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Assessing the potential clinical impact of reciprocal drug approval legislation on access to 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Canada (32%) had their initial FDA submissions rejected for safety reasons – including two drugs that were ultimately withdrawn from the market in Europe due to safety concerns.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 literature[7] 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 collectively as "not approved" in our analysis. Agents were classified as not approved for safety reasons if the rationale provided by FDA included (a) absence / inadequacy of a REMS (risk evaluation and mitigation strategy) program for post-approval safety monitoring, (b) requirement for further analyses of safety data from completed trials, and/or (c) requirement for additional clinical studies primarily aimed at clarifying the harms profile.

We used descriptive statistics to characterize the sample.

Results

We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or

Canada. Among these latter 86 drugs, the median time lag between non-U.S. approval and U.S. approval was 415 days (interquartile range, 175-1,069).

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 mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of these 10 novel drugs without therapeutic alternatives had their initial applications rejected by the FDA; the other six were either approved on their first submission to the FDA (n=3), voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA approval (n=1).

Of the 37 "novel" drugs first approved outside the U.S., FDA rejected 19 (51%) on their first submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications lacking approved therapies in the U.S., and three of those four were in orphan diseases.

Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) – were subsequently withdrawn from the market in Europe due to safety concerns.

Discussion

Advocates of reciprocal approval legislation have argued it would hasten Americans' access to clinically important therapies, but the magnitude of this potential benefit has not previously been addressed in detail. We show here that if such a law had been in effect in the U.S. from 2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S. patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical need"[3]), and only one of these (sugammadex, used for reversing neuromuscular blockade during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data suggest the potential positive clinical impact of proposed reciprocal approval legislation for American patients is likely modest, and most significant for those affected by select rare diseases.

This work also illustrates the potential for increased harms from reciprocal approval, which is infrequently discussed and has not been previously characterized. Of the 37 novel drugs

approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA at least in part for safety concerns, of which two were subsequently withdrawn from the market in Europe for safety issues. This finding could reflect a difference in relative thresholds for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies, as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety alerts and recalls for those first approved in Europe versus the U.S.[8]

Limitations of this study

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

Conclusions and policy implications

Our work is the first to quantify the potential clinical impact of reciprocal approval legislation. Although Americans may indeed gain speedier access under such laws to a handful of truly

novel, clinically important therapies first available outside the U.S., our data suggest this benefit would likely be realized by only a small number of patients. Our data also illustrate that in some cases, delayed approval by FDA due to safety concerns appropriately kept drugs off of the American market that were subsequently withdrawn in other geographies. Although other proposed benefits claimed for legislation like the RESULT Act, such as lower prices due to heightened competition, may be valuable and worth quantifying, our analysis suggests that from a purely clinical standpoint, the positive impact on American patients at-large would likely be minimal, and may be at least somewhat mitigated by the potential harm of exposing them to additional risks.

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Author Contributions: NSD and JSR: study concept and design, acquisition of data, analysis and interpretation of data, critical revision and final approval of the manuscript. ML and FSD: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, initial drafting of manuscript, critical revision and final approval of the manuscript. FSD is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf, and declare that (within the past three years): ML and FSD are employees of Pharmagellan LLC, a biotechnology advisory firm that provides paid consulting services to companies and investors in the drug, medical device, diagnostics, and

healthcare services industries. JSR receives support through Yale University from Medtronic, Inc. and Johnson and Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, from the Blue Cross Blue Shield Association (BCBSA) to better understand medical technology evidence generation, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.

Ethical approval: Because this project did not involve human subjects, ethical approval was not required.

Patient involvement: No patients were involved in the development of the research question or design of the study.

Data sharing: Data files available from the authors upon reasonable request.

