INTERNATIONAL SOCIETY OF DRUG BULLETINS

Newsletter

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WELCOME TO THE FIRST ISDB NEWSLETTER OF 2025

This first issue of 2025 includes updates on ISDB members' activities and published articles:

- An article from Public Citizen on industry lobbying to influence the U.S. position in critical global health negotiations.
- A focus on patient information leaflets (PILs) with an editorial from the Drug and Therapeutics Bulletin ("PILs: all harms and no benefits"). There is also an abstract of a recent BMJ article ("Patients deserve better information on new drugs") focusing on the need for better information for patients that includes details of the benefit, size of benefit and likelihood of experiencing a benefit of a new medicine. An editorial from Prescrire International discusses a pilot project in France to phase out PILs in paper form.
- An article from Prescrire International on the revision of the European Pharmaceutical legislation.
- An up-coming webinar, organised by Therapeutics Initiative, on medications that are ineffective and potentially harmful for patients with alcohol and other substance use disorders.

You will also find information on two recently published articles that are of particular interest for our network: one is focusing on Mundipharma's activities to promote opioids and the other is focusing on patient preferences for speed of access versus certainty of the survival benefit of new cancer drugs.

We also want to let you know that the preparation of a new ISDB website is on its way. We hope to unveil it soon!

At the start of the new year, **the Committee wishes you and your loved ones a Happy & Healthy 2025**!

ISDB General Assembly in 2025 - Save the Date

The next ISDB General Assembly will be held from **October 1- 3, 2025 in Verona, Italy.** We plan to start in the afternoon of Wednesday October 1, ending midday on Friday October 3, to make travel simpler.

Please let us know if you plan to attend. We need a general idea of numbers for planning of catering and practical organisation.

Please let us know your suggestions for topics to be debated in work sessions and/or if you would like to present a topic.

News from ISDB Members

Industry Lobbyists Work to Influence U.S. Position in Critical Global Health Negotiations

Public Citizen, October 28, 2024

In October 2020, India and South Africa, recognizing the unprecedented urgency of the COVID-19 pandemic, proposed a temporary waiver from certain provisions of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) in order to ensure that intellectual property (IP) would not be a barrier to timely and affordable access to medical tools for COVID-19. The negotiations that followed this proposal amounted to over three years of discussions at the WTO that stand in stark contrast to the urgent action required to address the COVID-19 pandemic.

After an initial period in which the U.S. and other wealthy countries blocked productive negotiations on the waiver, in May 2021, U.S. Trade Representative Katherine Tai announced the Biden administration's support for waiving IP provisions for COVID-19 vaccines—a welcome shift from the opposition shown under the Trump administration.

In June 2022, a limited waiver was adopted for COVID-19 vaccines. This decision relaxed a narrow band of requirements for "compulsory licensing" of vaccine patents, by which countries may authorize competition to support affordable and diverse vaccine supply. WTO members also committed to continue negotiations on whether to extend this decision on COVID-19 vaccines to therapeutics and diagnostics. Finally, in February 2024, the WTO officially declared that consensus could not be reached on the waiver extension.

Concurrently with the WTO waiver discussions, Member States of the World Health Organization (WHO) began negotiating a Pandemic Agreement, whose principal aim is to address the inequities observed during the global response to COVID-19. The Agreement could help foster international cooperation and coordination to address pandemics, including to avoid gridlocked talks at the WTO during pandemic emergencies.

The COVID-19 IP waiver proposal elicited an extensive lobbying effort from pharmaceutical companies and trade associations, including public ad campaigns claiming that the waiver would "eliminate" IP protections. The U.S., along with other high-income countries, have taken similar positions in the WHO Pandemic Agreement negotiations.

Public Citizen examined U.S. lobbying activity on the TRIPS waiver between 2021 and the first half of 2024. This data revealed an imbalance between those lobbying against the waiver compared to those lobbying in support. Additionally, lobbying disclosures show an opposition effort that extends well into 2024. We further examined U.S. lobbying activity on the ongoing negotiations at the WHO for a Pandemic Agreement.

