeutics approved by FDA, EMA, and/or Health Canada between 2000 and 2010.

MAIN OUTCOME MEASURES: Characteristics of new therapeutics approved by EMA and/or Health Canada before FDA, including mechanistic novelty, likely therapeutic impact, size of affected population, and FDA review outcome.

RESULTS: From 2001 to 2010, 282 drugs were approved in the U.S., Europe, or Canada, including 172 (61%) first approved in the U.S, 24 (9%) never approved in the U.S., and 86 (30%) approved in the U.S. after Europe and/or Canada. Of the 110 new drugs approved in Europe and/or Canada before the U.S., 37 (34%) had novel mechanisms of action compared with drugs already approved by FDA, but only 10 (9%) were for conditions lacking alternate available therapies in the U.S. at the time of ex-U.S. approval – of which the majority (9/10; 90%) were indicated for rare diseases. Twelve of the 37 agents with novel mechanisms of action approved first in Europe and/or Canada (32%) had their initial FDA submissions rejected for safety reasons – including two drugs that were ultimately withdrawn from the market in Europe due to safety concerns.

CONCLUSIONS: If enacted, reciprocal approval legislation would likely benefit only a small number of U.S. patients, and the benefit may be somewhat mitigated by an increased exposure to harms.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to quantify the potential impact of reciprocal approval legislation, based on prior approval histories by FDA and other regulatory bodies
- Although the time period covered by this study (through 2010) ensured that a significant fraction of subsequent approvals after the initial one were included, it did not allow us to examine more recent regulatory trends that could have impacted our analysis, such as the increased use of priority review and other expedited mechanisms by FDA
- Because we focused our analysis on the drugs first approved outside the U.S., we were not able to compare these agents with the drugs that were approved first in the U.S. with regard to clinical novelty and potential exposure to harms

Introduction

Several healthcare policy analysts^{1,2} have proposed that regulators grant accelerated or automatic “reciprocal approval” to novel therapies available in other countries. A recent proposal in the U.S., the “Reciprocity Ensures Streamlined Use of Lifesaving Treatments” (RESULT) Act (S. 2388), would require the Food and Drug Administration (FDA) to review within 30 days any application for a medical product already approved in Europe, Israel, Australia, Canada, or Japan, and grant them U.S. market approval if “there is a public health or unmet medical need for the covered product in the United States.”³ It would also allow the U.S. Congress to override any applications for reciprocal approval rejected by FDA.

Although a co-sponsor of the RESULT Act has argued that the legislation would “unleash life-saving drugs and devices in the United States,”⁴ the likely impact of reciprocal approval legislation remains ill-defined, particularly from the perspective of patients and physicians regarding clinical care and management decisions. Prior research has shown that approximately two-thirds of novel therapeutics are available in the U.S. before Europe and/or Canada,⁵ but the clinical importance of Americans’ delayed access to the remaining one-third is unknown.

To address this question, we analyzed a decade’s worth of drugs approved by U.S., European, and/or Canadian health authorities to quantify the potential clinical impact of proposed reciprocal approval legislation on American patients.

Methods

We included all new drugs approved for use in the U.S., Europe, and/or Canada from 2001 to 2010, identified in a prior study.⁵ We then used the public websites of the governing regulators for each market, the FDA, the European Medicines Agency (EMA), and Health Canada respectively, to ensure that all drugs conformed to the original paper's inclusion criteria and re-confirm FDA approval dates for all drugs unapproved by FDA in the original data set (using a cut-off date of May 1, 2016). In addition, we updated Health Canada approval dates using the Notice of Compliance (NOC) database, which provides the most accurate timing for Canadian market access.⁶

Drugs first approved outside the U.S. were categorized by novelty based on their pharmacologic mechanism of action, which we characterized using the biomedical literature and other public data sources. A drug was defined as "novel" for American patients if we could not identify any other already FDA-approved prescription medicine with the same pharmacologic mechanism, based on published reports, the FDA website, and UpToDate (Wolters Kluwer, www.uptodate.com). Fixed-dose combinations of approved drugs were deemed novel if no other combinations of agents in the same classes were already available in the U.S. Drugs with new indications but redundant targets were not classified as novel for the purposes of assessing U.S. market access, because Americans could obtain at least one equivalent drug off-label.

Notably, although a robust prior analysis in the literature⁷ characterized drugs' novelty based on their level of "innovation" (first-in-class, advance-in-class, or addition-to-class), we were

1
2 unable to leverage this approach. The definitions used in this earlier work depend in part on the
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4 FDA regulatory pathway used for approval, and thus could not be applied to evaluate drugs not
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6 yet approved in the U.S.
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12 For the subset of drugs first approved outside the U.S. that we defined as “novel,” we identified
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14 orphan drug designations via public regulatory agency websites. We also identified the
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16 outcome of their first FDA review and the main reason for rejection from FDA documents
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18 (<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) or, for agents that were never
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20 approved by FDA, company press releases and other public sources. We classified
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22 “approvable”, “not approvable”, “refuse to file”, and “complete response” outcomes
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24 collectively as “not approved” in our analysis. Agents were classified as not approved for safety
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26 reasons if the rationale provided by FDA included (a) absence / inadequacy of a REMS (risk
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28 evaluation and mitigation strategy) program for post-approval safety monitoring, (b)
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30 requirement for further analyses of safety data from completed trials, and/or (c) requirement
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32 for additional clinical studies primarily aimed at clarifying the harms profile.
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44 We used descriptive statistics to characterize the sample.
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50 Results

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53 We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met
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55 our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were
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57 never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or
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2 Canada. Among these latter 86 drugs, the median time lag between non-U.S. approval and U.S.
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4 approval was 415 days (interquartile range, 175-1,069).
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10 Of the 110 drugs first approved outside of the U.S., 37 (34%) were “novel”, in that no other
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12 FDA-approved prescription medicine had the same mechanism of action (Table). Two thirds of
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14 the novel drugs first approved outside of the U.S. (25 of 37; 68%) were subsequently approved
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16 by the FDA after a median of 414 days (interquartile range, 166-1,399). Of the 25 novel drugs
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18 that were subsequently approved by the FDA, eight (32%) were for conditions lacking alternate
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20 available therapies in the U.S at the time of non-U.S. approval, of which all but one
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22 (sugammadex (Bridion)) were for orphan indications. Of the 12 novel drugs not subsequently
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24 approved by the FDA, only two agents (agalsidase alfa (Replagal) and idebenone (Catena)), both
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26 for orphan indications, lacked available alternatives in the U.S. at the time of non-U.S. approval.
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28 All told, only 10 of the 110 drugs first approved outside the U.S. (9%) represented novel
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30 mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of
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32 non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of
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34 these 10 novel drugs without therapeutic alternatives had their initial applications rejected by
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36 the FDA; the other six were either approved on their first submission to the FDA (n=3),
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38 voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA
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40 approval (n=1).
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54 Of the 37 “novel” drugs first approved outside the U.S., FDA rejected 19 (51%) on their first
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56 submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications
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58 lacking approved therapies in the U.S., and three of those four were in orphan diseases.
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2 Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by
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4 the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) –
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6 were subsequently withdrawn from the market in Europe due to safety concerns.
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10 11 12 13 Discussion

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19 Advocates of reciprocal approval legislation have argued it would hasten Americans' access to
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21 clinically important therapies, but the magnitude of this potential benefit has not previously
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23 been addressed in detail. We show here that if such a law had been in effect in the U.S. from
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25 2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained
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27 earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S.
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29 patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an
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31 available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's
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33 requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical
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35 need"³), and only one of these (sugammadex, used for reversing neuromuscular blockade
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37 during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data
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39 suggest the potential positive clinical impact of proposed reciprocal approval legislation for
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41 American patients is likely modest, and most significant for those affected by select rare
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43 diseases.
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55 This work also illustrates the potential for increased harms from reciprocal approval, which is
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57 infrequently discussed and has not been previously characterized. Of the 37 novel drugs
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1 approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA
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4 at least in part for safety concerns, of which two were subsequently withdrawn from the
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7 market in Europe for safety issues. This finding could reflect a difference in relative thresholds
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10 for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies,
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12 as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety
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14 alerts and recalls for those first approved in Europe versus the U.S.⁸
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20 **Limitations of this study**

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22 We note three main considerations in interpreting our results. First, our stringent
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24 pharmacologic definition of “novelty” accounts for neither improved safety and/or efficacy over
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26 existing therapies, nor differences in delivery route, dosing, biochemical profile, or other
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28 attributes for drugs with “redundant” mechanisms – any of which could lead to a positive
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30 clinical impact, independent of novel pharmacology. Second, the use of FDA’s expedited review
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32 and approval programs has grown steadily in recent years,⁹ suggesting that our data may over-
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34 estimate the number of novel drugs first approved outside the U.S. Finally, our analysis of
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36 approvals outside the U.S. was limited to Europe and Canada, which do not reflect the full
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38 scope of countries whose regulators may satisfy currently proposed reciprocal approval
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40 legislation requirements, such as Japan and Israel.
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52 **Conclusions and policy implications**