Transparency: The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

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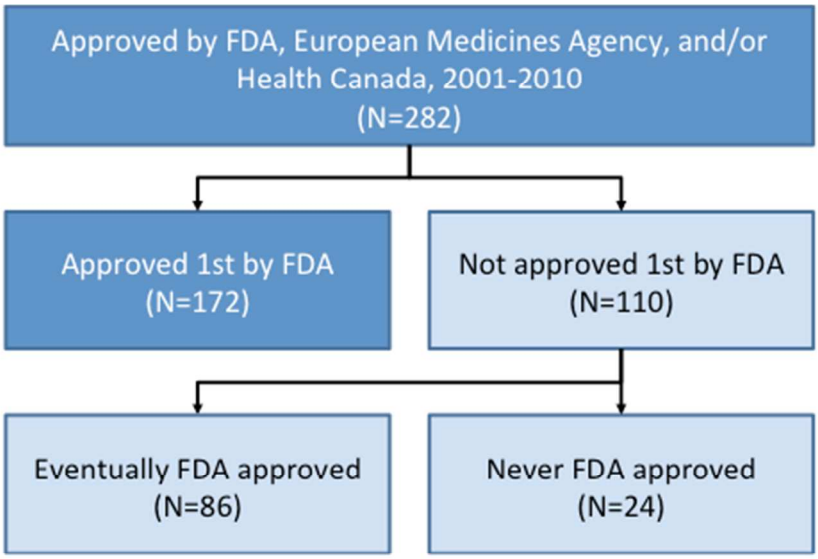
Figure: Drugs Approved by the U.S. Food and Drug Administration, European Medicines Agency, and / or Health Canada between 2001-2010, U.S. First Approval Status, and Drug Mechanism.



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

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	Artimesenin 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 –

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

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; CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency; EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-protein-activated K(+) current; IKur=ultrarapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type 4; RANKL=receptor activator of nuclear factor kappa-B ligand

^ First approved prescription medicine of this type (as opposed to over-the-counter forms)

^^ By EMA, FDA, and/or HC
[#] See text for details of definitions
* Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
§ Subsequently withdrawn in some / all regions
§§ "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
¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

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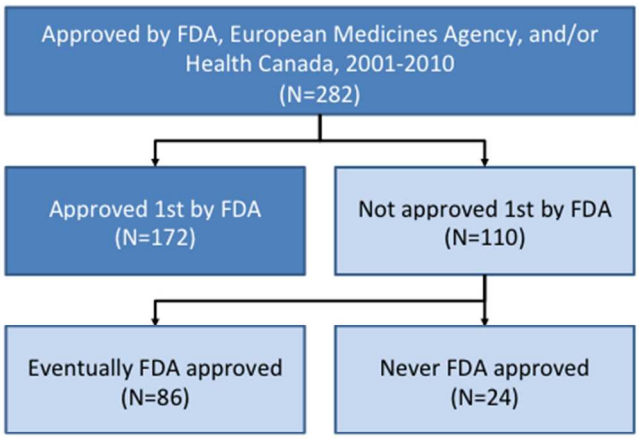
[a] Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
[b] EMA granted orphan status for gastric cancer, but drug was never approved for this indication
[c] Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
[d] Multiple alternative laxative therapies already available in U.S.
[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)
[f] Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
[g] Octreotide (Sandostatin LAR) already available in U.S.
[h] Orlistat (Xenical) already available in U.S.
[i] Plan B One-Step (levonorgestrel) already available in U.S.
[j] ACTH (adrenocorticotropic hormone) gel already available in U.S.



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Secondary Subject Heading:	Health policy
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Word count: 1,949

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.

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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.

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- 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

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, Lexicomp (Wolters Kluwer), Martindale: The Complete Drug Reference (Pharmaceutical Press), UpToDate (Wolters Kluwer), and other public sources. 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 literature[7] 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 collectively as "not approved" in our analysis. Agents were classified as not approved for safety reasons if the rationale provided by FDA included (a) absence / inadequacy of a REMS (risk evaluation and mitigation strategy) program for post-approval safety monitoring, (b)

requirement for further analyses of safety data from completed trials, and/or (c) requirement for additional clinical studies primarily aimed at clarifying the harms profile.

We used descriptive statistics to characterize the sample.

Results

We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or Canada. Among these latter 86 drugs, the median time lag between non-U.S. approval and U.S. approval was 415 days (interquartile range, 175-1,069).

