Healing an Ailing Pharmaceutical System: A Prescription for Reform

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Abstract

The pharmaceutical systems in the United States and Canada are dysfunctional. Costs are exorbitant and innovation is not commensurate with spending. Commercial goals distort research priorities and drug trials, unsafe drugs too often remain on the market, and misleading promotion fosters medication misuse. We propose reforms in pharmaceutical policy for the US and Canada that would provide universal drug coverage without fees at the point-of-use; reduce prices through negotiations with drug firms and, when necessary, compulsory licensing or public manufacture; preclude patenting minor variations of existing medications and drugs developed from publicly-funded research; establish new public agencies to fund drug development and clinical trials; raise standards for drug approval and post-approval safety monitoring; and discourage pharmaceutical marketing while upgrading its accuracy. The proposed reforms would make universal drug coverage affordable, while improving drug safety and stimulating innovation.

Introduction

Drugs are among medicine's most powerful tools. Yet the pharmaceutical systems of the United States and Canada are mired in dysfunction. The industry's pricing practices—charging whatever the market will bear, especially in the US—strain budgets and put vital medications out of reach for many patients.[1-5] Despite some notable advances, the industry's overall rate of real innovation remains incommensurate with our vast drug spending; many new drugs are marketed each year, yet only a minority represent substantial clinical improvements.[6-8] And commercial imperatives distort drug trials,[9] research priorities and drug regulation.[10 11]

While many recognize the need for change, proposed remedies vary widely.[3 12 13] Herein we propose comprehensive reforms for the US and Canada that address insurance coverage, pricing, drug development, clinical testing, regulatory approval, postmarketing monitoring, and promotion. Although some of our recommendations (see Panel) could be implemented within the existing US health care financing framework, full implementation would require a universal single-payer system. While Canada already has a single-payer system, reforms are also necessary in that country, whose system fully covers hospital and doctors' services but not drugs out of hospital.[14 15]

Our proposal rests on six principles. First, medical needs, not financial means, should determine access to medications. Second, drugs must be affordable to society. Third,

drug development should be geared towards real innovation that maximizes population health. Fourth, the human right to health[16] must take precedence over intellectual property rights – i.e. patents. Fifth, the safety and effectiveness of medications must be independently and rigorously evaluated. Finally, comprehensive and unbiased information on drugs should be available to prescribers and patients.[17]

Access to Prescription Drugs

The right to medically necessary pharmacotherapy is frequently abrogated in both the US and Canada (Table 1, Figure 1). High out-of-pocket costs leave millions unable to fill prescriptions,[14,15 18] and drive many into bankruptcy in both nations.[19,20]

In the US an estimated 28 million remain uninsured for healthcare,[21] while 3.5 million in Canada lack drug coverage.[14] Meanwhile, cost-sharing (copayments, deductibles, and co-insurance) impedes access on both sides of the border.[15 22] It reduces needed and unnecessary care to similar degrees;[23] reduces adherence to medications (although other factors also play a role);[24 25] and, for some conditions, exacerbates racial disparities,[26] raises non-drug healthcare spending, and worsens outcomes.[24 26-28] Notably, Wales, Northern Ireland, and Scotland have been able to provide universal drug coverage without cost-sharing, while using other cost control mechanisms to hold drug spending well below US or Canadian levels.[29 30]

To improve access and population health, we propose universal,[31] first-dollar coverage of all medically necessary drugs, echoing Archie Cochrane's famous invocation that "[a]ll effective treatments must be free."[32(1)] Each nation should establish a national formulary of covered drugs, encompassing all medications shown to improve the length or quality of life, although where equivalent agents are available the formulary should include only the safest, most effective, and least expensive one. A national technology-assessment office would provide data on comparative effectiveness to guide formulary decisions. Where clinically appropriate—e.g. for allergies or other unique circumstances—off-formulary drugs should also be covered.

Drug Prices

Spending on outpatient drugs is higher in the US ($1,026 per capita annually) and Canada ($713) than in other OECD nations (averaging $515, and as low as $240 in Denmark).[29] High prices (especially in the US) rather than high use explain these differences. For example, in 2014 a daily 50-unit dose of insulin glargine cost $186.38 per month in the US (after applicable discounts), vs. $63.65 in the UK and $46.60 in France.[33]

Despite claims to the contrary, research and development (R&D) costs cannot justify these high prices.[34 (p. 46)] For instance, the total R&D expenditures of ten firms that recently introduced new cancer drugs amounted to $9 billion, while those drugs generated $67 billion in revenues.[35] Drug firms continue to sharply increase US prices decades after re-

couping R&D costs,[1 36-38] and their mean profits are consistently threefold higher than the average of other Fortune 500 firms—23% vs. 7% in 2016.[39]

Several steps could reduce drug prices, while ensuring that no uniquely effective medications are withheld. Each nation's regulatory agency would continue to approve drugs without regard to price. Once approved, however, a public agency would negotiate with manufacturers over prices, guided (in part) by comparative-effectiveness data. Experience internationally, and in the US, indicates that such negotiations can lower prices,[40] likely by about 50% for branded drugs in the US (online supplementary material, appendix, note c).

While negotiations and a national formulary could reduce prices for many medications, where patented drugs lack competitors firms could still demand unreasonable prices, forcing nations to exclude the drug or strain their budgets.[41 42] Hence, additional options to assure reasonable pricing are necessary (E-Figure 1). For instance, if price negotiations over brand-name drugs failed, governments would issue a compulsory license to allow generic manufacturing, a mechanism already sanctioned under international trade law,[43] US patent law,[44] and the Bayh-Dole Act.[45] Indeed, in 2001, both the Bush (US) [43] [46] and Chretien (Canada) administrations,[47] facing fears of anthrax bioterrorism, threatened to break the patent on ciprofloxacin, causing Bayer to lower the price.

In some circumstances, however, even compulsory licensing might not yield reasonable pricing; prices for some generic drugs have soared after sole generic manufacturers cor-

nered the market.[1 37] We thus advocate the creation of public manufacturing capacity to produce drugs when no reasonably priced option is available. This capacity would also be available to augment production in the face of public-health emergencies or drug shortages.[48]

Finally, drugs developed through public funding by new public entities (described below) would remain unpatented, and available for generic manufacture throughout the globe at greatly reduced cost.