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55 Our work is the first to quantify the potential clinical impact of reciprocal approval legislation.
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58 Although Americans may indeed gain speedier access under such laws to a handful of truly
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1 novel, clinically important therapies first available outside the U.S., our data suggest this benefit
2 would likely be realized by only a small number of patients. Our data also illustrate that in some
3 cases, delayed approval by FDA due to safety concerns appropriately kept drugs off of the
4 American market that were subsequently withdrawn in other geographies. Although other
5 proposed benefits claimed for legislation like the RESULT Act, such as lower prices due to
6 heightened competition, may be valuable and worth quantifying, our analysis suggests that
7 from a purely clinical standpoint, the positive impact on American patients at-large would likely
8 be minimal, and may be at least somewhat mitigated by the potential harm of exposing them
9 to additional risks.
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8 measures that are used for public reporting, from the Blue Cross Blue Shield Association
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10 (BCBSA) to better understand medical technology evidence generation, and from the Food and
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12 Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.
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19 required.
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23 **Patient involvement:** No patients were involved in the development of the research question
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25 or design of the study.
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29 **Data sharing:** Data files available from the authors upon reasonable request.
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33 **Transparency:** The authors affirm that the manuscript is an honest, accurate, and transparent
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37 and that any discrepancies from the study as planned have been explained.
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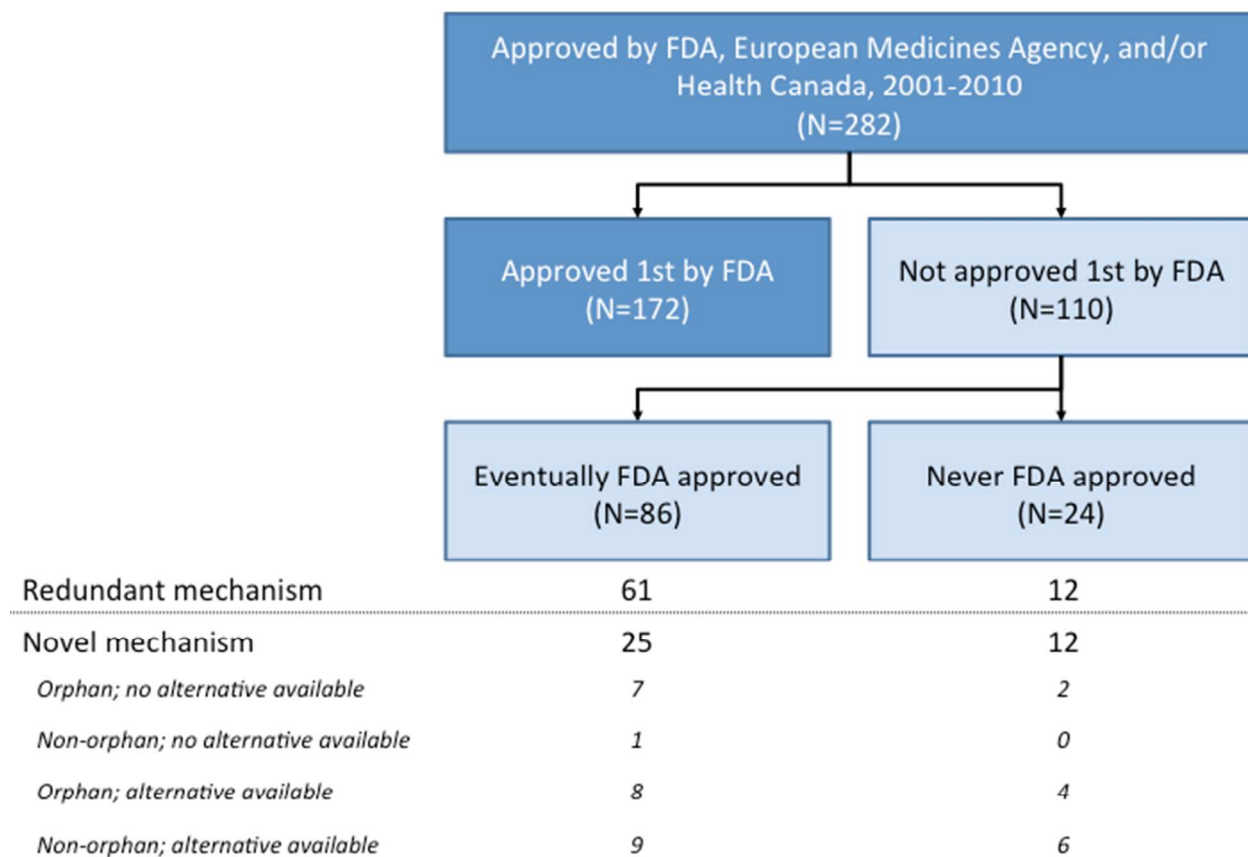
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Figure: Drugs Approved by the U.S. Food and Drug Administration, European Medicines Agency, and / or Health Canada between 2001-2010, U.S. First Approval Status, and Drug Mechanism.



Notes: FDA = U.S. Food and Drug Administration.

Table

Prescription drugs first approved outside of the U.S. with novel mechanisms, 2001-2010.

Prescription drug	First approval date (agency)	Lag until FDA approval (days)	Mechanism	Main indication(s)	Orphan?^^	Alternative therapeutic class(es) available in US?\$\$	Outcome of first FDA submission#
Agalsidase alfa (Replagal)	3/29/01 (EMA)	n/a	Agalsidase alfa replacement	Fabry disease	Yes	No	Withdrawn by sponsor
Agalsidase beta (Fabrazyme)	3/29/01 (EMA)	756	Agalsidase beta replacement	Fabry disease	Yes	No	Not approved – Efficacy
Agomelatine (Thymanax)	11/20/08 (EMA)	n/a	Mixed melatonin agonist / serotonin receptor antagonist	Depression	No	Yes¶	Never filed
Alemtuzumab (Campath)	3/28/01 (EMA)	40	Anti-CD52 antibody	Leukemia (CLL)	Yes	Yes¶¶	Not approved – Efficacy
Alglucosidase alfa (Myozyme)	1/26/06 (EMA)	92	Alglucosidase alfa replacement	Pompe disease	Yes	No	Approved
Artemether / lumefantrine (Coartem)	11/28/00 (EMA)	3,052	Artemesinin anti-parasitic (artemether); poorly defined (lumefantrine)	Malaria	Yes	Yes ^a	Approved
Carglumic acid (Carbaglu)	10/17/02 (EMA)	2,709	Carbamoyl phosphate synthetase 1 activator	N-acetylglutamate synthase deficiency	Yes	No	Withdrawn by sponsor
Catumaxomab (Removab)	2/19/09 (EMA)	n/a	Anti-EpCAM / CD3 antibody	Malignant ascites	No ^b	Yes ^c	Never filed
Denosumab (Prolia)	12/17/09 (EMA)	166	Anti-RANKL antibody	Osteoporosis	No	Yes¶	Not approved – Safety
Histamine dihydrochloride (Ceplene)	7/24/08 (EMA)	n/a	Therapeutic histamine receptor agonist	Leukemia (AML)	Yes	Yes¶	Not approved – Efficacy
Icatibant (Firazyr)	4/24/08 (EMA)	1,218	Selective bradykinin B2-receptor antagonist	Hereditary angioedema	Yes	No	Not approved – Efficacy
Idebenone (Catena)	7/23/08 (HC)§	n/a	Antioxidant / coenzyme Q10 analog [^]	Friedreich's ataxia	Yes	No	Never filed
Ivabradine (Corlentor)	7/27/05 (EMA)	3,548	Selective sinoatrial pacemaker modulating f-current inhibitor	Heart failure	No	Yes¶	Approved
Laronidase (Aldurazyme)	2/20/03 (EMA)	69	Laronidase replacement	Mucopolysaccharidosis type 1	Yes	No	Approved
Laropiprant / nicotinic acid (Pelzont)	4/24/08 (EMA)§	n/a	Combined DGAT2 / DP1 antagonist	Dyslipidema	No	Yes¶	Not approved – Safety
Maraviroc (Selzentry)	7/19/07 (EMA)	18	CCR5 antagonist	HIV	No	Yes¶	Approved
Methylnaltrexone bromide (Relistor)	3/28/08 (HC)	27	Peripherally-acting opioid antagonist	Opioid-induced constipation	Yes	Yes ^d	Approved
Mifamurtide (Mepact)	12/18/08 (EMA)	n/a	NOD2 agonist	Osteosarcoma	Yes	Yes¶¶	Not approved – Efficacy ^e
Miglustat (Zavesca)	7/25/02 (EMA)	371	Glucosylceramide synthase inhibitor	Gaucher disease	Yes	Yes ^f	Not approved –