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

mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of these 10 novel drugs without therapeutic alternatives had their initial applications rejected by the FDA; the other six were either approved on their first submission to the FDA (n=3), voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA approval (n=1).

Of the 37 "novel" drugs first approved outside the U.S., FDA rejected 19 (51%) on their first submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications lacking approved therapies in the U.S., and three of those four were in orphan diseases. Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) – were subsequently withdrawn from the market in Europe due to safety concerns.

Discussion

Advocates of reciprocal approval legislation have argued it would hasten Americans' access to clinically important therapies, but the magnitude of this potential benefit has not previously been addressed in detail. We show here that if such a law had been in effect in the U.S. from 2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S. patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an

available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical need"[3]), and only one of these (sugammadex, used for reversing neuromuscular blockade during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data suggest the potential positive clinical impact of proposed reciprocal approval legislation for American patients is likely modest, and most significant for those affected by select rare diseases.

This work also illustrates the potential for increased harms from reciprocal approval, which is infrequently discussed and has not been previously characterized. Of the 37 novel drugs approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA at least in part for safety concerns, of which two were subsequently withdrawn from the market in Europe for safety issues. This finding could reflect a difference in relative thresholds for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies, as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety alerts and recalls for those first approved in Europe versus the U.S.[8]

Limitations of this study

We note several considerations in interpreting our results in the broader context of U.S. regulatory policy. First, although we studied a substantial and relevant time range of drug approvals in this work, the fact we studied approvals through 2010 means that we did not capture the effect of recent regulatory trends, such as increased use of FDA's expedited review

and approval programs.[9] These accelerated pathways appear to be applied most often to novel agents,[10] and thus could be expected to even further decrease the potential future clinical impact of reciprocal approval legislation on U.S. patients. Second, our analysis assumes that Americans have access to therapeutic agents off-label. Although recent attention in off-label prescribing has focused more on promotional activities than clinical practice,[11] any future tightening of off-label access in the U.S. could increase the potential clinical impact of reciprocal approval legislation beyond what is reported here. Third, it is important to note that patient access depends on both regulatory and payer policies, and our work here only addresses the first of these. More stringent or lenient market access thresholds in different geographies could substantially affect U.S. patients' access to clinically impactful therapies relative to patients in other regions, independent of reciprocal approval legislation or any other regulatory policies. And finally, our work did not consider the potential impact of regulator review speed on reciprocal approval legislation, as it may impact which regulator drug manufacturers decide to first submit marketing applications. However, prior work[5] has consistently demonstrated that the FDA reviews marketing applications more quickly and that drug manufacturers more frequently submit these applications first to the FDA, ahead of other regulatory agencies, suggesting that taking either into account would not affect our findings.

We also note two methodologic considerations in interpreting our results. First, our stringent pharmacologic definition of "novelty" accounts for neither improved safety and/or efficacy over existing therapies, nor differences in delivery route, dosing, biochemical profile, or other attributes for drugs with "redundant" mechanisms – any of which could lead to a positive clinical impact, independent of novel pharmacology. Second, our analysis of approvals outside

the U.S. was limited to Europe and Canada, which do not reflect the full scope of countries whose regulators may satisfy currently proposed reciprocal approval legislation requirements, such as Japan and Israel.

Conclusions and policy implications

Our work is the first to quantify the potential clinical impact of reciprocal approval legislation. Although Americans may indeed gain speedier access under such laws to a handful of truly novel, clinically important therapies first available outside the U.S., our data suggest this benefit would likely be realized by only a small number of patients. Our data also illustrate that in some cases, delayed approval by FDA due to safety concerns appropriately kept drugs off of the American market that were subsequently withdrawn in other geographies. Although other proposed benefits claimed for legislation like the RESULT Act, such as lower prices due to heightened competition or the ability to mitigate drug shortages, may be valuable and worth quantifying, our analysis suggests that purely from the standpoint of access to medically important therapies, the positive clinical impact on American patients at-large would likely be minimal, and may be at least somewhat mitigated by the potential harm of exposing them to additional risks.