Preclinical Drug Development

The patent protection and market exclusivity that prop-up drug prices are typically portrayed as critical to incentivizing innovation. This portrayal is misleading for two reasons.

First, despite achieving some important advances, the pharmaceutical industry's overall record on innovation is desultory relative to its vast revenues and profits.[49] Most new drugs offer little new besides higher cost (Table 2), while firms often extend market exclusivity through trivial modifications and secondary patenting.[50 51]

Second, it is far from clear that patents are the most important stimulus to therapeutic advance. Throughout history, curiosity and the intrinsic rewards of discovery, rather than financial incentives, have often driven scientific breakthroughs. Even today, most basic

research underlying later drug innovation is carried out in non-profit or public institutions, and funded by the National Institutes of Health (NIH) and the Canadian Institutes of Health Research (CIHR). Prior to the 1980 Bayh-Dole Act, the fruits of publicly-funded research remained in the public domain in the US. After 1980, however, publicly-funded researchers have been allowed to patent their discoveries and sell them to drug firms,[52] as occurred with sofosbuvir. Although Bayh-Dole permits government to "march in" and break patents of such drugs, this provision has never been used.[45]

Thus, we propose the repeal of Bayh-Dole to keep drugs developed with public funding in the public domain. Meanwhile, for drugs developed fully by the private sector, the patent system should be reformed to encourage therapeutically innovative drugs, not more look-alike, “me-too” agents.

In the US, the criteria for issuing drug patents have been stretched far beyond the original requirement that a patentable discovery had to be useful, novel, and non-obvious.[53 54] As others have argued,[3 55 56] patent reforms could both lower prices and advance innovation. Minor variations or combinations of existing agents, drug isomers,[3] and tweaks to drug-delivery devices that don't add important functionality should not be patentable. Some countries have already mandated similar restrictions on patentability.[57]

Because the reforms we advocate risk reducing incentives for industry to develop marketable products from important new discoveries, we propose the creation of new Institutes for Prescription Drug Development within the NIH and the CIHR. The new insti-

tutes would have two divisions (E-Figure 1). The first—the Drug Innovation Division—would focus on the development of non-patentable agents to the point of readiness for clinical-trial testing. This "public track" would—alongside private R&D—fund the development of novel pharmaceutical molecules. We propose public funding equal to about half of current pre-clinical private R&D (appendix, note j). All novel molecules developed by the Drug Innovation Division would remain in the public domain. This approach is a form of "delinkage" of drug development and pricing that others have proposed.[58 59]

The Drug Innovation Divisions might conduct some intramural drug development, but would mostly fund extramural efforts by academic or other non-commercial investigators. The Divisions would prioritize drugs for development based on their potential clinical utility, focusing on diseases that are neglected, commercially unprofitable, lacking in effective treatments, or of particular public health salience. The new, unpatented agents could be produced as generics by companies anywhere—a major advance for global health.

Clinical Testing

Following preclinical drug development, human clinical trials must assess efficacy and safety. Yet industry-sponsored trials have sometimes used unsound methods and reported incomplete findings, calling into question the interpretability, and sometimes the veracity, of their conclusions[9] (E-Table 1). For instance, trials have compared new agents

to placebos rather than to the best existing therapies, under-dosed comparator agents in head-to-head trials, or relied on surrogate endpoints[60] that may not predict outcomes. Some commercially-funded researchers have also selectively published (and republished) positive results, [9 61] or concealed negative findings,[62] while firms have ended trials prematurely for purely commercial reasons.[63]

Meanwhile, corporate ownership of trial data can obscure safety problems and impede further research.[64] Although requiring pre-registration of trials has been an important step forward, transparency problems persist.[65]

To address these problems, drug regulatory agencies should raise evidentiary standards. Trials should, whenever possible, compare new agents to existing therapies, and use a superiority design to discourage investment in unneeded "me-too" drugs. When new agents mimic existing ones, testing should generally be done on patients who fail to respond to (or tolerate) existing products. And with infrequent exceptions, trials should assess hard clinical (rather than surrogate) outcomes.[66 63]

Anonymized patient-level data from all trials (including older trials), should be made publicly-available[65] (whether or not a drug gains approval), to facilitate accountability and further research.

Finally, because of concerns regarding the objectivity of industry-funded trials and the need to test unpatented and unprofitable therapies, we propose the creation of new Clini-

cal Trials Divisions within the new NIH and CIHR Institutes (E-Figure 1).[64 67] These Divisions would select for human testing promising molecules developed by nonprofit laboratories, academic investigators (including those of the NIH/CIHR Drug Innovation Divisions), and pharmaceutical companies. The divisions would fund and oversee trials, which would, in most cases, be designed and conducted by extramural, non-commercial investigators. These trials might also assess existing agents for new indications or non-drug therapies.

Publicly-funded trials would offer important benefits: minimizing commercial conflicts-of-interest; redirecting research from "me-too" drugs towards real innovations, and facilitating the development of unprofitable but essential treatments.[64 67] Although firms could still elect to fund trials of molecules that arise from their research,[67] because such trials are costly and would be subject to enhanced regulatory scrutiny (based on past evidence of companies manipulating results), publicly-funded trials would likely predominate in the long term.

Drug Approval Reform

Canadian and US regulatory agencies too frequently allow unsafe drugs to reach the market (E-table 2) and inadequately monitor them post-approval (E-Table 3). Both agencies' independence has been eroded by their reliance, starting in the 1990s, on funding from "user fees" paid by pharmaceutical companies. In the US, the FDA's receipt of these funds is explicitly linked to its shortening of review times.[68 69]

Meanwhile, an increasing share of new drugs qualifies for programs that further reduce review times. By 2014, 69% of drugs submitted for review to the FDA gained "expedited review" through a variety of newly-created designations or pathways.[70] (The comparable Canadian figure for 2016 is 45% [Lexchin J, unpublished data]). Although intended to accelerate the availability of innovative agents, drug firms have exploited these programs to speed the marketing of many "me-too" drugs.[8 70] Some of these expedited-review pathways have weaker standards of evidence. The recently enacted 21st Century Cures Act in the US creates even more such pathways, and mandates that the FDA evaluate the potential use of "real world evidence"— i.e. evidence not obtained from clinical trials— for approval of new indications for drugs.[71 72]

Such evidentiary changes may well increase the risk that unsafe drugs will enter the market.[73 74] And most,[68 69 75-77] but not all,[74] studies suggest that shorter review times are deleterious.