Key Findings:

- More than 500 lobbyists were hired to lobby on the waiver between 2021 and the present. Of these, nearly 90% were hired by entities opposed to the waiver. Those hiring the most lobbyists were pharmaceutical and biotechnology companies or industry groups with pharmaceutical or biotechnology company-affiliated members.
- In 2022, the year in which the most lobbyists were hired, entities opposed to the waiver outnumbered those hired by supporters 32 to 1.
- Two dozen entities disclosed lobbying on the waiver through the first half of 2024 when COVID waiver talks concluded. The majority of these entities were pharmaceutical or biotechnology companies and the trade associations that represent them.
- Fewer entities have lobbied on the Pandemic Agreement. Entities included the Chamber of Commerce and the Biotechnology Innovation Organization, who hired dozens of lobbyists to influence the Pandemic Agreement negotiations.

Read more

Articles published in the January 2025 issue of Worst Pills, Best Pills News

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Worst Pills, Best Pills News

Your expert, independent second opinion for prescription drug information

ROBERT STEINBROOK, M.D., EDITOR

January 2025 ✦ VOL. 31, NO. 1

Lancet Commission: Nearly Half of Dementia Cases Are Preventable

An August 2024 report from the *Lancet* Commission on dementia highlights approaches that, if fully implemented, could prevent or delay up to 45% of dementia cases. Convened by the *Lancet*, an international medical journal based in the United Kingdom, the commission identified factors contributing to dementia that are often modifiable without drugs.

The risks recently added to the list of 14 potentially modifiable factors are untreated vision loss and high LDL ("bad") cholesterol, the type of cholesterol that can build up in the arteries and increase a person's risk of heart attack and stroke. The 12 other modifiable risk factors, previously identified in the 2020 *Lancet* Commission report, are less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, infrequent social contact and air pollution.

According to the 2024 report, "The potential for prevention is high and, overall, nearly half of dementias could theoretically be prevented by eliminating these 14 risk factors. These findings provide hope."

Background on dementia

Approximately 6.7 million older U.S. adults suffer from dementia. By 2060 that number is expected to increase to 14 million. Although dementia affects about 11% of Americans aged 65 years or older and is strongly correlated with increasing age, it is not a normal part of aging.

Approximately 6.7 million older U.S. adults suffer from dementia. By 2060 that number is expected to increase to 14 million.

Alzheimer's disease is the most common form of dementia, representing 60-80% of cases. The second leading form is vascular dementia, including stroke-related dementia, which accounts for 5-10% of cases. Other forms of dementia include those associated with Lewy body protein deposits or damage to the nerve cells in the frontal and temporal regions of the brain. More than one of these forms of dementia can occur simultaneously.

The pathophysiology of dementia remains uncertain, and there are no curative therapies. Of the FDA-approved drugs for Alzheimer's disease, Public Citizen's Health Research Group has classified lecanemab (LEQEMBI) and donanemab (KISUNLA) as Do Not Use because of their marginal effects in slowing disease progression and the risk of potentially fatal brain bleeding. We have classified the acetylcholinesterase inhibitor donepezil (ARICEPT, ARICEPT 23 and generics), the first FDA-approved drug exclusively for Alzheimer's disease, as Do Not Use because its minimal effectiveness makes its risks unacceptable. Better drugs for Alzheimer's disease and other forms of dementia are urgently needed.

The *Lancet* Commission report

For the 2024 report, the members of the *Lancet* Commission agreed on the best available evidence, prioritizing systematic reviews, meta-analyses and recent data and conducting new meta-analyses. The report synthesizes data spanning many decades and millions of individual patients to develop a comprehensive "life course perspective of dementia prevention" that considered the relative importance of a variety of plausible risk factors. Although most of the evidence was from wealthier nations, global data were assessed. The commission found that low- and mid-income nations, and minority