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								Safety
1	Omega-3 fatty acid ethyl esters (Lovaza)	3/4/03 (EMA)	617	Poorly defined*^	Hypertriglyceridemia	No	Yes [¶]	Approved
2								
3	Pegvisomant (Somavert)	7/25/02 (EMA)	243	GH receptor antagonist	Acromegaly	Yes	Yes ^g	Not approved – Safety
4								
5	Pirfenidone (Esbriet)	12/16/10 (EMA)	1,399	Poorly defined*	Idiopathic pulmonary fibrosis	Yes	No	Not approved – Efficacy
6								
7	Porfimer sodium (PhotoBarr)	7/13/95 (HC)	167	Photosensitizing agent	Cancers / dysplasias (various)	Yes	No	Approved
8								
9	Rimonabant (Accomplia)	4/27/06 (EMA) [§]	n/a	CB-1 receptor antagonist	Obesity	No	Yes ^h	Not approved – Safety
10								
11	Rivaroxaban (Xarelto)	7/24/08 (EMA)	1,072	Direct factor Xa inhibitor	Anticoagulation	No	Yes [¶]	Not approved – Safety
12								
13	Roflumilast (Daxas)	4/22/10 (EMA)	312	PDE4 inhibitor	Chronic obstructive pulmonary disease	No	Yes [¶]	Not approved – Safety
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15	Stiripentol (Diacomit)	10/18/06 (EMA)	n/a	Poorly defined*	Severe myoclonic epilepsy in infants	Yes	Yes [¶]	Never filed
16								
17	Strontium ranelate (Protelos)	6/23/04 (EMA)	n/a	Poorly defined*	Osteoporosis	No	Yes [¶]	Never filed
18								
19	Sugammadex (Bridion)	5/30/08 (EMA)	2,755	Rocuronium chelator	Neuromuscular blockade reversal	No	No	Not approved – Safety
20								
21	Tegafur / gimeracil / oteracil (Teysono / S-1)	12/16/10 (EMA)	n/a	Thymidylate synthase inhibitor (tegafur); 5-FU degradation inhibitor (gimeracil); orotate phosphoribosyl-transferase inhibitor (oteracil)	Gastric cancer	Yes	Yes [¶]	Never filed
22								
23								
24	Tocilizumab (Actemra)	11/20/08 (EMA)	414	Anti-IL-6 antibody	Rheumatoid arthritis	No	Yes [¶]	Not approved – Safety
25								
26	Trabectedin (Yondelis)	7/19/07 (EMA)	3,018	Poorly defined*	Soft tissue sarcomas	Yes	Yes ^{¶¶}	Not approved – Efficacy
27								
28	Ulipristal acetate (Ella)	3/19/09 (EMA)	512	Mixed progesterone receptor antagonist / agonist	Emergency contraception	No	Yes ⁱ	Approved
29								
30	Ustekinumab (Stelara)	11/20/08 (EMA)	309	Anti-IL-12/IL-23 antibody	Psoriasis	No	Yes [¶]	Not approved – Safety
31								
32	Vernakalant hydrochloride (Brinavess)	6/24/10 (EMA)	n/a	IKur/IKAch atrial potassium current blocker	Atrial fibrillation	No	Yes [¶]	Not approved – Safety
33								
34	Vigabatrin (Sabril)	1/14/94 (HC)	5,698	GABA-T inhibitor	Infantile spasms	Yes	Yes ^j	Approved
35								
36	Ziconotide (Prialt)	11/18/04 (EMA)	40	N-type calcium channel inhibitor	Pain	Yes	Yes [¶]	Not approved – Safety
37								

38
 39 **Notes:** n/a=not approved in U.S. as of May 1, 2016; 5-FU=fluorouracil; AML=acute myeloid leukemia; CB-1=cannabinoid receptor type 1; CCR5= C-C chemokine receptor type 5;
 40 CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency;
 41 EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-
 42 protein-activated K(+) current; IKur=ultra-rapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type
 43 4; RANKL=receptor activator of nuclear factor kappa-B ligand
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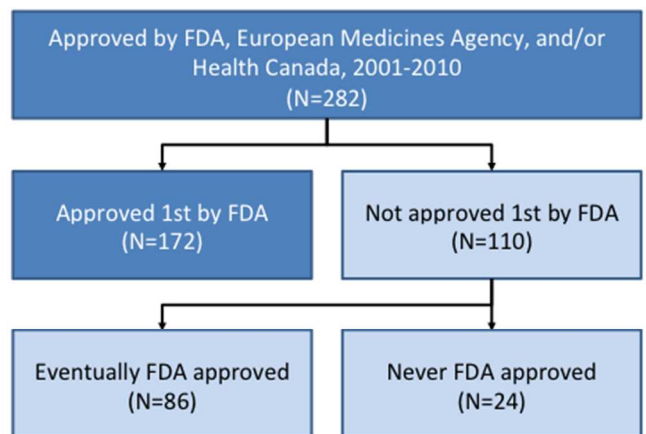
45 ^ First approved prescription medicine of this type (as opposed to over-the-counter forms)
 46 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
 47

1 ^ By EMA, FDA, and/or HC
 2 # See text for details of definitions
 3 * Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
 4 § Subsequently withdrawn in some / all regions
 5 §§ "Yes" indicates that at time of approval by EMA and/or HC, at least one therapeutic alternative was available in the U.S. for main indication
 6 ¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
 7 ¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

10 ^a Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
 11 ^b EMA granted orphan status for gastric cancer, but drug was never approved for this indication
 12 ^c Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
 13 ^d Multiple alternative laxative therapies already available in U.S.
 14 ^e Efficacy implied by sponsor as main rationale for rejection; see <http://www.prnewswire.com/news-releases/idm-pharma-receives-not-approvable-letter-for-mifamurtide-l-mtp-pe-for-the-treatment-of-osteosarcoma-58556887.html> (accessed September 9, 2016)
 15 ^f Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
 16 ^g Octreotide (Sandostatin LAR) already available in U.S.
 17 ^h Orlistat (Xenical) already available in U.S.
 18 ⁱ Plan B One-Step (levonorgestrel) already available in U.S.
 19 ^j ACTH (adrenocorticotrophic hormone) gel already available in U.S.



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Redundant mechanism	61	12
Novel mechanism	25	12
<i>Orphan; no alternative available</i>	7	2
<i>Non-orphan; no alternative available</i>	1	0
<i>Orphan; alternative available</i>	8	4
<i>Non-orphan; alternative available</i>	9	6

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Assessing the potential clinical impact of reciprocal drug approval legislation on access to novel therapeutics in the U.S.: a cohort study

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2 **Assessing the potential clinical impact of reciprocal drug approval legislation on access to**
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4 **novel therapeutics in the U.S.: a cohort study**
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ABSTRACT

OBJECTIVE: To quantify the potential effect of reciprocal approval legislation on access to clinically impactful therapeutics in the U.S.

DESIGN: Cohort study.

SETTING: New therapeutics approved by FDA, EMA, and/or Health Canada between 2000 and 2010.

MAIN OUTCOME MEASURES: Characteristics of new therapeutics approved by EMA and/or Health Canada before FDA, including mechanistic novelty, likely clinical impact, size of affected population, and FDA review outcome.

RESULTS: From 2001 to 2010, 282 drugs were approved in the U.S., Europe, or Canada, including 172 (61%) first approved in the U.S, 24 (9%) never approved in the U.S., and 86 (30%) approved in the U.S. after Europe and/or Canada. Of the 110 new drugs approved in Europe and/or Canada before the U.S., 37 (34%) had novel mechanisms of action compared with drugs already approved by FDA, but only 10 (9%) were for conditions lacking alternate available therapies in the U.S. at the time of ex-U.S. approval – of which the majority (9/10; 90%) were indicated for rare diseases. Twelve of the 37 agents with novel mechanisms of action approved first in Europe and/or Canada (32%) had their initial FDA submissions rejected for safety reasons – including two drugs that were ultimately withdrawn from the market in Europe due to safety concerns.

CONCLUSIONS: If enacted, reciprocal approval legislation would likely benefit only a small number of U.S. patients, and the benefit may be somewhat mitigated by an increased exposure to harms.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to quantify the potential clinical impact of reciprocal approval legislation, based on prior approval histories by FDA and other regulatory bodies
- Although the time period covered by this study (through 2010) ensured that a significant fraction of subsequent approvals after the initial one were included, it did not allow us to examine more recent regulatory trends that could have affected our analysis, such as the increased use of priority review and other expedited mechanisms by FDA
- Because we focused our analysis on the drugs first approved outside the U.S., we were not able to compare these agents with the drugs that were approved first in the U.S. with regard to clinical novelty and potential exposure to harms

Introduction

In the U.S., a new drug is approved when the Food and Drug Administration (FDA) reviews the manufacturer's application to the agency and determines that the drug meets appropriate safety and efficacy standards. A manufacturer can apply for marketing authorization in other countries before, while, or after submitting an application to the FDA, and the drug's approval status outside the U.S. has no formal impact on the FDA's decision-making process.