We propose several reforms to the drug approval process. First, industry funding of drug-regulatory agencies should be ended; governments should fully fund agency budgets. Second, expedited review should be reserved for drugs likely to offer genuine clinical advances. For instance, "first-in-class" drugs should not automatically qualify for expedited approval since many are not superior to existing products.[8] Third, requirements that trials use hard clinical endpoints and active comparators should be waived only in exceptional circumstances. Fourth, while experts who receive commercial funding may

appropriately offer testimony before advisory panels evaluating drugs, such experts should not be allowed to participate in the panels' voting or decision-making.[78] Fifth, drugs should be required to demonstrate superiority—whether in efficacy, safety, or convenience of dosing or administration—over any existing agents to be eligible for market-exclusivity.

Postmarketing Surveillance

As regulatory agencies have approved more drugs based on surrogate endpoints and smaller and/or fewer clinical trials, they have often mandated postmarketing studies to confirm benefits or exclude serious risks.[79] However, this approach has serious shortcomings (E-Table 3). While large postmarketing studies are critical to assuring safety (especially for rare side-effects), this should not be an excuse for weakening preapproval safety requirements. And while big-data approaches to pharmaco-surveillance (e.g. the FDA Sentinel System) hold promise, their results to date are modest, and cannot substitute for clinical trials.[80]

Unfortunately, enforcement of mandates to perform postmarketing studies is currently lax. The FDA has failed to fully use its authority to penalize firms that don't complete such studies,[79 81] while Health Canada has allowed firms to continue marketing drugs for years without completing required trials.[82]

We propose several reforms to upgrade postmarketing safety efforts. Funding for such efforts within the FDA and Health Canada should be increased to a level on par with spending for review of new drug applications, and safety offices' current inferior position in these agencies' hierarchies should be elevated to equal those of offices tasked with drug approval. Safety-monitoring offices should be empowered to independently order safety advisories and remove unsafe drugs from the market, and agencies should use their legal authority far more aggressively to pursue pharmaceutical companies that fail to complete required postmarketing studies in a timely fashion. Finally, information about delays must be made publicly available.

Some of these reforms could be accomplished without legislation: since 2007, for instance, the FDA has had authority to penalize companies that failed to conduct timely postmarketing studies. Yet it has failed to exercise that power in any meaningful way.[81] Recent legislation allows Health Canada to levy substantial fines in case of company noncompliance.[83]

Promotion

Drug promotion—including industry "detailing" of physicians' offices—consumes billions of dollars annually, more than total expenditure for medical student education (in the US);[84 85 86] expenditures for sales and marketing exceed those for R&D.[87] In addition to diverting funds that might be better used to develop lifesaving medications, such promotion is frequently misleading or inaccurate[88 89] (E-Table 4). This is especially true for

direct-to-consumer advertising (DTC)—a relatively new but now widespread phenomenon in the US[90] and, in attenuated form, in Canada.[91] DTC advertising that explicitly mentions the brand name of a prescription-only medicine along with its indication is banned in all other developed nations except New Zealand.

Promotional spending dwarfs the tiny budgets of the FDA and Health Canada components that regulate marketing. The FDA is overwhelmed by the sheer volume of materials to review,[92 93 94] and Health Canada has delegated most of the regulatory oversight of promotion to third parties.[91]

We propose a major expansion of promotional review. First, regulatory agencies need more resources to carry out rigorous assessments of all promotional materials. This will require more (and more predictable) funding.[92] Such funding should not be contingent on meeting deadlines to complete reviews, which can foster a lenient approach, and should come only from government to avoid conflicts of interest.[92]

Improved monitoring should be coupled with stiffer sanctions for misleading or off-label promotion. In the past, even massive fines haven't deterred industry violations because,[95] as one expert noted, "When you're selling $1 billion a year or more of a drug, it's very tempting for a company to just ignore the traffic ticket and keep speeding."[96] Hence, authorities should be empowered to suspend firms' right to promote its products or, in extreme cases, pursue criminal complaints against drug executives.

While we also favor prohibiting DTC advertising and industry detailing, constitutional challenges based on "commercial speech" rights may preclude such bans in the US.[97] However, other tools are clearly constitutional, such as eliminating tax deductions for promotional activities; additionally, where alternative agents are available, drugs promoted in these fashions might be excluded from the formulary. Industry detailing could also be countered by not-for-profit "academic detailing"[98] to optimize physician prescribing practices.[99]

Finally, industry funding can bias continuing medical education (CME)[100] and clinical guidelines.[101] Licensing authorities should not accept industry-funded CME for mandated credits. CME could, instead, be undertaken and coordinated by a body similar to the Australian NPS MedicineWise organization,[102] while clinical guideline development should, at a minimum, follow the recommendations outlined by the Institute of Medicine.[103]

The Economics of a National Pharmaceutical Program

Our proposal would have large economic and budgetary implications. Others have previously estimated the economic impact of a national pharmaceutical program for Canada.[104] E-table 5 presents provisional estimates of the costs and savings under our proposal for the U.S. While any such projection is subject to considerable uncertainty, we estimate that these reforms would modestly reduce total pharmaceutical spending. Savings from reducing brand-name drug prices would more than offset the new costs of increased med-

ication use by previously uninsured and underinsured patients, new public R&D, and enhanced FDA funding.