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EDITORIAL

PILs: all harms and no benefits

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In 1981, *DTB* highlighted the importance of providing information to patients to help them use medicines safely and effectively and published a checklist of what a patient needs to know about a medicine.[1] At that time, however, the only written details patients received were on the dispensing label and additional printed information was provided for very few medicines (eg, corticosteroids and anticoagulants).[2] *DTB* recognised the need for 'clearly written and easily understandable package information leaflets for all preparations' to enable patients to decide whether or not to take a medicine and argued that these leaflets should be provided to all patients.[2 3] In the UK, patient information leaflets (PILs) became a legal requirement for all new medicines in 1994 and for all medicines in 1999.[4 5] Details of what must be included in a PIL are regulated by law and include the name, strength and form of the product, what it is used for, how it is used, adverse effects and drug interactions, excipients, and the names of the market authorisation holder and manufacturer.[6 7] Information in the PIL must be presented in a standardised format and in a manner that is non-promotional.

It has long been recognised that PILs have many limitations and survey results report that people find them too complex, poorly designed and sometimes overwhelming.[8–10] The leaflets are not valued by patients who may read them only once and rarely look at them again or throw them away unread.[10 11] Across Europe, as part of an initiative to reduce the carbon footprint of medicines and minimise waste, the EU is consulting on a proposal to replace printed PILs with an electronic version that can be accessed from a QR code on the packaging.[12] Moving to an electronic PIL, however, will not address the fundamental problem of its content. Despite previous initiatives to improve the quality, usability and accessibility of PILs they have not evolved to meet the information needs of patients and healthcare professionals.[8 13] Given the abundance of information (and misinformation) on medicines that is available online, the PIL may be seen as a quaint regulatory artefact that serves little purpose (other than to get in the way whenever you open a medicine packet) and there is a pressing need to rethink its purpose as well as its design, format and content.

A recent article in *The BMJ* provided a welcome analysis of the information that patients need on new medicines and explored ways that PILs could be made more relevant.[14] The authors point out that PILs do not provide important information on the effect of a drug on clinical outcomes, the magnitude of that effect or the likelihood of a patient benefiting from that effect. Nevertheless, if information on the benefit of treatment is to be included in the PIL, it will need to be non-promotional and presented in a meaningful way, particularly for medicines where the clinical trial outcome was continuous rather than dichotomous. It is also important that such information is provided by a trusted organisation and not by one that would overplay the benefits or herald them as 'ground breaking' or 'game changing'.

The current shortcomings of the PIL need to be tackled so that patients are presented with balanced information on possible benefits as well as potential harms. The challenge is for governments and drug regulatory agencies to address the concerns raised in *The BMJ* article and mandate changes to the PIL to transform it from an annoying slip of paper that is disregarded by most people to a resource that can be used as part of a shared decision-making process.

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DOI: 10.1136/dtb.2024.000067

Patients deserve better information on new drugs

By Courtney Davis, Anita K Wagner, Barbara Mintzes, Henry Scowcroft, Steven Woloshin, Huseyin Naci

BMJ 2024; 387 doi: https://doi.org/10.1136/bmj-2024-081720, published on 29 October 2024

Full article available at: https://www.bmj.com/content/387/bmj-2024-081720

Courtney Davis and colleagues argue that drug regulatory agencies should improve their oversight and direct provision of relevant, useful, and trustworthy information on new drugs. To make informed and evidence based decisions about new medicines, patients need to consider the benefits, harms, and uncertainties associated with different treatment options. Numerous studies report that people do not find the content of patient information leaflets in the EU and UK and medication guides in the US useful. They do not routinely include information on the goal of treatment, potential benefits, or important uncertainties. Without this information, patients may overestimate or underestimate likely benefits or misunderstand the purpose of treatment.

The article states that patients want clear information about the nature and magnitude of the benefits demonstrated in clinical studies, as well as the likelihood of experiencing those benefits. Research suggests that people care about the sources and quality of the evidence underpinning information they are given, and that they want information about relevant scientific uncertainties and evidence gaps. Therefore, regulated information sources should clarify whether and how study endpoints are clinically relevant for patients, and how reliable findings are. Providing a brief explanation about the nature and predictive value of surrogate endpoints can improve patient understanding and decision making.