Several healthcare policy analysts^{1,2} have proposed that U.S. regulators grant accelerated or automatic "reciprocal approval" to novel therapies available in other countries. A recent proposal, the "Reciprocity Ensures Streamlined Use of Lifesaving Treatments" (RESULT) Act (S. 2388), would require the FDA to review within 30 days any application for a medical product already approved in Europe, Israel, Australia, Canada, or Japan, and grant it U.S. market approval if "there is a public health or unmet medical need for the covered product in the United States."³ Although the FDA could decline to grant reciprocal approval to an agent approved first outside the U.S., the U.S. Congress would gain the authority to override this decision.

Although a co-sponsor of the RESULT Act has argued that the legislation would "unleash life-saving drugs and devices in the United States,"⁴ the likely clinical impact of reciprocal approval legislation remains ill-defined, particularly from the perspective of patients and physicians regarding clinical care and management decisions. Prior research has shown that approximately

1 two-thirds of novel therapeutics are available in the U.S. before Europe and/or Canada,⁵ but the
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3 clinical importance of Americans' delayed access to the remaining one-third is unknown.
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10 To address this question, we analyzed a decade's worth of drugs approved by U.S., European,
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12 and/or Canadian health authorities to quantify the potential clinical impact of proposed
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14 reciprocal approval legislation on American patients.
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23 **Methods**

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25 We included all new drugs approved for use in the U.S., Europe, and/or Canada from 2001 to
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27 2010, identified in a prior study.⁵ We then used the public websites of the governing regulators
28
29 for each market, the FDA, the European Medicines Agency (EMA), and Health Canada
30
31 respectively, to ensure that all drugs conformed to the original paper's inclusion criteria and re-
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33 confirm FDA approval dates for all drugs unapproved by FDA in the original data set (using a
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35 cut-off date of May 1, 2016). In addition, we updated Health Canada approval dates using the
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37 Notice of Compliance (NOC) database, which provides the most accurate timing for Canadian
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39 market access.⁶
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49 Drugs first approved outside the U.S. were categorized by novelty based on their pharmacologic
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51 mechanism of action, which we characterized using the biomedical literature and other public
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53 data sources. A drug was defined as "novel" for American patients if we could not identify any
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55 other already FDA-approved prescription medicine with the same pharmacologic mechanism,
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1 based on published reports, the FDA website, Lexicomp (Wolters Kluwer), Martindale: The
2 Complete Drug Reference (Pharmaceutical Press), UpToDate (Wolters Kluwer), and other public
3 sources. Fixed-dose combinations of approved drugs were deemed novel if no other
4 combinations of agents in the same classes were already available in the U.S. Drugs with new
5 indications but redundant targets were not classified as novel for the purposes of assessing U.S.
6 market access, because Americans could obtain at least one equivalent drug off-label.
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20 Notably, although a robust prior analysis in the literature⁷ characterized drugs' novelty based
21 on their level of "innovation" (first-in-class, advance-in-class, or addition-to-class), we were
22 unable to leverage this approach. The definitions used in this earlier work depend in part on the
23 FDA regulatory pathway used for approval, and thus could not be applied to evaluate drugs not
24 yet approved in the U.S.
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37 For the subset of drugs first approved outside the U.S. that we defined as "novel," we identified
38 orphan drug designations via public regulatory agency websites. We also identified the
39 outcome of their first FDA review and the main reason for rejection from FDA documents
40 (<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) or, for agents that were never
41 approved by FDA, company press releases and other public sources. We classified
42 "approvable", "not approvable", "refuse to file", and "complete response" outcomes
43 collectively as "not approved" in our analysis. Agents were classified as not approved for safety
44 reasons if the rationale provided by FDA included (a) absence / inadequacy of a REMS (risk
45 evaluation and mitigation strategy) program for post-approval safety monitoring, (b)
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1 requirement for further analyses of safety data from completed trials, and/or (c) requirement
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4 for additional clinical studies primarily aimed at clarifying the harms profile.
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10 We used descriptive statistics to characterize the sample.
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14 15 16 17 **Results**

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19 We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met
20 our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were
21 never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or
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Of the 110 drugs first approved outside of the U.S., 37 (34%) were “novel”, in that no other
FDA-approved prescription medicine had the same mechanism of action (Table). Two thirds of
the novel drugs first approved outside of the U.S. (25 of 37; 68%) were subsequently approved
by the FDA after a median of 414 days (interquartile range, 166-1,399). Of the 25 novel drugs
that were subsequently approved by the FDA, eight (32%) were for conditions lacking alternate
available therapies in the U.S at the time of non-U.S. approval, of which all but one
(sugammadex (Bridion)) were for orphan indications. Of the 12 novel drugs not subsequently
approved by the FDA, only two agents (agalsidase alfa (Replagal) and idebenone (Catena)), both
for orphan indications, lacked available alternatives in the U.S. at the time of non-U.S. approval.
All told, only 10 of the 110 drugs first approved outside the U.S. (9%) represented novel

1 mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of
2 non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of
3 these 10 novel drugs without therapeutic alternatives had their initial applications rejected by
4 the FDA; the other six were either approved on their first submission to the FDA (n=3),
5 voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA
6 approval (n=1).
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20 Of the 37 “novel” drugs first approved outside the U.S., FDA rejected 19 (51%) on their first
21 submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications
22 lacking approved therapies in the U.S., and three of those four were in orphan diseases.
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28 Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by
29 the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) –
30 were subsequently withdrawn from the market in Europe due to safety concerns.
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39 Discussion

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45 Advocates of reciprocal approval legislation have argued it would hasten Americans’ access to
46 clinically important therapies, but the magnitude of this potential benefit has not previously
47 been addressed in detail. We show here that if such a law had been in effect in the U.S. from
48 2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained
49 earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S.
50 patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an
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1 available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's
2 requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical
3 need"³), and only one of these (sugammadex, used for reversing neuromuscular blockade
4 during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data
5 suggest the potential positive clinical impact of proposed reciprocal approval legislation for
6 American patients is likely modest, and most significant for those affected by select rare
7 diseases.
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23 This work also illustrates the potential for increased harms from reciprocal approval, which is
24 infrequently discussed and has not been previously characterized. Of the 37 novel drugs
25 approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA
26 at least in part for safety concerns, of which two were subsequently withdrawn from the
27 market in Europe for safety issues. This finding could reflect a difference in relative thresholds
28 for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies,
29 as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety
30 alerts and recalls for those first approved in Europe versus the U.S.⁸
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47 **Limitations of this study**

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49 We note several considerations in interpreting our results in the broader context of U.S.
50 regulatory policy. First, although we studied a substantial and relevant time range of drug
51 approvals in this work, the fact we studied approvals through 2010 means that we did not
52 capture the effect of recent regulatory trends, such as increased use of FDA's expedited review
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1 and approval programs.⁹ These accelerated pathways appear to be applied most often to novel
2 agents,¹⁰ and thus could be expected to even further decrease the potential future clinical
3 impact of reciprocal approval legislation on U.S. patients. Second, our analysis assumes that
4 Americans have access to therapeutic agents off-label. Although recent attention in off-label
5 prescribing has focused more on promotional activities than clinical practice,¹¹ any future
6 tightening of off-label access in the U.S. could increase the potential clinical impact of reciprocal
7 approval legislation beyond what is reported here. Third, it is important to note that patient
8 access depends on both regulatory and payer policies, and our work here only addresses the
9 first of these. More stringent or lenient market access thresholds in different geographies could
10 substantially affect U.S. patients' access to clinically impactful therapies relative to patients in
11 other regions, independent of reciprocal approval legislation or any other regulatory policies.
12 And finally, our work did not consider the potential impact of regulator review speed on
13 reciprocal approval legislation, as it may impact which regulator drug manufacturers decide to
14 first submit marketing applications. However, prior work⁵ has consistently demonstrated that
15 the FDA reviews marketing applications more quickly and that drug manufacturers more
16 frequently submit these applications first to the FDA, ahead of other regulatory agencies,
17 suggesting that taking either into account would not affect our findings.
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48 We also note two methodologic considerations in interpreting our results. First, our stringent
49 pharmacologic definition of "novelty" accounts for neither improved safety and/or efficacy over
50 existing therapies, nor differences in delivery route, dosing, biochemical profile, or other
51 attributes for drugs with "redundant" mechanisms – any of which could lead to a positive
52 clinical impact, independent of novel pharmacology. Second, our analysis of approvals outside
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1 the U.S. was limited to Europe and Canada, which do not reflect the full scope of countries
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3 whose regulators may satisfy currently proposed reciprocal approval legislation requirements,
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5 such as Japan and Israel.
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10 11 12 **Conclusions and policy implications**