Discussion

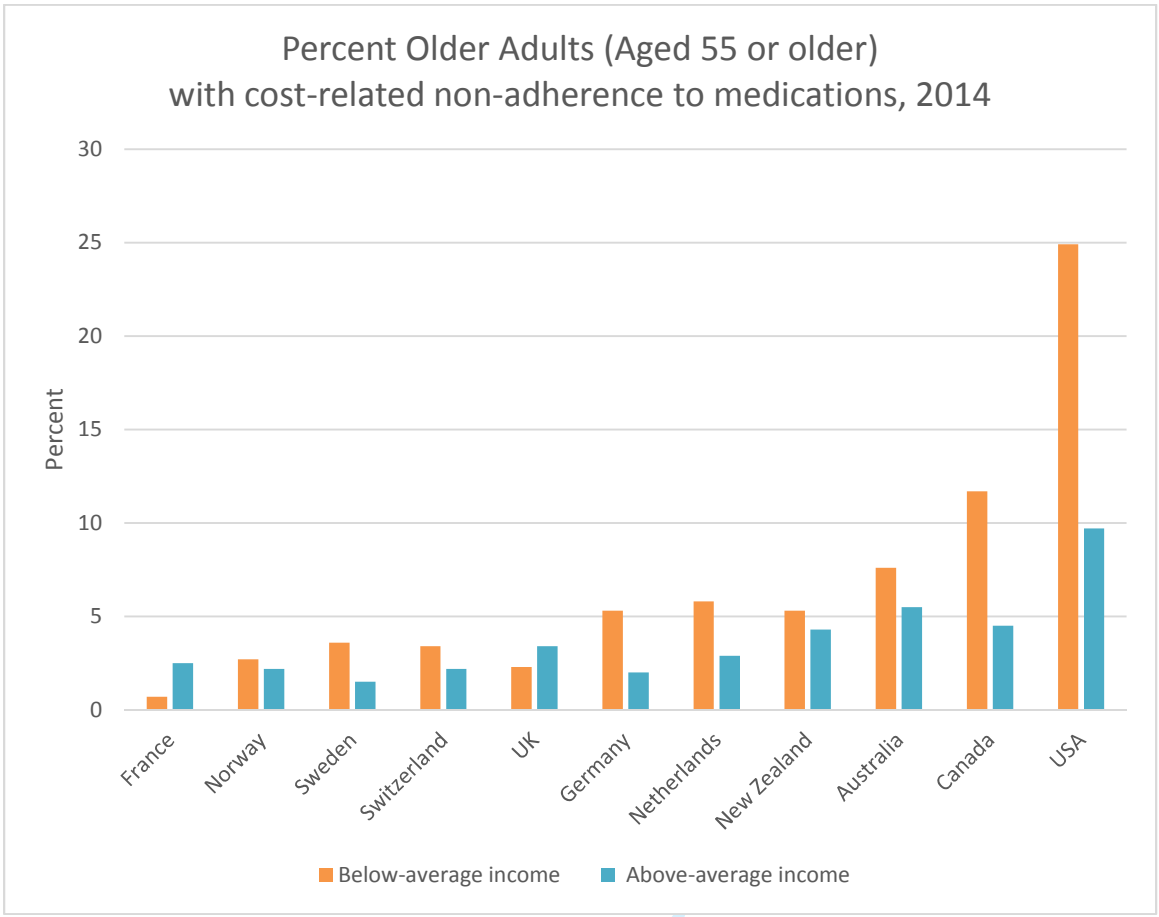
Jonas Salk, inventor of the polio vaccine, eschewed patenting, declaring: "Could you patent the sun?" Today, in contrast, profiteering too often reigns, to the detriment of population health.

Our proposal calls for a fundamental reorientation of drug policy: it would make drugs more affordable for patients and society, promote innovation, fortify efforts to assure the safety and effectiveness of medications, and upgrade the evidence available to prescribers and the public. Because drugs developed through the proposed new public pathways would remain in the public domain, they could be produced generically throughout the world, benefiting many nations.

The reforms we advocate face formidable political opposition, foremost from drug firms whose 2016 profits totaled $67.7 billion.[39] However, most Americans—both Democrats and Republicans—now favor government action to lower drug prices,[105] while 91% of Canadians support a universal pharmaceutical benefit — unmistakable popular mandates for change.[106] The trail from sentiment to policy will doubtless be arduous. Yet history is replete with examples of sweeping reforms—often enabled by unpredictable shifts in political circumstances—that overcame entrenched interests. We aim with this proposal

to provide a blueprint for reform that anticipates—and may kindle—transformative changes in our nations' pharmaceutical systems.

Figure 1: Cost-Related Medication Non-Adherence in 11 High-Income Nations



Source of data: Morgan SG, Lee A. Cost-related non-adherence to prescribed medicines among older adults: a cross-sectional analysis of a survey in 11 developed countries. BMJ Open 2017;7:e014287.

Panel: Summary of Key Pharmaceutical Reform Provisions

I. Access to prescription drugs

- *Each nation would establish a formulary of all medically-necessary prescription medications.*
- *If agents with equivalent efficacy and safety were available, only the least expensive would be included.*
- *All residents would have full coverage for all formulary medications without copayments, co-insurance or deductibles.*
- *When clinically necessary (e.g. allergies), non-formulary alternatives would also be covered.*

II. Drug Prices

- *Government would negotiate with pharmaceutical firms to lower drug prices.*
- *"Compulsory licensing" would allow generic manufacturers to produce essential patented medications if the patent holder refused to offer a reasonable price.*
- *Government would commission public production of essential drugs in cases where price negotiation failed and no reasonably priced generic is available.*
- *New public divisions of the NIH and CIHR (described below) would develop non-patented drugs and make them available for low-cost generic manufacture.*

III. Preclinical Drug Development

- *Preclude patents for trivial modifications of existing agents, and restrict market exclusivity for me-too drugs unless they are shown to be superior in effectiveness, convenience or side-effect to others in the same class.*
- *Repeal provisions of the Bayh-Dole Act in the US that allow private firms to obtain exclusive licenses for drugs developed through publicly-funded research.*
- *Establish public drug-development agencies ("Drug Innovation Divisions") in the US and Canada that would fund and oversee the early stages of drug development.*

IV. Clinical Testing

- *Require higher standards for clinical trials used in drug approval applications.*
- *Increase the transparency and public availability of (anonymized) clinical trial data.*
- *Publicly-fund the majority of clinical trials through new "Clinical Trials Divisions" of the NIH and CIHR.*