Key messages

- Patients need to weigh the potential benefits and harms of new drugs to make informed treatment decisions that reflect their treatment goals and preferences.
- Complete, current, and non-promotional information about the potential benefits and harms of new drugs is essential to make evidence based decisions.
- Existing information sources for patients are focused primarily on communicating information about drug harms.
- Drug regulatory agencies are uniquely positioned to oversee and provide useful and trustworthy information about new drugs.
- They should ensure that information about medicines better meets the needs of patients.

EDITORIAL

Phasing out patient leaflets in paper form: eco-responsible or irresponsible?

In 2023, the European Commission embarked on a thorough revision of Europe's pharmaceutical legislation. One of the proposed changes is to gradually phase out package leaflets in paper format and replace them with an electronic version (1).

France has decided to trial the use of electronic package leaflets for certain drugs in hospitals and community pharmacies in 2024, as part of its "*ecological planning*" strategy for the healthcare system (2-4). In hospitals, package leaflets would be replaced immediately with a QR code affixed to the box, enabling users to access an electronic version of the package leaflet, potentially accompanied by interactive forms or videos providing practical information. In community pharmacies, both formats would be provided at first, but the paper format would eventually be phased out and printed at the pharmacy if requested by the patient (2). The ministries concerned claim that the initiative is intended to reduce the carbon footprint of drugs, which are estimated to account for 20% of the total emissions generated by France's healthcare sector (3,5).

The package leaflet is the patient's main source of information about their treatments. In France, its inclusion in the packaging of every drug is still a legal obligation. It specifies the drug's authorised uses, recommended dosages, adverse effects, any contraindications to its use and its interactions with other substances or foods. It provides essential details about how and when to take the drug, and about any special warnings and precautions that must be taken, for example when driving or in certain situations such as pregnancy. Its presence in the box is crucial to medication safety (6).

Prescrire opposes the plan to phase out paper package leaflets, proposed in the revision of European pharmaceutical legislation that is currently in progress. The people most likely to suffer from the shift from paper to electronic leaflets are those who live in places with limited internet access or who are not comfortable using digital technology, such as older patients who often take multiple medications, and vulnerable patients (1). Members of the European Parliament have made the phasing out of paper package leaflets conditional on a "*consultation of patients, carers and other relevant stakeholders*" (7). Prescrire hopes that member states will go further in their defence of paper package leaflets.

The provision of an electronic package leaflet alongside the paper leaflet may indeed be an advance, provided that the electronic version comes from a reliable source, that it is dated and kept up to date, and that updates are clearly highlighted (6).

Prescrire

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OUTLOOK

Revision of European pharmaceutical legislation: a disappointing vote in the Parliament

● In April 2024, MEPs voted on the European Commission's proposals for the revision of European pharmaceutical legislation.

● Overall, despite a number of welcome advances, MEPs failed to take advantage of the opportunity to strengthen drug evaluation and patient safety.

On 10 April 2024, members of the European Parliament (MEPs) held a plenary vote on the European Commission's proposals for the revision of European pharmaceutical legislation, which consist of a directive and a regulation (known as the "pharmaceutical package") (see editorial "European pharmaceutical legislation: too many opportunities missed by MEPs" p. 255) (1,2).

This article looks at how the Parliament voted on the main amendments proposed by Prescrire (and in many cases by other civil society groups). It is not an exhaustive analysis of how MEPs voted.

MEPs often overly favourable to the pharmaceutical industry

In the plenary vote, MEPs largely accepted the amendments proposed by their rapporteurs.

The amendments on the proposed directive submitted by the rapporteur (who is a member of the European People's Party, the largest party in Parliament) mainly defended the interests of pharmaceutical companies. She had met with numerous industry representatives, and very few representatives from civil society (**a**). Her proposals sought, in particular: to strengthen the protection of clinical data (and thus prolong the period during which companies enjoy a monopoly for their drugs); to relax the requirements on companies pertaining to the assessment of the environmental impact of drugs; and to allow companies to choose not to market their drugs in countries that are of no economic interest to them (3). These amendments, along with several others that are favourable to the interests of pharmaceutical companies, were approved by a large majority in the plenary vote (1,2).