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15 Our work is the first to quantify the potential clinical impact of reciprocal approval legislation.
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17 Although Americans may indeed gain speedier access under such laws to a handful of truly
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19 novel, clinically important therapies first available outside the U.S., our data suggest this benefit
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21 would likely be realized by only a small number of patients. Our data also illustrate that in some
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23 cases, delayed approval by FDA due to safety concerns appropriately kept drugs off of the
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25 American market that were subsequently withdrawn in other geographies. Although other
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27 proposed benefits claimed for legislation like the RESULT Act, such as lower prices due to
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29 heightened competition or the ability to mitigate drug shortages, may be valuable and worth
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31 quantifying, our analysis suggests that purely from the standpoint of access to medically
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33 important therapies, the positive clinical impact on American patients at-large would likely be
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35 minimal, and may be at least somewhat mitigated by the potential harm of exposing them to
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37 additional risks.
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54 interpretation of data, critical revision and final approval of the manuscript. ML and FSD: study
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56 concept and design, acquisition of data, analysis and interpretation of data, statistical analysis,
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2 initial drafting of manuscript, critical revision and final approval of the manuscript. FSD is the
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4 guarantor.
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26 measures that are used for public reporting, from the Blue Cross Blue Shield Association
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28 (BCBSA) to better understand medical technology evidence generation, and from the Food and
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30 Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.
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34 **Ethical approval:** Because this project did not involve human subjects, ethical approval was not
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36 required.
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39 **Patient involvement:** No patients were involved in the development of the research question
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41 or design of the study.
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45 **Data sharing:** Data files available from the authors upon reasonable request.
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49 **Transparency:** The authors affirm that the manuscript is an honest, accurate, and transparent
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51 account of the study being reported; that no important aspects of the study have been omitted;
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53 and that any discrepancies from the study as planned have been explained.
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53 [accessed September 9, 2016.](https://www.congress.gov/bill/114th-congress/senate-bill/2388)
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¹⁰ Downing NS, Krumholz HM, Ross JS, Shah ND. 2015. Regulatory watch: Characterizing the US FDA's approach to promoting transformative innovation. *Nat Rev Drug Disc* 14:740-741.

¹¹ Kim J, Kapczynski A. 2016. Promotion of drugs for off-label uses: The US Food and Drug Administration at a crossroads. *JAMA Int Med* doi: 10.1001/jamainternmed.2016.7151 [online ahead of print].

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2 **Figure title:** Drugs Approved by the U.S. Food and Drug Administration, European Medicines
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4 Agency, and / or Health Canada between 2001-2010, U.S. First Approval Status, and Drug
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6 Mechanism.
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12 **Notes:** FDA = U.S. Food and Drug Administration.
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Table

Prescription drugs first approved outside of the U.S. with novel mechanisms, 2001-2010.

Prescription drug	First approval date (agency)	Lag until FDA approval (days)	Mechanism	Main indication(s)	Orphan?^^	Alternative therapeutic class(es) available in US?\$\$	Outcome of first FDA submission#
Agalsidase alfa (Replagal)	3/29/01 (EMA)	n/a	Agalsidase alfa replacement	Fabry disease	Yes	No	Withdrawn by sponsor
Agalsidase beta (Fabrazyme)	3/29/01 (EMA)	756	Agalsidase beta replacement	Fabry disease	Yes	No	Not approved – Efficacy
Agomelatine (Thymanax)	11/20/08 (EMA)	n/a	Mixed melatonin agonist / serotonin receptor antagonist	Depression	No	Yes¶	Never filed
Alemtuzumab (Campath)	3/28/01 (EMA)	40	Anti-CD52 antibody	Leukemia (CLL)	Yes	Yes¶¶	Not approved – Efficacy
Alglucosidase alfa (Myozyme)	1/26/06 (EMA)	92	Alglucosidase alfa replacement	Pompe disease	Yes	No	Approved
Artemether / lumefantrine (Coartem)	11/28/00 (EMA)	3,052	Artemesinin anti-parasitic (artemether); poorly defined (lumefantrine)	Malaria	Yes	Yes ^a	Approved
Carglumic acid (Carbaglu)	10/17/02 (EMA)	2,709	Carbamoyl phosphate synthetase 1 activator	N-acetylglutamate synthase deficiency	Yes	No	Withdrawn by sponsor
Catumaxomab (Removab)	2/19/09 (EMA)	n/a	Anti-EpCAM / CD3 antibody	Malignant ascites	No ^b	Yes ^c	Never filed
Denosumab (Prolia)	12/17/09 (EMA)	166	Anti-RANKL antibody	Osteoporosis	No	Yes¶	Not approved – Safety
Histamine dihydrochloride (Ceplene)	7/24/08 (EMA)	n/a	Therapeutic histamine receptor agonist	Leukemia (AML)	Yes	Yes¶	Not approved – Efficacy
Icatibant (Firazyr)	4/24/08 (EMA)	1,218	Selective bradykinin B2-receptor antagonist	Hereditary angioedema	Yes	No	Not approved – Efficacy
Idebenone (Catena)	7/23/08 (HC)§	n/a	Antioxidant / coenzyme Q10 analog [^]	Friedreich's ataxia	Yes	No	Never filed
Ivabradine (Corlentor)	7/27/05 (EMA)	3,548	Selective sinoatrial pacemaker modulating f-current inhibitor	Heart failure	No	Yes¶	Approved
Laronidase (Aldurazyme)	2/20/03 (EMA)	69	Laronidase replacement	Mucopolysaccharidosis type 1	Yes	No	Approved
Laropiprant / nicotinic acid (Pelzont)	4/24/08 (EMA)§	n/a	Combined DGAT2 / DP1 antagonist	Dyslipidema	No	Yes¶	Not approved – Safety
Maraviroc (Selzentry)	7/19/07 (EMA)	18	CCR5 antagonist	HIV	No	Yes¶	Approved
Methylnaltrexone bromide (Relistor)	3/28/08 (HC)	27	Peripherally-acting opioid antagonist	Opioid-induced constipation	Yes	Yes ^d	Approved
Mifamurtide (Mepact)	12/18/08 (EMA)	n/a	NOD2 agonist	Osteosarcoma	Yes	Yes¶¶	Not approved – Efficacy ^e
Miglustat (Zavesca)	7/25/02 (EMA)	371	Glucosylceramide synthase inhibitor	Gaucher disease	Yes	Yes ^f	Not approved –

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								Safety
1	Omega-3 fatty acid ethyl esters (Lovaza)	3/4/03 (EMA)	617	Poorly defined* [^]	Hypertriglyceridemia	No	Yes [¶]	Approved
2								
3	Pegvisomant (Somavert)	7/25/02 (EMA)	243	GH receptor antagonist	Acromegaly	Yes	Yes ^g	Not approved – Safety
4								
5	Pirfenidone (Esbriet)	12/16/10 (EMA)	1,399	Poorly defined*	Idiopathic pulmonary fibrosis	Yes	No	Not approved – Efficacy
6								
7	Porfimer sodium (PhotoBarr)	7/13/95 (HC)	167	Photosensitizing agent	Cancers / dysplasias (various)	Yes	No	Approved
8								
9	Rimonabant (Accomplia)	4/27/06 (EMA) [§]	n/a	CB-1 receptor antagonist	Obesity	No	Yes ^h	Not approved – Safety
10								
11	Rivaroxaban (Xarelto)	7/24/08 (EMA)	1,072	Direct factor Xa inhibitor	Anticoagulation	No	Yes [¶]	Not approved – Safety
12								
13	Roflumilast (Daxas)	4/22/10 (EMA)	312	PDE4 inhibitor	Chronic obstructive pulmonary disease	No	Yes [¶]	Not approved – Safety
14								
15	Stiripentol (Diacomit)	10/18/06 (EMA)	n/a	Poorly defined*	Severe myoclonic epilepsy in infants	Yes	Yes [¶]	Never filed
16								
17	Strontium ranelate (Protelos)	6/23/04 (EMA)	n/a	Poorly defined*	Osteoporosis	No	Yes [¶]	Never filed
18								
19	Sugammadex (Bridion)	5/30/08 (EMA)	2,755	Rocuronium chelator	Neuromuscular blockade reversal	No	No	Not approved – Safety
20								
21	Tegafur / gimeracil / oteracil (Teysono / S-1)	12/16/10 (EMA)	n/a	Thymidylate synthase inhibitor (tegafur); 5-FU degradation inhibitor (gimeracil); orotate phosphoribosyl-transferase inhibitor (oteracil)	Gastric cancer	Yes	Yes [¶]	Never filed
22								
23								
24	Tocilizumab (Actemra)	11/20/08 (EMA)	414	Anti-IL-6 antibody	Rheumatoid arthritis	No	Yes [¶]	Not approved – Safety
25								
26	Trabectedin (Yondelis)	7/19/07 (EMA)	3,018	Poorly defined*	Soft tissue sarcomas	Yes	Yes ^{¶¶}	Not approved – Efficacy
27								
28	Ulipristal acetate (Ella)	3/19/09 (EMA)	512	Mixed progesterone receptor antagonist / agonist	Emergency contraception	No	Yes ⁱ	Approved
29								
30	Ustekinumab (Stelara)	11/20/08 (EMA)	309	Anti-IL-12/IL-23 antibody	Psoriasis	No	Yes [¶]	Not approved – Safety
31								
32	Vernakalant hydrochloride (Brinavess)	6/24/10 (EMA)	n/a	IKur/IKAch atrial potassium current blocker	Atrial fibrillation	No	Yes [¶]	Not approved – Safety
33								
34	Vigabatrin (Sabril)	1/14/94 (HC)	5,698	GABA-T inhibitor	Infantile spasms	Yes	Yes ^j	Approved
35								
36	Ziconotide (Prialt)	11/18/04 (EMA)	40	N-type calcium channel inhibitor	Pain	Yes	Yes [¶]	Not approved – Safety
37								