V. Drug Approval Reform

- *Full public funding of the drug-regulatory agencies, ending their reliance on industry user fees.*
- *Less frequent use of expedited reviews.*
- *Restrict membership on regulatory advisory committees to experts without financial ties to drug companies.*

VI. Postmarketing Surveillance

- *Enforce requirements to promptly perform postmarketing studies.*
- *Increase funding and authority for regulatory agencies' postmarketing monitoring programs.*

VII. Promotion

- *Ensure that regulatory agencies have adequate resources to review promotional materials.*
- *Stiffen sanctions for misleading drug promotion.*
- *Eliminate tax deductions for expenditures for direct-to-consumer (DTC) advertising and other marketing, and, in some cases exclude drugs promoted via DTC advertising from the formulary.*
- *Promote academic detailing in lieu of industry detailing*
- *Reduce the role of industry funding in continuing medical education (CME) and guideline development.*

Table 1: Examples of problems in drug access and pricing in the US and Canada

Problem	Examples
Inadequate access to drugs due to cost	In the US in 2014—after the full implementation of the ACA—an estimated 35 million non-elderly adults failed to fill a prescription in the previous year because of cost.[18]
	Among 11 high-income nations surveyed in 2014, the US (16.8%) and Canada (8.3%) had the highest rates of "cost-related non-adherence" (defined as skipping medication doses, or not having a prescription filled, over the last year as a result of cost) for adults aged 55 or older. All other nations, apart from Australia (6.8%), had rates below 5% (see Figure 2).[15]
Discriminatory cost-sharing	US private insurers often discourage high cost enrollees from choosing their plan by imposing high copayments for medications needed by ill individuals with high expenses. For instance, among 48 US health care plans, 12 placed all nucleoside reverse transcriptase inhibitors (used to treat HIV) into the highest cost-sharing tier, which imposed co-insurance 30% or greater.[107]
High drug prices for essential medicines	The US price of the CML drug imatinib—less than $30,000 per year when the drug was introduced in 2001—was repeatedly raised well after all R&D costs were recouped.[38] It now costs $146,000 per year,[108] compromising some patients' access to this life-saving drug,[38 109]
	Firms have boosted the prices of decades-old generic drugs such as pyrimethamine[37] and epinephrine[36], whose R&D outlays were long ago recouped.[1]
Payer restrictions on drug access	Some state Medicaid programs in the US restricted the use of newer hepatitis C medications due to cost, for instance requiring drug or alcohol abstinence—restrictions not present in clinical guidelines.[110]
	The province of Ontario only funds eculizumab, sofosbuvir and ledipasvir/sofosbuvir under its Exceptional Access Program because of the cost.[111]

Note: ACA = Affordable Care Act. R&D = research and development. CML = chronic myelogenous leukemia.

Table 2: Global evidence of lagging innovation in the drug development process

Nation	Examples
Canada	Among 564 drugs evaluated by the Canadian Patented Medicine Prices Review Board between 2010 and 2016, only 37 (6.6%) were substantial improvements or breakthroughs.[112]
	Among "first-in-class" drugs approved by Health Canada between 1997 and 2012, only 16.3% represented therapeutic innovations. Among not "first-in-class" drugs, only 4.6% were therapeutic innovations.[8]
US	Among new molecular entities approved by the FDA between 1987 and 2011, only about one third were "first-in-class," while slightly less than half were addition-to-class "me too" drugs.[113]
	Among new cancer drugs approved between 2009 and 2013 by the FDA, a majority were "next-in-class." Prices for these drugs averaged over $100,000 per year, with no association between price and drug efficacy or innovativeness.[2]
	Among new cancer drugs approved between April 2014 and February 2016, only 19% met the modest goals for improving overall survival proposed by the American Society of Clinical Oncology Cancer Research Committee.[7]
	Among cancer drugs approved by the FDA between 2008 and 2012, about two-thirds received marketing approval based on surrogate outcomes, and half of these were demonstrated to have no benefit on survival in later studies.[114]
	Among the cancer drugs found by Kim and Prasad to lack survival benefits,[114] almost none had evidence for a benefit in quality of life when compared to placebo, observational groups, or other agents.[115]
Australia	A minority of drugs approved by the Australian Drug Evaluation Committee between 2005 and 2007 were found to be therapeutically innovative.[116]
Europe	Among new drugs on the British National Formulary from 2001 to 2012, approximately one quarter were considered "highly innovative."[117]
	The European Medicine Agency (EMA) granted approval to 48 cancer medications for 68 indications over a four year period ending in 2013; after a median follow-up of more than 5 years, only 35/68 (51%) of these approvals were found to either prolong survival or improve patients' quality of life.[118]
	Among 61 new "biotech" products approved by the EMA from 1995 to 2003, approximately one quarter were deemed a "therapeutic innovation."[119]
	Among therapeutic drugs approved by the EMA between 1995 and 2004, 28% were found to be "important therapeutic innovations."[120]