The rapporteur for the proposed regulation (who is a member of the Progressive Alliance of Socialists and Democrats) had met with numerous representatives from civil society, and proposed amendments more in line with the demands from this sector. He presented amendments similar to those proposed by Prescrire (and other civil society groups), some of which were voted on in the plenary session (1-3).

Missed opportunities

In September 2023, Prescrire proposed a list amendments designed to improve the Commissio proposals in several areas of major importance f achieving high-quality health care. They include – Requiring comparative trials to be conducte versus standard treatment, where one exists, befo marketing authorisation is granted (**b**);
– Rejecting the idea of shortening the Europea Medicines Agency (EMA) evaluation period f marketing authorisation applications from 210 da to 180 days, and of abolishing the five-yearly renew of marketing authorisations, which would put patien at risk (3).

The European Parliament did not vote in favo of any amendments to this effect, and thus not on failed to seize the opportunity to improve the quali of the clinical evaluation of drugs before their mark introduction, but in fact agreed to water down th requirements (1,2).

Prescrire had proposed an amendment to th regulation that was taken up by the rapporteur, b not voted through in the plenary session. It wa designed to restrict to exceptional circumstanc the EMA's use of the "*phased review*" (or rollir review) evaluation process trialled during the covid- pandemic, since this experiment proved to be ve draining on the Agency's resources.

Another amendment to the regulation proposed b Prescrire and taken up by the rapporteur, but n voted through in the plenary session, was to refus the institutionalisation of a very high-level exemptio from the legislation, referred to as a regulato "sandbox", which would allow the EMA and Europea Commission to depart from standard marketin authorisation regulations without going through th European legislative procedure. Prescrire also oppose "*temporary emergency*" marketing authorisations, o the grounds that conditional marketing authorisatio already provide an adequate option, but no amendme to that effect was tabled or adopted (2-3).

Along with numerous representatives from civ society, Prescrire opposed the inclusion in th regulation of "transferable exclusivity (or da exclusivity or regulatory protection) vouchers" (TEV which are intended to encourage the developme of high-priority antimicrobial drugs, but have th potential to substantially increase spending on oth medicines by extending the duration of the mark monopoly for highly profitable drugs (**c**)(3). N amendment to that effect was adopted (2).

The Commission had proposed a reduction in th basic clinical data exclusivity period, combined wi extensions designed to incentivise companies conduct trials versus standard treatment or to mark

rugs across all member states, for example. This roposal, which was supported by Prescrire and any other organisations, was largely stripped of s substance by the Parliament (amendments 196 nd 199 to 207 to the proposed directive).

A number of welcome advances, to be maintained or strengthened

he improvements introduced by the MEPs that had een called for by Prescrire, among others, included ie following:

Requiring pharmaceutical companies to report ie amount of indirect public funding (tax credits) iey receive in addition to direct public funding, ecifying the drugs concerned, and centralising iese data on the EMA website (amendments 169 173 to the proposed directive);

Barring anyone who provides scientific advice to pharmaceutical company on behalf of the EMA om subsequent involvement in assessing the arketing authorisation application for the same roduct (amendments 176 and 177 to the proposed egulation); and ensuring transparency about nhanced scientific and regulatory support for riority medicinal products (amendment 180 to the roposed regulation);

Improving the quality of the information provided patient leaflets and on packaging (at the single ose level for antimicrobial drugs) (amendments 34 and 186 to the proposed directive);

Maintaining the provision of patient leaflets in paper rm (unless electronic-only patient leaflets have been pproved via prior consultation of patients, carers and her relevant stakeholders) (amendment 176 to the roposed directive); and removing the ability of the uropean Commission to unilaterally scrap the paper aflet (amendment 180 to the proposed directive);