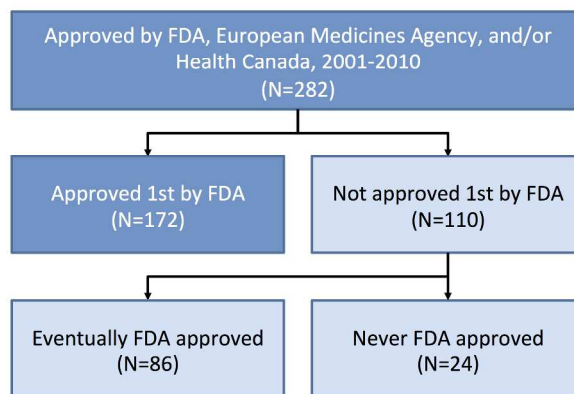
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 39 **Notes:** n/a=not approved in U.S. as of May 1, 2016; 5-FU=fluorouracil; AML=acute myeloid leukemia; CB-1=cannabinoid receptor type 1; CCR5= C-C chemokine receptor type 5;
 40 CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency;
 41 EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-
 42 protein-activated K(+) current; IKur=ultrarapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type
 43 4; RANKL=receptor activator of nuclear factor kappa-B ligand
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45 [^] First approved prescription medicine of this type (as opposed to over-the-counter forms)
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1 ^ By EMA, FDA, and/or HC
 2 # See text for details of definitions
 3 * Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
 4 § Subsequently withdrawn in some / all regions
 5 §§ "Yes" indicates that at time of approval by EMA and/or HC, at least one therapeutic alternative was available in the U.S. for main indication
 6 ¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
 7 ¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

10 ^a Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
 11 ^b EMA granted orphan status for gastric cancer, but drug was never approved for this indication
 12 ^c Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
 13 ^d Multiple alternative laxative therapies already available in U.S.
 14 ^e Efficacy implied by sponsor as main rationale for rejection; see <http://www.prnewswire.com/news-releases/idm-pharma-receives-not-approvable-letter-for-mifamurtide-l-mtp-pe-for-the-treatment-of-osteosarcoma-58556887.html> (accessed September 9, 2016)
 15 ^f Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
 16 ^g Octreotide (Sandostatin LAR) already available in U.S.
 17 ^h Orlistat (Xenical) already available in U.S.
 18 ⁱ Plan B One-Step (levonorgestrel) already available in U.S.
 19 ^j ACTH (adrenocorticotrophic hormone) gel already available in U.S.

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Redundant mechanism	61	12
Novel mechanism	25	12
<i>Orphan; no alternative available</i>	7	2
<i>Non-orphan; no alternative available</i>	1	0
<i>Orphan; alternative available</i>	8	4
<i>Non-orphan; alternative available</i>	9	6

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BMJ Open

Assessing the potential clinical impact of reciprocal drug approval legislation on access to novel therapeutics in the U.S.: a cohort study

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2 **Assessing the potential clinical impact of reciprocal drug approval legislation on access to**
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4 **novel therapeutics in the U.S.: a cohort study**
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ABSTRACT

OBJECTIVE: To quantify the potential effect of reciprocal approval legislation on access to clinically impactful therapeutics in the U.S.

DESIGN: Cohort study.

SETTING: New therapeutics approved by FDA, EMA, and/or Health Canada between 2000 and 2010.

MAIN OUTCOME MEASURES: Characteristics of new therapeutics approved by EMA and/or Health Canada before FDA, including mechanistic novelty, likely clinical impact, size of affected population, and FDA review outcome.

RESULTS: From 2001 to 2010, 282 drugs were approved in the U.S., Europe, or Canada, including 172 (61%) first approved in the U.S, 24 (9%) never approved in the U.S., and 86 (30%) approved in the U.S. after Europe and/or Canada. Of the 110 new drugs approved in Europe and/or Canada before the U.S., 37 (34%) had novel mechanisms of action compared with drugs already approved by FDA, but only 10 (9%) were for conditions lacking alternate available therapies in the U.S. at the time of ex-U.S. approval – of which the majority (9/10; 90%) were indicated for rare diseases. Twelve of the 37 agents with novel mechanisms of action approved first in Europe and/or Canada (32%) had their initial FDA submissions rejected for safety reasons – including two drugs that were ultimately withdrawn from the market in Europe due to safety concerns.

CONCLUSIONS: If enacted, reciprocal approval legislation would likely benefit only a small number of U.S. patients receiving treatment for rare diseases, and the benefit may be somewhat mitigated by an increased exposure to harms.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first study to quantify the potential clinical impact of reciprocal approval legislation, based on prior approval histories by FDA and other regulatory bodies
- Although we examined a 10 year period of approvals from 2001 through 2010, ensuring that a significant fraction of subsequent approvals after the initial one were included, we were not able to examine whether more recent regulatory trends would have affected our findings, such as the increased use of priority review and other expedited mechanisms by FDA
- Because we focused our analysis on the drugs first approved outside the U.S., we were not able to compare these agents with the drugs that were approved first in the U.S. with regard to clinical novelty and potential exposure to harms

Introduction

In the U.S., a new drug is approved when the Food and Drug Administration (FDA) reviews the manufacturer's application to the agency and determines that the drug meets appropriate safety and efficacy standards. A manufacturer can apply for marketing authorization in other countries before, while, or after submitting an application to the FDA, and the drug's approval status outside the U.S. has no formal impact on the FDA's decision-making process.

Several healthcare policy analysts^{1,2} have proposed that U.S. regulators grant accelerated or automatic "reciprocal approval" to novel therapies available in other countries. A recent proposal, the "Reciprocity Ensures Streamlined Use of Lifesaving Treatments" (RESULT) Act (S. 2388), would require the FDA to review within 30 days any application for a medical product already approved in Europe, Israel, Australia, Canada, or Japan, and grant it U.S. market approval if "there is a public health or unmet medical need for the covered product in the United States."³ Although the FDA could decline to grant reciprocal approval to an agent approved first outside the U.S., the U.S. Congress would gain the authority to override this decision.

Although a co-sponsor of the RESULT Act has argued that the legislation would "unleash life-saving drugs and devices in the United States,"⁴ the likely clinical impact of reciprocal approval legislation remains ill-defined, particularly from the perspective of patients and physicians regarding clinical care and management decisions. Prior research has shown that approximately

1 two-thirds of novel therapeutics are available in the U.S. before Europe and/or Canada,⁵ but the
2 clinical importance of Americans' delayed access to the remaining one-third is unknown.
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10 To address this question, we analyzed a decade's worth of drugs approved by U.S., European,
11 and/or Canadian health authorities to quantify the potential clinical impact of proposed
12 reciprocal approval legislation on American patients.
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23 **Methods**

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25 We included all new drugs approved for use in the U.S., Europe, and/or Canada from 2001 to
26 2010, identified in a prior study.⁵ To be clear, this sample was limited to approvals of new
27 molecular entities or novel biologic drugs and excluded reformulations of previously approved
28 active pharmaceutical ingredients, combination therapies of active pharmaceutical ingredients
29 that had been approved previously, and generic drug approvals. We then used the public
30 websites of the governing regulators for each market, the FDA, the European Medicines Agency
31 (EMA), and Health Canada respectively, to ensure that all drugs conformed to the original
32 paper's inclusion criteria and re-confirm FDA approval dates for all drugs unapproved by FDA in
33 the original data set (using a cut-off date of May 1, 2016). In addition, we updated Health
34 Canada approval dates using the Notice of Compliance (NOC) database, which provides the
35 most accurate timing for Canadian market access.⁶
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Drugs first approved outside the U.S. were categorized by novelty based on their pharmacologic mechanism of action, which we characterized using the biomedical literature and other public data sources. A drug was defined as “novel” for American patients if we could not identify any other already FDA-approved prescription medicine with the same pharmacologic mechanism, based on published reports, the FDA website, Lexicomp (Wolters Kluwer), Martindale: The Complete Drug Reference (Pharmaceutical Press), UpToDate (Wolters Kluwer), and other public sources. Fixed-dose combinations were deemed novel only if no other combinations of agents in the same classes were already available in the U.S. Drugs with new indications but redundant targets were not classified as novel for the purposes of assessing U.S. market access, because Americans could obtain at least one equivalent drug off-label.

Notably, although a robust prior analysis in the literature⁷ characterized drugs’ novelty based on their level of “innovation” (first-in-class, advance-in-class, or addition-to-class), we were unable to leverage this approach. The definitions used in this earlier work depend in part on the FDA regulatory pathway used for approval, and thus could not be applied to evaluate drugs not yet approved in the U.S.