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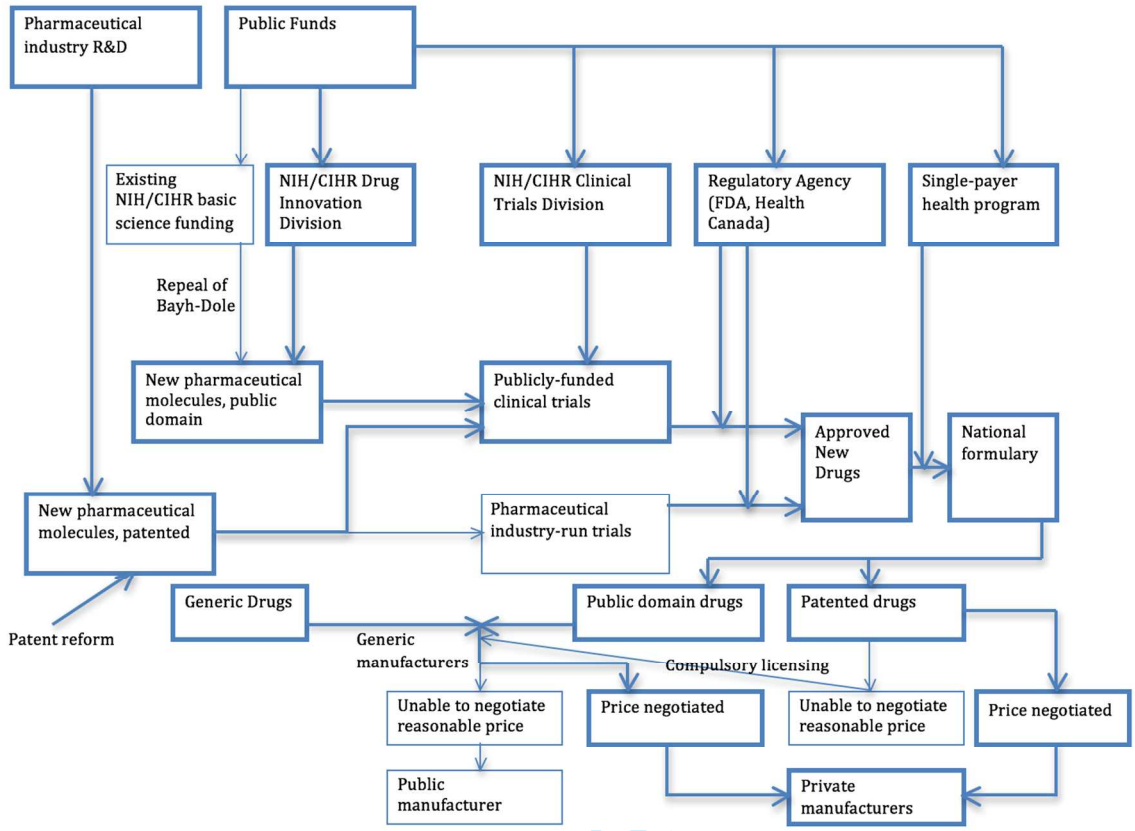
the above." (Text drawn from the *British Medical Journal* website as per submission instructions).

Online supplementary material

E-Figure 1: Pathways of Drug Development and Pricing



Note: R&D = research and development. NIH = National Institutes of Health. CIHR = Canadian Institutes of Health Research. FDA = US Food and Drug Administration

E-Table 1: Examples of problems in industry-sponsored clinical trial design

Problem	Examples
Inappropriate comparator	A meta-analysis evaluating the effect of fluconazole in neutropenic cancer patients found that in some trials the drug was inexplicably compared against nystatin, which is considered ineffective. Moreover, in three arm trials comparing fluconazole to nystatin and to oral amphotericin (a poorly absorbed and ineffective drug), the latter two groups were inexplicably combined post-hoc into a single group, biasing the results in favor of fluconazole.[1]
Inappropriate use of surrogate end points	Many drugs approved on the basis of surrogate outcomes have later been found to cause previously unsuspected harm (in some cases death), e.g. aprotinin, clofibrate, encainide, erythryopietin, estrogen/progestin, flecainide, flosequinan, fluoride, ibopamine, milrinone, moxonidine, and rosiglitazone.[2]
Selective publication (or suppression) of results and misinterpretation of results	Of 74 antidepressant trials conducted on drugs that were approved by the FDA from 1987 to 2004, 31% were not published. Whereas positive trials were mostly published, many negative or equivocal trials were either not published, or published in a fashion that contradicted the FDA's interpretation of the results.[3]
Inappropriate cessation of trials	Pharmaceutical companies sometimes stop clinical trials prematurely for purely commercial reasons, which has negative scientific effects and violates ethical precepts of responsible research.[4]
Preponderance of positive results and conclusions	According to a meta-analysis of 75 studies, industry-funded clinical trials are more likely than those not funded by industry to find positive results and reach conclusions favouring the study drug.[5]

E-Table 2: Examples of problems in drug approval and regulation

Problem	Examples
Safety compromised by pressure to accelerate drug review and approve	Drugs approved shortly before PDUFA*-imposed deadlines for reviewing new drug applications have higher odds of being withdrawn for safety reasons, getting a new black-box safety warning, or having a dosage-form discontinued after they are marketed, suggesting that regulators compromise safety standards when a deadline is looming.[6]
	Compared to drugs approved before the implementation of PDUFA in 1992, drugs approved after 1992 had a 1.35 higher odds of withdrawal for a safety reason or getting a new black box warning.[7]
Trade-off between review time and drug safety	Each standard deviation reduction in the time the FDA spent reviewing drugs was associated with an approximately 20% increase in serious adverse drug reactions, including those associated with hospitalization and death.[8]
Drugs approved with dubious risk-benefit ratio	In March 2017, the FDA approved a minor variant of desmopressin for the treatment of idiopathic nocturia in adults, despite the fact that the drug only trivially reduced the number of episodes of nocturia per night (2.1 episodes per night for desmopressin vs. 1.9 for placebo), and received a black box warning for hyponatremia.[9]
	Duloxetine was approved in the European Union for stress urinary incontinence. A reanalysis using patient-level data showed that the drug's harms outweighed its benefits for this indication.[10]
"Priority review" pathways and compromised safety	Among drugs approved by Health Canada between 1995 and 2010, those assigned "priority" review as compared to "standard" review were more likely to develop serious safety issues in the post-approval period, even in the case of me-too drugs.[11]
	Among drugs approved by Health Canada between 1998 and 2013, those approved under the "Notice of Compliance with conditions"—a pathway for drugs for serious conditions that are approved based on limited data (equivalent to the US fast-track review)—had a higher rate of having serious safety issues than those approved under the standard pathway. Few drugs approved under this accelerated pathway represent major therapeutic advances.[12]
	Among new drugs approved between 1999 and 2014 by the FDA, those approved through one of three expedited programs (fast track, accelerated approval, and priority review) had a 48% higher rate of receiving a black box warning or a new contradiction added to their labelling than those that went through the standard pathway.[13]

**PDUFA = The Prescription Drug Users Fee Act.*

E-Table 3: Examples of problems in postmarketing surveillance of drugs

Problem	Examples
Failure to perform required postmarketing studies	Among drugs approved in 2008, only a minority of required postmarketing studies had been completed within approximately 5 years, and only 9% of the required studies had been submitted to the FDA.[14]
	Only 15.2% of studies required by the FDA between 2007 and 2011 were started by 2011; none had yet been fully fulfilled.[15]
	Ten drugs approved in Canada under its "Notice of Compliance with conditions" pathway have remained on the market for more than 6 years without the completion of required postmarketing studies; of these, 6 have been on the market for more than 10 years (Joel Lexchin, unpublished data).
Post-approval safety problems	Cox-II inhibitors had serious safety issues that both the industry and the FDA delayed addressing.[16]