Envisaging a European-wide requirement that harmaceutical companies hold safety stocks of ritical medicinal products (considered to be of ajor therapeutic interest) in order to prevent nortages (amendment 293 to the proposed egulation); and enabling member states to impose nctions if companies fail to comply with "*obligations elated to the availability and supply of medicinal roducts*" (amendments 347 and 363 to the proposed egulation);

Ensuring the EMA has adequate funding to fulfil s transparency obligations (amendments 23 and 340 the proposed regulation);

Removing from the directive the reference to the ght (which already exists) of member states to restrict prohibit access to contraceptives or abortifacients mendment 85 to the proposed directive);

Requiring member states to maintain national ansparency registers with information on the enefits offered to persons qualified to prescribe rugs (amendment 298 to the proposed irective) (1,2).

The Council will issue its opinion on the two gislative texts sometime in 2024 or 2025, after hich "trilogue" interinstitutional negotiations will be held between the Council, Parliament and Commission.

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a- *The MEP in question was associated with a move to suppress or amend the report on the pharmaceutical research and development system by the European Parliament's Panel for the Future of Science and Technology. This report favoured greater public oversight of the European pharmaceutical sector (ref 4).*

b- *MEPs did vote for one amendment to the proposed directive (number 36) referring to the need to conduct comparative trials versus standard treatment, where one exists, before marketing authorisation is granted, but this only concerns a recital to the directive, and its substance was not included in an article (ref 1).*

c- *Transferable exclusivity vouchers can be used by the holder for another of their drugs, thus extending the duration of their market monopoly. These vouchers can also be sold to another company.*

Selected references from Prescrire's literature search

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French Senate hearing on drug shortages

On 22 November 2023, Prescrire contributed to a hearing held by the French Senate's Committee for European Affairs as it prepared a resolution on the European Commission's revision of pharmaceutical legislation, with a specific focus on drug shortages.

The priorities emphasised by Prescrire included: strengthening supply chain continuity by introducing the obligation to hold contingency stocks, coupled with penalties for companies that fail to comply with these requirements; ensuring that the European list of "critical medicines" (drugs that are considered to be essential and must therefore be permanently available) is drawn up in an independent and transparent manner; maintaining the provision of patient leaflets in paper form; and supporting the idea of public production of critical drugs.

In mid-2024, senators included these recommendations in their final resolution sent to the French government (1).

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► Translated from *Rev Prescrire* August 2024
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Therapeutics Initiative
Better prescribing. Better health.

Medications that are ineffective and potentially harmful

Up-coming webinar on "Addressing medications that are ineffective and potentially harmful for patients with alcohol and other substance use disorders"

Organised by Therapeutics Initiative, Canada

WHEN: Wednesday, January 29th, 2025 at 12:00 PM PST [convert to your local time]

WHERE: This is a free online webinar. After you register you will receive a confirmation email including connection details.

SPEAKER: Dr. Evan Wood, Professor of Medicine, Canada Research Chair in Addiction Medicine, Faculty of Medicine, University of British Columbia.

In this **TI Best Evidence** webinar, Dr. Evan Wood will raise awareness of evidence-based interventions included in a new national guideline for the clinical management of high-risk drinking and alcohol use disorder, highlight the difference between evidence-based and common non-evidence-based interventions (including routine antidepressant use) that impact care of this population, and help participants understand the applicability of these recommendations to persons with other substance use disorders.

Read more

Other news

In the US, opioid-maker Purdue is bankrupt. Its global counterparts make millions

By Madlen Davies, Hristio Boytchev and David Ovalle - September 17, 2024

Full article available at: https://www.theexamination.org/articles/in-the-us-opioid-maker-purdue-is-bankrupt-its-global-counterparts-make-millions

Summarised by Barbara Mintzes

In an in-depth media report published jointly by the Examination and the Washington Post, investigative journalists Davies, Boytchev and Ovalle have highlighted Mundipharma's activities to promote and market opioids. Mundipharma is described as "a group of international companies, that essentially operate as the international counterpart of Purdue Pharma." Mundipharma companies are also owned by the Sackler family and are very much in the business of selling prescription opioids. As Davies and colleagues highlight, "Some of the same tactics used to persuade a generation of American doctors that potent painkillers could be safely prescribed have been used abroad..."