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initial drafting of manuscript, critical revision and final approval of the manuscript. FSD is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf, and declare that (within the past three years): ML and FSD are employees of Pharmagellan LLC, a biotechnology advisory firm that provides paid consulting services to companies and investors in the drug, medical device, diagnostics, and healthcare services industries. JSR receives support through Yale University from Medtronic, Inc. and Johnson and Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, from the Blue Cross Blue Shield Association (BCBSA) to better understand medical technology evidence generation, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.

Ethical approval: Because this project did not involve human subjects, ethical approval was not required.

Patient involvement: No patients were involved in the development of the research question or design of the study.

Data sharing: Data files available from the authors upon reasonable request.

Transparency: The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure title: 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	Artimesenin 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 –

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

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; CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency; EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-protein-activated K(+) current; IKur=ultrarapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type 4; RANKL=receptor activator of nuclear factor kappa-B ligand

^ First approved prescription medicine of this type (as opposed to over-the-counter forms)

^^ By EMA, FDA, and/or HC
[#] See text for details of definitions
* Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
§ Subsequently withdrawn in some / all regions
§§ "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
¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

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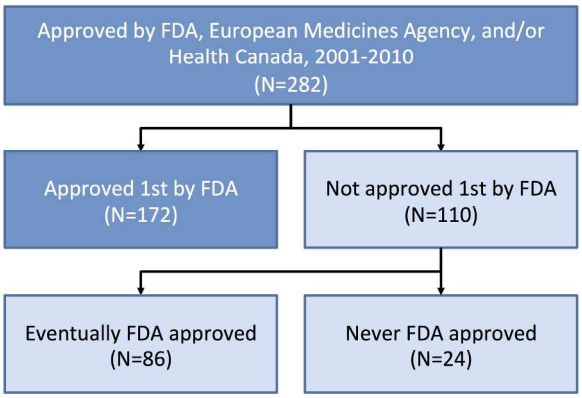
[a] Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
[b] EMA granted orphan status for gastric cancer, but drug was never approved for this indication
[c] Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
[d] Multiple alternative laxative therapies already available in U.S.
[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)
[f] Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
[g] Octreotide (Sandostatin LAR) already available in U.S.
[h] Orlistat (Xenical) already available in U.S.
[i] Plan B One-Step (levonorgestrel) already available in U.S.
[j] ACTH (adrenocorticotropic hormone) gel already available in U.S.



Redundant mechanism	61	12
Novel mechanism	25	12
Orphan; no alternative available	*7*	*2*
Non-orphan; no alternative available	*1*	*0*
Orphan; alternative available	*8*	*4*
Non-orphan; alternative available	*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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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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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 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
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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] To be clear, this sample was limited to approvals of new molecular entities or novel biologic drugs and excluded reformulations of previously approved active pharmaceutical ingredients, combination therapies of active pharmaceutical ingredients that had been approved previously, and generic drug approvals. 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, 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 literature[7] 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

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

We used descriptive statistics to characterize the sample.

Results

We identified 282 drugs approved in the U.S., Europe, or Canada from 2001 to 2010 that met our inclusion criteria (Figure), 172 (61%) of which were first approved in the U.S., 24 (9%) were never approved in the U.S., and 86 (30%) were approved in the U.S. after Europe and/or Canada. Among these latter 86 drugs, the median time lag between non-U.S. approval and U.S. approval was 415 days (interquartile range, 175-1,069).

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 mechanisms in diseases for which no alternative therapy was available in the U.S. at the time of non-U.S. approval, and nine of these were for orphan indications. Importantly, only four of these 10 novel drugs without therapeutic alternatives had their initial applications rejected by the FDA; the other six were either approved on their first submission to the FDA (n=3), voluntarily withdrawn by the sponsor before FDA evaluation (n=2), or never submitted for FDA approval (n=1).