E-Table 4: Examples of problems in drug promotion

Problem	Examples
Misleading promotion	Nearly one half of print advertisements in medical journals were non-compliant with FDA guidelines on appropriate promotion.[17]
	A systematic review found that print advertising in journals aimed at doctors frequently "provides poor quality information."[18]
	Between 1991 and 2015 pharmaceutical firms paid $11 billion in criminal and civil penalties to the US federal and state governments for unlawful promotional activities.[19]
Expenditures for promotion	Drug promotion consumes at least $27.7 billion and as much as $57.5 billion dollars annually, more than 10% of total industry revenues.[20 21]
	In 2004 spending on promotion was nearly two-fold higher than total industry R&D spending, or about one quarter of industry revenues.[20]
Inappropriate prescribing	A systematic review found that when doctors received information directly from pharmaceutical companies their prescribing practices either did not change or deteriorated, as measured by cost, frequency and quality.[22]

E-Table 5: Estimated effects of proposed reforms on US national pharmaceutical expenditures, 2017*

Savings from lowering drug prices

$360.1 billion	Total current retail prescription drug expenditures [a]
$51.0 billion	Retail drug expenditures by discounted payers (Medicaid, the VA and other non-Medicare federal programs).
14%	Percent of retail drug spending by discounted payers ($51.0 billion/$360.1 billion)
28%	Percent of total drug expenditures that are non-retail[b]
500.1	Total (retail + nonretail) drug spending ($360.1 billion / [1 - 0.28]).
429.3	Total drug spending by non-discounted payers ($500.1 billion – [$500.1 billion * 0.14])[c]
72%	Percent of national drug expenditures on brand-name drugs [d]
$309.1	Total drug spending by non-discounted payers on brand-name drugs ($429.3*0.72)
50%	Estimated average reduction in brand-name drug prices[e]
$154.6 billion	*Savings from reduced brand-name drug prices (0.50 x $309.1 billion)*

Costs from increased utilization due to new coverage for uninsured persons

28 million	Number of persons uninsured[f]
$813	Increased prescription drug spending per newly insured person[g]
$22.8 billion	*Increase in prescription drug spending for newly insured persons (= $813 x 28 million)*

Costs from increased utilization due to the elimination of cost-sharing for persons who are currently insured

17%	Estimated percent increase in utilization of outpatient prescription drugs by previously-insured persons due to the elimination of cost-sharing [h]
$52.9 billion	*Increase in drug expenditures due to the elimination of cost-sharing for currently-insured persons (17% of the $345.6 billion in estimated prescription drug expenditures by and on behalf of this group, with 10% of the increase offset by savings on non-drug expenditures).*

New costs for public R&D

$ 39.0 billion	NIH Clinical Trials Division [I] (funding for 90% of clinical trials)
$ 21.7 billion	NIH Drug Innovation Division [j] (funding of half of current pre-clinical private R&D)
$ 60.7 billion	*New Public R&D costs* [k]

New regulatory agency costs

$1.2 billion	Replacement of FDA Drug User Fees [l]

$1.8 billion	Bolstered postmarket drug safety monitoring [m]
$0.2 billion	Expanded FDA promotional monitoring [n]
$3.2 billion	*New regulatory costs*
Net savings and costs	
$ 154.6 billion	Overall savings
$ 139.5 billion	Overall new costs
$ 15.1 billion	*Estimated net savings, 2017*[o]

* Methods, sources and assumptions are described below. Figures in this table may not add up due to rounding. VA = US Veterans Health Administration. R&D = research and development. NIH = National Institutes of Health. FDA = US Food and Drug Administration.

Online Appendix: Methodology for E-Table 5

[a] The figures for national drug expenditures (total and by payer) are CMS's 2017 National Health Expenditure (NHE) estimates.[23]

[b] The NHE estimates of drug spending are for retail drug spending only; spending for drugs administered by hospitals or physicians are included in the expenditure estimates for those providers. Hence, to calculate total (retail + non-retail) drug spending using the NHE retail drug spending estimates, we followed the approach of the Department of Health and Human Services, which estimates that non-retail drug spending constitutes 28% of total drug spending.[24]

[c] Given that many public payers (e.g. Medicaid and the VA, but not Medicare) already obtain significantly discounted drug prices, we excluded these payers from our calculation of potential savings. However, our non-retail drug spending estimate is calculated as indicated in note b above (i.e. 28% of total drug spending), and is not disaggregated by payer. Thus, in order to estimate total drug spending by non-discounted payers, we assumed that the percent of retail drug spending by discounted payers in the NHE (14% of total retail spending) also applied to total drug spending.

[d] This percentage is from Kesselheim et al.[25] A similar estimate (74.2%) is provided by the IQVIA Institute for Human Data Science based on invoice drug prices for 2016.[26(p. 45)]

[e] We estimate that drug prices could be reduced by approximately 50% based on international price comparisons from several sources. For instance, Squires reports Gerard Anderson's

analysis of IMS health data (exhibit 6)[27] on the average prices paid for the 30 most commonly prescribed drugs in the US and 8 other OECD nations (Australia, Canada, France, Germany, Netherlands, New Zealand, Switzerland, and the United Kingdom). Overall, the ratio of median drug prices in these 9 nations to the median price in the US was 0.51 (including both generic and brand-name agents), consistent with our assumption that the US could cut drug prices in half.