For the subset of drugs first approved outside the U.S. that we defined as “novel,” we identified orphan drug designations via public regulatory agency websites. We also identified the outcome of their first FDA review and the main reason for rejection from FDA documents (<https://www.accessdata.fda.gov/scripts/cder/drugsatfda/>) or, for agents that were never approved by FDA, company press releases and other public sources. We classified “approvable”, “not approvable”, “refuse to file”, and “complete response” outcomes

1 collectively as “not approved” in our analysis. Agents were classified as not approved for safety
2 reasons if the rationale provided by FDA included (a) absence / inadequacy of a REMS (risk
3 evaluation and mitigation strategy) program for post-approval safety monitoring, (b)
4 requirement for further analyses of safety data from completed trials, and/or (c) requirement
5 for additional clinical studies primarily aimed at clarifying the harms profile.
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18 We used descriptive statistics to characterize the sample.
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24 Results

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27 We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met
28 our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were
29 never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or
30 Canada. Among these latter 86 drugs, the median time lag between non-U.S. approval and U.S.
31 approval was 415 days (interquartile range, 175-1,069).
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43 Of the 110 drugs first approved outside of the U.S., 37 (34%) were “novel”, in that no other
44 FDA-approved prescription medicine had the same mechanism of action (Table). Two thirds of
45 the novel drugs first approved outside of the U.S. (25 of 37; 68%) were subsequently approved
46 by the FDA after a median of 414 days (interquartile range, 166-1,399). Of the 25 novel drugs
47 that were subsequently approved by the FDA, eight (32%) were for conditions lacking alternate
48 available therapies in the U.S at the time of non-U.S. approval, of which all but one
49 (sugammadex (Bridion)) were for orphan indications. Of the 12 novel drugs not subsequently
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1 approved by the FDA, only two agents (agalsidase alfa (Replagal) and idebenone (Catena)), both
2 for orphan indications, lacked available alternatives in the U.S. at the time of non-U.S. approval.
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4 All told, only 10 of the 110 drugs first approved outside the U.S. (9%) represented novel
5 mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of
6 non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of
7 these 10 novel drugs without therapeutic alternatives had their initial applications rejected by
8 the FDA; the other six were either approved on their first submission to the FDA (n=3),
9 voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA
10 approval (n=1).
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28 Of the 37 “novel” drugs first approved outside the U.S., FDA rejected 19 (51%) on their first
29 submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications
30 lacking approved therapies in the U.S., and three of those four were in orphan diseases.
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33 Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by
34 the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) –
35 were subsequently withdrawn from the market in Europe due to safety concerns.
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46 Discussion

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53 Advocates of reciprocal approval legislation have argued it would hasten Americans’ access to
54 clinically important therapies, but the magnitude of this potential benefit has not previously
55 been addressed in detail. We show here that if such a law had been in effect in the U.S. from
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2 2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained
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4 earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S.
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6 patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an
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8 available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's
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10 requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical
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12 need"³), and only one of these (sugammadex, used for reversing neuromuscular blockade
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14 during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data
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16 suggest the potential positive clinical impact of proposed reciprocal approval legislation for
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18 American patients is likely modest, and most significant for those affected by select rare
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20 diseases.
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30 This work also illustrates the potential for increased harms from reciprocal approval, which is
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32 infrequently discussed and has not been previously characterized. Of the 37 novel drugs
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34 approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA
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36 at least in part for safety concerns, of which two were subsequently withdrawn from the
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38 market in Europe for safety issues. This finding could reflect a difference in relative thresholds
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40 for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies,
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42 as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety
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44 alerts and recalls for those first approved in Europe versus the U.S.⁸
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54 **Limitations of this study**

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1 We note several considerations in interpreting our results in the broader context of U.S.
2 regulatory policy. First, although we studied a substantial and relevant time range of drug
3 approvals in this work, the fact we studied approvals through 2010 means that we did not
4 capture the effect of recent regulatory trends, such as increased use of FDA's expedited review
5 and approval programs.⁹ These accelerated pathways appear to be applied most often to novel
6 agents,¹⁰ and thus could be expected to even further decrease the potential future clinical
7 impact of reciprocal approval legislation on U.S. patients. Second, our analysis assumes that
8 Americans have access to therapeutic agents off-label. Although recent attention to off-label
9 prescribing has focused more on promotional activities than clinical practice,¹¹ any future
10 restrictions to drugs for off-label use in the U.S. could increase the potential clinical impact of
11 reciprocal approval legislation beyond what is reported here. However, it is worth noting that
12 current legal challenges and regulatory decisions suggest that off-label promotion and use is
13 becoming less, not more, restricted.^{12,13} Third, it is important to note that patient access
14 depends on both regulatory and payer policies, and our work here only addresses the first of
15 these. More stringent or lenient market access thresholds in different geographies could
16 substantially affect U.S. patients' access to clinically impactful therapies relative to patients in
17 other regions, independent of reciprocal approval legislation or any other regulatory policies.
18 And finally, our work did not consider the potential impact of regulator review speed on
19 reciprocal approval legislation, as it may impact which regulator drug manufacturers decide to
20 first submit marketing applications. However, prior work⁵ has consistently demonstrated that
21 the FDA reviews marketing applications more quickly and that drug manufacturers more
22 frequently submit these applications first to the FDA, ahead of other regulatory agencies,
23 suggesting that taking either into account would not affect our findings.
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5 We also note two methodologic considerations in interpreting our results. First, our stringent
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7 pharmacologic definition of “novelty” accounts for neither improved safety and/or efficacy over
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9 existing therapies, nor differences in delivery route, dosing, biochemical profile, or other
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11 attributes for drugs with “redundant” mechanisms – any of which could lead to a positive
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13 clinical impact, independent of novel pharmacology. Second, our analysis of approvals outside
14
15 the U.S. was limited to Europe and Canada, which do not reflect the full scope of countries
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17 whose regulators may satisfy currently proposed reciprocal approval legislation requirements,
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19 such as Japan and Israel.
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28 **Conclusions and policy implications**

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31 Our work is the first to quantify the potential clinical impact of reciprocal approval legislation.
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33 Although Americans may indeed gain speedier access under such laws to a handful of truly
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35 novel, clinically important therapies first available outside the U.S., our data suggest this benefit
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37 would likely be realized by only a small number of patients receiving treatment for rare
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39 diseases. Our data also illustrate that in some cases, delayed approval by FDA due to safety
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41 concerns appropriately kept drugs off of the American market that were subsequently
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43 withdrawn in other geographies. Although other proposed benefits claimed for legislation like
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45 the RESULT Act, such as lower prices due to heightened competition or the ability to mitigate
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47 drug shortages, may be valuable and worth quantifying, our analysis suggests that purely from
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49 the standpoint of access to medically important therapies, the positive clinical impact on
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51 American patients at-large would likely be minimal, and may be at least somewhat mitigated by
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53 the potential harm of exposing them to additional risks.
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Ethical approval: Because this project did not involve human subjects, ethical approval was not required.

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2 **Patient involvement:** No patients were involved in the development of the research question
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4 or design of the study.
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7 **Data sharing:** Data files available from the authors upon reasonable request.
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10 **Transparency:** The authors affirm that the manuscript is an honest, accurate, and transparent
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12 account of the study being reported; that no important aspects of the study have been omitted;
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14 and that any discrepancies from the study as planned have been explained.
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¹² Kim J, Kapczynski A. Promotion of drugs for off-label uses: The US Food and Drug Administration at a crossroads. *JAMA Int Med* 2016;doi: 10.1001/jamainternmed.2016.7151 [online ahead of print].

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2 **Figure title:** Drugs Approved by the U.S. Food and Drug Administration, European Medicines
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4 Agency, and / or Health Canada between 2001-2010, U.S. First Approval Status, and Drug
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7 Mechanism.
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12 **Notes:** FDA = U.S. Food and Drug Administration.
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Table

Prescription drugs first approved outside of the U.S. with novel mechanisms, 2001-2010.