Of the 37 "novel" drugs first approved outside the U.S., FDA rejected 19 (51%) on their first submission, 12 for safety reasons. Only four of these 19 rejected drugs were for indications lacking approved therapies in the U.S., and three of those four were in orphan diseases. Notably, of the 12 drugs initially rejected for safety reasons, nine were eventually approved by the FDA, whereas two – laropiprant / nicotinic acid (Pelzont) and rimonabant (Accomplia) – were subsequently withdrawn from the market in Europe due to safety concerns.

Discussion

Advocates of reciprocal approval legislation have argued it would hasten Americans' access to clinically important therapies, but the magnitude of this potential benefit has not previously been addressed in detail. We show here that if such a law had been in effect in the U.S. from

2001 to 2010, covering drugs approved in Europe or Canada, Americans might have gained earlier access to over 100 drugs, although only 37 would have been clinically novel for U.S. patients. Furthermore, only 10 of those 37 novel agents were for indications lacking an available therapeutic alternative in the U.S. (thus definitively satisfying the proposed law's requirement that drugs granted reciprocal approval satisfy a "public health or unmet medical need"[3]), and only one of these (sugammadex, used for reversing neuromuscular blockade during anesthesia) was in a non-orphan indication. Extrapolating to the present day, these data suggest the potential positive clinical impact of proposed reciprocal approval legislation for American patients is likely modest, and most significant for those affected by select rare diseases.

This work also illustrates the potential for increased harms from reciprocal approval, which is infrequently discussed and has not been previously characterized. Of the 37 novel drugs approved in Europe and/or Canada before the U.S., 12 (32%) were initially rejected by the FDA at least in part for safety concerns, of which two were subsequently withdrawn from the market in Europe for safety issues. This finding could reflect a difference in relative thresholds for the demonstration of harms versus benefits between U.S. and non-U.S. approval agencies, as a recent analysis of medical devices demonstrated an almost two-fold higher rate of safety alerts and recalls for those first approved in Europe versus the U.S.[8]

Limitations of this study

We note several considerations in interpreting our results in the broader context of U.S. regulatory policy. First, although we studied a substantial and relevant time range of drug approvals in this work, the fact we studied approvals through 2010 means that we did not capture the effect of recent regulatory trends, such as increased use of FDA's expedited review and approval programs.[9] These accelerated pathways appear to be applied most often to novel agents,[10] and thus could be expected to even further decrease the potential future clinical impact of reciprocal approval legislation on U.S. patients. Second, our analysis assumes that Americans have access to therapeutic agents off-label. Although recent attention to off-label prescribing has focused more on promotional activities than clinical practice,[11] any future restrictions to drugs for off-label use in the U.S. could increase the potential clinical impact of reciprocal approval legislation beyond what is reported here. However, it is worth noting that current legal challenges and regulatory decisions suggest that off-label promotion and use is becoming less, not more, restricted.[12,13] Third, it is important to note that patient access depends on both regulatory and payer policies, and our work here only addresses the first of these. More stringent or lenient market access thresholds in different geographies could substantially affect U.S. patients' access to clinically impactful therapies relative to patients in other regions, independent of reciprocal approval legislation or any other regulatory policies. And finally, our work did not consider the potential impact of regulator review speed on reciprocal approval legislation, as it may impact which regulator drug manufacturers decide to first submit marketing applications. However, prior work[5] has consistently demonstrated that the FDA reviews marketing applications more quickly and that drug manufacturers more frequently submit these applications first to the FDA, ahead of other regulatory agencies, suggesting that taking either into account would not affect our findings.

We also note two methodologic considerations in interpreting our results. First, our stringent pharmacologic definition of "novelty" accounts for neither improved safety and/or efficacy over existing therapies, nor differences in delivery route, dosing, biochemical profile, or other attributes for drugs with "redundant" mechanisms – any of which could lead to a positive clinical impact, independent of novel pharmacology. Second, our analysis of approvals outside the U.S. was limited to Europe and Canada, which do not reflect the full scope of countries whose regulators may satisfy currently proposed reciprocal approval legislation requirements, such as Japan and Israel.