A more recent report from Gagnon and Wolfe, also relying on IMS data, examined 640 brand-name drugs and utilized US sales-weighted averages, provides a similar estimate. Gagnon and Wolfe found that in 2014, OECD median average drugs prices were 42% those of the US, and asserted that "one can safely conclude that Medicare Part D … pays at least twice as much as the OECD median for patented drugs."[28]

Others analyses of comparative prices using different approaches support the view that US drug prices are significantly higher than other high-income nations'. For instance, Kanavos et al., also using IMS data, estimated drug "price indices" weighted for consumption patterns for the US, the UK, Switzerland, Germany, France, Canada, and Australia.[29] Depending on the comparator nation, whether the analysis examined retail or manufacturing prices, and whether US or nation-specific weighting was utilized, they found that US drug prices were between 5% and 198% higher than other nations'. Their analysis based on retail drug prices using US weights found that as compared to a price index of 100 for the US, the index was 49 in Australia, 50 in Canada, 61 in France, 95 in Germany, 88 in Switzerland, and 46 in the UK.

Overall, our estimate of a 50% reduction in drug prices with drug negotiations is consistent with the prices in nations that most effectively lowered drug prices in this study.

Finally, our estimate is supported by the lower prices paid by the US Veterans Health Administration (VA), which negotiates for drug prices and maintains a formulary. A dated estimate from the Congressional Budget Office puts prices paid by the VA for branded drugs at 42% of the average wholesale price.[30] Frakt et al., drawing on four studies, assert that the VA obtains drug prices approximately 60% of those paid by Medicare.[31] Together, these estimates accord with our estimate of an approximately 50% reduction in drug prices through negotiations and a formulary.

As noted, we do not apply this 50% reduction to Medicaid or other federal health programs which currently receive substantial discounts (including the VA, but not Medicare). It seems likely that the prices paid by these programs would also be reduced, albeit to a lesser extent.

An alternative approach to computing likely savings (which some have adopted[32]) would rely on differences in national per-capita drug spending. For instance, an assumption that the United States could reduce its overall per-capita drug spending to the OECD average (approximately half that in the US) would project substantially larger savings than those we estimated. However, this approach does not take into account differences in the quantity of drugs consumed. Hence, we elected to conservatively estimate savings based on price differences.

[f] The figure for the number of uninsured is CBO's 2017 projection.[33]

[g] This figure is based on a study of Mulcahy et al examining the impact of the ACA on drug spending for previously uninsured individuals.[34] This figure accounts only for new program spending, and does not incorporate reductions in out-of-pocket payments. To be conservative, we used the higher of the two figures reported by Mulcahy et al, an estimate based on individuals newly covered by Medicaid, which carries low or no cost-sharing for medications.

[h] We rely here on the estimate of overall "relative spending" from Choudhry et al., whose randomized trial evaluated the effect of eliminating copayments for drugs in patients who have suffered a myocardial infarction, which most closely resembles the policy change we envision. In that study, although eliminating cost-sharing for medications increased medication spending, it did not increase total healthcare spending because it was completely offset by savings on non-drug expenditures.[35] However, we conservatively estimated that only 10% of the added expenditures for drugs would be offset by reduced non-drug spending.

We apply the estimated 17% increase in drug spending from eliminating cost-sharing to our estimate of total drug spending after adjustment for a 50% reduction in brand-name drug prices for non-discounted payers (i.e. total current estimated 2017 drug spending of $500.1 billion minus estimated savings of $154.6 billion). Since this includes spending on inpatient drugs (the utilization of which would likely be less affected by the elimination of cost-sharing), our spending estimate likely overstates the cost of eliminating cost-sharing.

[i] This figure is based on estimates by PhRMA,[36] the pharmaceutical industry lobbying group, and D. Baker.[32]

PhRMA reported that R&D spending for the entire U.S pharmaceutical industry totaled $67.4 billion in 2010, of which $50.7 billion was spent by PhRMA member companies. For more recent years, PhRMA only provides estimates for PhRMA member firms' spending, which in 2015 totaled $58.8 billion.[36] We assumed that the ratio of PhRMA member company R&D spending to overall industry R&D spending in 2010 (75.2%) remained the same in 2015. Thus, for 2015, we estimate $78.17 billion in total industry R&D spending. In order to inflate this figure to 2017, we assumed that R&D spending rose at the same rate as total outpatient prescription drug spending (11% between 2015 and 2017).[23] Thus, for 2017 we estimate approximately $86.7 billion in total private sector R&D in 2017.

We follow Baker in assuming that approximately half of industry drug development spending is preclinical and half clinical.[32] Applying this ratio to the 2017 R&D estimate of $86.7 billion suggests that about $43.4 billion will be spent on clinical testing in 2017. Under the assumption that 90% of clinical trials would be publicly funded, we estimate that $39.0 billion in funding would be required to support public clinical trials.

[j] As noted above, we assume that approximately half of preclinical drug development will be publicly funded, i.e. 25% (50% of 50%) of the total R&D figure of $86.7 billion, or $21.7 billion.

[k] Chakravarthy et al. estimate that NIH spending would have to roughly increase 2.5 fold to replace *total* private sector R&D.[37] Since the 2016 NIH budget totaled $31.3 billion, this translates into an approximate total NIH budget of $78.3 billion, or an increase of $47.0 billion. We have projected a considerably higher estimate, a $61.6 billion increase in NIH funding. However, our figure was meant to only cover 90% of clinical trials and 50% of basic science research (not 100% of the cost of both components, the basis for Chakravarthy et al's figure). Thus, our estimate of added spending for public sector drug development may overstate costs; a lower sum may suffice.

[l] For 2017, the FDA was projected to receive a total of $1.2 billion in human drug-related user fees: $866 million for prescription drugs (PDUFA), $324 million for generic drugs (GDUFA), and $22 million for biosimilars (BSUFA).[38]

[m] FDA spending for human drug and biologic programs totaled $1.768 billion in 2017 ($1,408 million and $360 million, respectively). The vast majority of these funds currently go towards drug approval activities. Hence, we estimate that an additional $1.8 billion would be required to bring funding for post-marketing surveillance activities on a par with the funding for drug approval activities.[38]

[n] In 2015, FDA spending on "Drug Marketing, Advertising, and Communication Activities" was $17.127 million.[39] An approximately ten-fold increase in this figure, rounded to one decimal point in billions, yields our figure of $0.2 billion.

[o] Overall, this estimate is likely conservative. For instance, it excludes longer-term savings from patent reform, improved prescribing resulting from drug promotion reform, and increasing the share of drugs in the public domain through the new "public track" programs.

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