Prescription drug	First approval date (agency)	Lag until FDA approval (days)	Mechanism	Main indication(s)	Orphan?^^	Alternative therapeutic class(es) available in US?\$\$	Outcome of first FDA submission#
Agalsidase alfa (Replagal)	3/29/01 (EMA)	n/a	Agalsidase alfa replacement	Fabry disease	Yes	No	Withdrawn by sponsor
Agalsidase beta (Fabrazyme)	3/29/01 (EMA)	756	Agalsidase beta replacement	Fabry disease	Yes	No	Not approved – Efficacy
Agomelatine (Thymanax)	11/20/08 (EMA)	n/a	Mixed melatonin agonist / serotonin receptor antagonist	Depression	No	Yes¶	Never filed
Alemtuzumab (Campath)	3/28/01 (EMA)	40	Anti-CD52 antibody	Leukemia (CLL)	Yes	Yes¶¶	Not approved – Efficacy
Alglucosidase alfa (Myozyme)	1/26/06 (EMA)	92	Alglucosidase alfa replacement	Pompe disease	Yes	No	Approved
Artemether / lumefantrine (Coartem)	11/28/00 (EMA)	3,052	Artemesinin anti-parasitic (artemether); poorly defined (lumefantrine)	Malaria	Yes	Yes ^a	Approved
Carglumic acid (Carbaglu)	10/17/02 (EMA)	2,709	Carbamoyl phosphate synthetase 1 activator	N-acetylglutamate synthase deficiency	Yes	No	Withdrawn by sponsor
Catumaxomab (Removab)	2/19/09 (EMA)	n/a	Anti-EpCAM / CD3 antibody	Malignant ascites	No ^b	Yes ^c	Never filed
Denosumab (Prolia)	12/17/09 (EMA)	166	Anti-RANKL antibody	Osteoporosis	No	Yes¶	Not approved – Safety
Histamine dihydrochloride (Ceplene)	7/24/08 (EMA)	n/a	Therapeutic histamine receptor agonist	Leukemia (AML)	Yes	Yes¶	Not approved – Efficacy
Icatibant (Firazyr)	4/24/08 (EMA)	1,218	Selective bradykinin B2-receptor antagonist	Hereditary angioedema	Yes	No	Not approved – Efficacy
Idebenone (Catena)	7/23/08 (HC)§	n/a	Antioxidant / coenzyme Q10 analog [^]	Friedreich's ataxia	Yes	No	Never filed
Ivabradine (Corlentor)	7/27/05 (EMA)	3,548	Selective sinoatrial pacemaker modulating f-current inhibitor	Heart failure	No	Yes¶	Approved
Laronidase (Aldurazyme)	2/20/03 (EMA)	69	Laronidase replacement	Mucopolysaccharidosis type 1	Yes	No	Approved
Laropiprant / nicotinic acid (Pelzont)	4/24/08 (EMA)§	n/a	Combined DGAT2 / DP1 antagonist	Dyslipidema	No	Yes¶	Not approved – Safety
Maraviroc (Selzentry)	7/19/07 (EMA)	18	CCR5 antagonist	HIV	No	Yes¶	Approved
Methylnaltrexone bromide (Relistor)	3/28/08 (HC)	27	Peripherally-acting opioid antagonist	Opioid-induced constipation	Yes	Yes ^d	Approved
Mifamurtide (Mepact)	12/18/08 (EMA)	n/a	NOD2 agonist	Osteosarcoma	Yes	Yes¶¶	Not approved – Efficacy ^e
Miglustat (Zavesca)	7/25/02 (EMA)	371	Glucosylceramide synthase inhibitor	Gaucher disease	Yes	Yes ^f	Not approved –

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								Safety
1	Omega-3 fatty acid ethyl esters (Lovaza)	3/4/03 (EMA)	617	Poorly defined*^	Hypertriglyceridemia	No	Yes [¶]	Approved
2								
3	Pegvisomant (Somavert)	7/25/02 (EMA)	243	GH receptor antagonist	Acromegaly	Yes	Yes ^g	Not approved – Safety
4								
5	Pirfenidone (Esbriet)	12/16/10 (EMA)	1,399	Poorly defined*	Idiopathic pulmonary fibrosis	Yes	No	Not approved – Efficacy
6								
7	Porfimer sodium (PhotoBarr)	7/13/95 (HC)	167	Photosensitizing agent	Cancers / dysplasias (various)	Yes	No	Approved
8								
9	Rimonabant (Accomplia)	4/27/06 (EMA) [§]	n/a	CB-1 receptor antagonist	Obesity	No	Yes ^h	Not approved – Safety
10								
11	Rivaroxaban (Xarelto)	7/24/08 (EMA)	1,072	Direct factor Xa inhibitor	Anticoagulation	No	Yes [¶]	Not approved – Safety
12								
13	Roflumilast (Daxas)	4/22/10 (EMA)	312	PDE4 inhibitor	Chronic obstructive pulmonary disease	No	Yes [¶]	Not approved – Safety
14								
15	Stiripentol (Diacomit)	10/18/06 (EMA)	n/a	Poorly defined*	Severe myoclonic epilepsy in infants	Yes	Yes [¶]	Never filed
16								
17	Strontium ranelate (Protelos)	6/23/04 (EMA)	n/a	Poorly defined*	Osteoporosis	No	Yes [¶]	Never filed
18								
19	Sugammadex (Bridion)	5/30/08 (EMA)	2,755	Rocuronium chelator	Neuromuscular blockade reversal	No	No	Not approved – Safety
20								
21	Tegafur / gimeracil / oteracil (Teysono / S-1)	12/16/10 (EMA)	n/a	Thymidylate synthase inhibitor (tegafur); 5-FU degradation inhibitor (gimeracil); orotate phosphoribosyl-transferase inhibitor (oteracil)	Gastric cancer	Yes	Yes [¶]	Never filed
22								
23								
24	Tocilizumab (Actemra)	11/20/08 (EMA)	414	Anti-IL-6 antibody	Rheumatoid arthritis	No	Yes [¶]	Not approved – Safety
25								
26	Trabectedin (Yondelis)	7/19/07 (EMA)	3,018	Poorly defined*	Soft tissue sarcomas	Yes	Yes ^{¶¶}	Not approved – Efficacy
27								
28	Ulipristal acetate (Ella)	3/19/09 (EMA)	512	Mixed progesterone receptor antagonist / agonist	Emergency contraception	No	Yes ⁱ	Approved
29								
30	Ustekinumab (Stelara)	11/20/08 (EMA)	309	Anti-IL-12/IL-23 antibody	Psoriasis	No	Yes [¶]	Not approved – Safety
31								
32	Vernakalant hydrochloride (Brinavess)	6/24/10 (EMA)	n/a	IKur/IKAch atrial potassium current blocker	Atrial fibrillation	No	Yes [¶]	Not approved – Safety
33								
34	Vigabatrin (Sabril)	1/14/94 (HC)	5,698	GABA-T inhibitor	Infantile spasms	Yes	Yes ^j	Approved
35								
36	Ziconotide (Prialt)	11/18/04 (EMA)	40	N-type calcium channel inhibitor	Pain	Yes	Yes [¶]	Not approved – Safety
37								

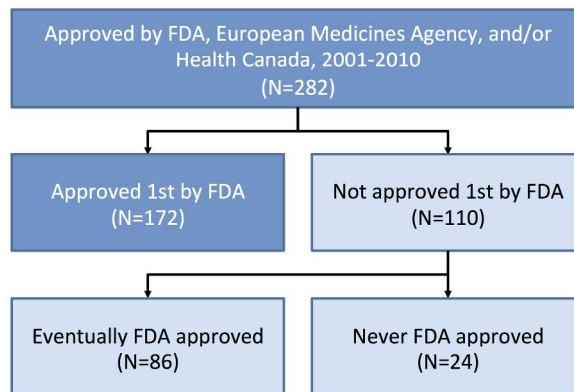
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 39 **Notes:** n/a=not approved in U.S. as of May 1, 2016; 5-FU=fluorouracil; AML=acute myeloid leukemia; CB-1=cannabinoid receptor type 1; CCR5= C-C chemokine receptor type 5;
 40 CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency;
 41 EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-
 42 protein-activated K(+) current; IKur=ultrarapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type
 43 4; RANKL=receptor activator of nuclear factor kappa-B ligand
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45 ^ First approved prescription medicine of this type (as opposed to over-the-counter forms)
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1 ^ By EMA, FDA, and/or HC
 2 # See text for details of definitions
 3 * Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
 4 § Subsequently withdrawn in some / all regions
 5 §§ "Yes" indicates that at time of approval by EMA and/or HC, at least one therapeutic alternative was available in the U.S. for main indication
 6 ¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
 7 ¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

10 ^a Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
 11 ^b EMA granted orphan status for gastric cancer, but drug was never approved for this indication
 12 ^c Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
 13 ^d Multiple alternative laxative therapies already available in U.S.
 14 ^e Efficacy implied by sponsor as main rationale for rejection; see <http://www.prnewswire.com/news-releases/idm-pharma-receives-not-approvable-letter-for-mifamurtide-l-mtp-pe-for-the-treatment-of-osteosarcoma-58556887.html> (accessed September 9, 2016)
 15 ^f Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
 16 ^g Octreotide (Sandostatin LAR) already available in U.S.
 17 ^h Orlistat (Xenical) already available in U.S.
 18 ⁱ Plan B One-Step (levonorgestrel) already available in U.S.
 19 ^j ACTH (adrenocorticotrophic hormone) gel already available in U.S.





Redundant mechanism	61	12
Novel mechanism	25	12
<i>Orphan; no alternative available</i>	7	2
<i>Non-orphan; no alternative available</i>	1	0
<i>Orphan; alternative available</i>	8	4
<i>Non-orphan; alternative available</i>	9	6

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