Conclusions and policy implications

Our work is the first to quantify the potential clinical impact of reciprocal approval legislation. Although Americans may indeed gain speedier access under such laws to a handful of truly novel, clinically important therapies first available outside the U.S., our data suggest this benefit would likely be realized by only a small number of patients receiving treatment for rare diseases. Our data also illustrate that in some cases, delayed approval by FDA due to safety concerns appropriately kept drugs off of the American market that were subsequently withdrawn in other geographies. Although other proposed benefits claimed for legislation like the RESULT Act, such as lower prices due to heightened competition or the ability to mitigate drug shortages, may be valuable and worth quantifying, our analysis suggests that purely from the standpoint of access to medically important therapies, the positive clinical impact on American patients at-large would likely be minimal, and may be at least somewhat mitigated by the potential harm of exposing them to additional risks.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf, and declare that (within the past three years): ML and FSD are employees of Pharmagellan LLC, a biotechnology advisory firm that provides paid consulting services to companies and investors in the drug, medical device, diagnostics, and healthcare services industries. JSR receives support through Yale University from Medtronic, Inc. and Johnson and Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, from the Blue Cross Blue Shield Association (BCBSA) to better understand medical technology evidence generation, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.

Ethical approval: Because this project did not involve human subjects, ethical approval was not required.

Patient involvement: No patients were involved in the development of the research question or design of the study.

Data sharing: Data files available from the authors upon reasonable request.

Transparency: The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figure title: 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	Artimesenin 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 –

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

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; CD=cluster of differentiation; CLL=chronic lymphocytic leukemia; DGAT2=diacylglycerol O-acyltransferase 2; DP1= prostaglandin D2 receptor 1; EMA=European Medicines Agency; EpCAM=epithelial cell adhesion molecule; GABA-T=gamma-aminobutyric acid transaminase; GH=growth hormone; HC=Health Canada; HIV=human immunodeficiency virus; IKAch=G-protein-activated K(+) current; IKur=ultrarapid outward current; IL=interleukin; NOD2=nucleotide-binding oligomerization domain-containing protein 2; PDE4=phosphodiesterase type 4; RANKL=receptor activator of nuclear factor kappa-B ligand

^ First approved prescription medicine of this type (as opposed to over-the-counter forms)

^^ By EMA, FDA, and/or HC
[#] See text for details of definitions
* Ill-defined mechanism of action; impossible to identify pharmacologic analog previously approved in U.S.
§ Subsequently withdrawn in some / all regions
§§ "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
¶ Multiple alternative therapies available in U.S. for this indication at time of non-U.S. approval
¶¶ Multiple chemotherapy agents already available in U.S. with efficacy in this indication at time of non-U.S. approval

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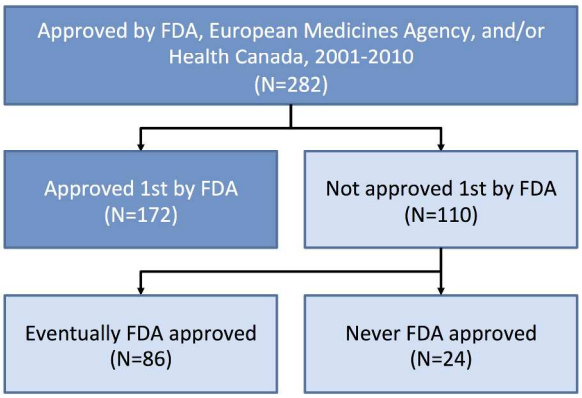
[a] Atovaquone / proguanil hydrochloride (Malarone) already available in U.S.
[b] EMA granted orphan status for gastric cancer, but drug was never approved for this indication
[c] Therapeutic paracentesis already available as accepted (non-pharmacologic) therapeutic option in U.S.
[d] Multiple alternative laxative therapies already available in U.S.
[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)
[f] Enzyme replacement (imiglucerase (Cerezyme)) already available in U.S.
[g] Octreotide (Sandostatin LAR) already available in U.S.
[h] Orlistat (Xenical) already available in U.S.
[i] Plan B One-Step (levonorgestrel) already available in U.S.
[j] ACTH (adrenocorticotropic hormone) gel already available in U.S.



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

279x215mm (300 x 300 DPI)