Purdue's aggressive promotion of sales of oxycodone in primary care in the US and Canada has been credited with playing a central role in creating an epidemic of harm from opioid addiction and deaths from overdoses in North America.

In a press release by the US justice department, an FBI official, Steven M. D'Antuono, states that, "Purdue, through greed and violation of the law, prioritized money over the health and well-being of patients…"

Davies and colleagues investigated Mundipharma's activities in countries in Europe, South America, Asia and Australia until mid 2024, and financial reporting from 2020 to 2022. This is after Purdue stopped promoting opioids to US doctors in 2018 due to litigation, and after Purdue went bankrupt in 2019. They note that Mundipharma companies logged an estimated US $2.5 billion in sales in Australia, China and five top European countries from 2020 to 2022. Mundipharma profits of US $531 million over this period were reported in 9 countries requiring financial disclosure, with total profits likely higher. No information was publicly available on dividends to the Sackler family.

Although North America has experienced the highest rate of opioid prescriptions and overdose deaths globally, these have increased elsewhere during the past decade as well. In Sweden, for example, deaths linked to oxycodone, increased tenfold between 2006 and 2022, and in Norway, prescription opioids have become the most common cause of overdose deaths since 2016. Andrew Kolodny, medical director of the Opioid Policy Research Collaboration at Brandeis University is quoted in the article as explaining that this increase has also occurred in Europe and elsewhere globally "because the drug companies are using the same playbook as in the US."

These are some examples of international Mundipharma activities described in this report:

Brazil

Mundipharma provided US $39,000 to the Brazilian Society for the Study of Pain from 2019 to 2023, including payment to Carlos Marcelo de Barros, the president of the society, for an online lecture on pain. De Barros helped write legislation proposed by politician Bia Kicis to standardise pain treatment and bring in specialised training as well as awareness-raising activities.

A Mundipharma video promoting its opioid brand Targin is posted on a Brazilian production company's Youtube page stating the company aims to make 2023 the "year of Targin".

China

A 2019 Associated Press report found that company sales representatives told doctors, "that time-release OxyContin was less addictive than other opioids, pushing large doses of the drugs and, at times, donning white coats to misrepresent themselves as medical professionals to patients." Mundipharma conducted an internal investigation following this report.

Another internal company investigation found that Mundipharma paid doctors to sit on advisory boards as a means of promoting its products, with no clear rationale for selection of advisors, and more than 1000 healthcare workers paid as advisors.

Australia

In 2019, the Australian regulator, the Therapeutic Goods Administration (TGA), fined Mundipharma around US$200,000 for Targin advertising that was deemed to be "misleading, imbalanced and otherwise inaccurate." Mundipharma disagreed with the TGA's interpretation of its advertising messages.

Europe

Mundipharma paid more than US$15 million to healthcare organisations, professional and patient groups in five European countries (including the UK and France) for events, sponsorships and consulting from 2019 to 2021 according to the group Euros for Docs.

In Italy, Mundipharma was accused of paying an anesthesiologist at a public hospital to promote opioids. The company was fined US$44,000 but does not admit liability. The anesthesiologist was also charged but acquitted due to illegal use of wiretapping.

In Germany, Mundipharma funds the German Society for Pain Medicine, which provides training in pain management for clinician and was founded by an ex Mundipharma executive, Harry Kletzko. Harry Kletzko was also vice-president of the German Pain League, a patient group that receives Mundipharma funding. This group's website states that opioids "are usually well tolerated even in long term therapy" and does not mention addiction and overdose among listed side effects.

The article concludes with a quote from Andrea Burden, assistant professor of pharmacoepidemiology at the ETH Zurich university, "We are entering into the same situation in Europe as in the United States 15 years ago…We can't assume we are smarter than Americans here in Europe. If we don't pay attention to the signs and act, we will prove ourselves to be dumber. Much dumber"

Postscript

Perhaps it is not a case of who is smarter or dumber, but how to effectively prevent Mundipharma and other opioid manufacturers from using the same tactics internationally that fuelled the opioid epidemic in North America. With around

600,000 deaths due to overdoses in the US and Canada from the early 2000's to 2022, this is not a minor public health concern.

Davies and colleagues are careful to state throughout that Mundipharma is a set of independently operating companies. One anecdote, however, highlights the fictional side of any separation from the Sackler family and the sales tactics Purdue used in the US. In November 2013, Mortimer Sackler was the director of four Mundipharma companies in Europe. In an email to a German executive, he writes: "I am surprised the sales plan for next year isn't higher. Why the conservatism? The five year plan for Germany is totally unacceptable. What is being done to improve it and put it back on a growth track?...." This email was written in 2013; Purdue's first US conviction for misleading marketing was in 2007.

In Australia, Mundipharma is not a member of Medicines Australia, the national pharmaceutical industry association; in the UK it is not a member of the Association of the British Pharmaceutical Industry (ABPI). In New Zealand, it is not a member of Medicines New Zealand. In Europe, it is not a member of the European Federation of Pharmaceutical Industry Associations (EFPIA). In all these jurisdictions, Mundipharma is therefore not subject to industry self-regulatory transparency about payments to physicians, professional organisations and patient groups. This is a major gap, given the types of promotional activities highlighted in this investigative report. This also highlights the limits of transparency based solely on industry self-regulation, as any company - even a major manufacturer of opioids - can simply opt out.

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Preferences for speed of access versus certainty of the survival benefit of new cancer drugs: a discrete choice experiment

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Summary

Background

The extent to which patients with cancer are willing to accept uncertainty about the clinical benefit of new cancer drugs in exchange for faster access is not known. This study aims to examine preferences for access versus certainty, and to understand factors that influence these preferences.

Methods

A US nationally representative sample of older adults were recruited via Cint, an online platform for survey research, to take part in an online discrete choice experiment. To be eligible, respondents had to self-report some experience with cancer–ie, they themselves, a close friend or a family member, previously or currently diagnosed with cancer. In the experiment, respondents chose between two cancer drugs, conside-

ring five attributes: functional status, life expectancy, certainty of the survival benefit of a new drug, effect of the drug on a surrogate endpoint, and delay in US Food and Drug Administration (FDA) approval time. The first primary outcome was the relative importance of certainty of survival benefit and wait time to respondents. The second primary outcome was willingness to wait for greater certainty of survival benefit, including subgroup analysis by cancer experience, age, education status, race or ethnicity and income. Secondary outcomes were changes in sensitivity to certainty and wait time, depending on the drug's effect on a surrogate endpoint, respondents' functional status, and life expectancy. The study plan was registered with ClinicalTrials.gov, NCT05936632.

Findings

Between July 7 and July 20, 2023, 998 eligible respondents completed the survey. 870 respondents (461 [53%] male, 406 [47%] female, and three [<1%] other) were included in the final analysis. Respondents showed strong preferences for high certainty of survival benefit (coefficient 2·61, 95% CI 2·23 to 2·99), and strong preferences against a 1-year delay in FDA approval time (coefficient -1·04, 95% CI -1·31 to -0·77). Given very low certainty a drug would provide survival benefit (no evidence linking a surrogate endpoint to overall survival), respondents were willing to wait up to 21·68 months (95% CI 17·61 to 25·74) for high certainty (strong evidence) of survival benefit. A drug's effect on a surrogate endpoint had no significant impact on drug choices (coefficient 0·02, 95% CI -0·21 to 0·25). Older respondents (aged ≥55 years), non-White, lower-income (<$40 000 per year) individuals, and those with the lowest life expectancy, were most sensitive to wait time.

Interpretation

Many cancer drugs approved through the FDA's accelerated approval pathway do not offer any survival benefit to patients. In this study, individuals expressed strong preferences for certainty that a cancer drug would offer survival benefit. Some individuals also expressed a higher willingness to wait for greater certainty than would be necessary to assess the survival benefit (over progression-free survival benefit) of most cancer drugs used in the metastatic setting.