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Evaluation of threats to cash flows from the U.S. prescription drug market.

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Année académique 2023-2024
Travail de fin d'études (TFE) en vue d'obtenir le titre de
Intitulé du master en science de gestion
Horaire décalé

Summary

Reception of letters denying access to the American market can be very damaging for a pharmaceutical company. Indeed, such a letter, at best, delays important cash flows and therefore impacts the ability to finance other projects and to meet shareholders expectations. This work, after covering the basic necessary knowledge, considers the sources of risks to the cash flows from the lucrative US market.

As the discussions moves forward, it appears that money, time and politics are at the heart of every potential problem.

Résumé

La réception de lettres refusant l'accès au marché américain peut être très dommageable pour une entreprise pharmaceutique. En effet, une telle lettre, au mieux, retarde d'importants flux de trésorerie et impacte donc la capacité à financer d'autres projets et à répondre aux attentes des actionnaires. Ce travail, après avoir couvert les connaissances de base nécessaires, examine les sources de risques pour les flux de trésorerie du lucratif marché américain. Au fur et à mesure discussions avancent, il semble que l'argent, le temps et la politique soient au cœur de tous les problèmes potentiels.

Foreword

On May 2022, UCB, a publicly traded Belgian pharmaceutical company, announced that the Food and Drug Administration (FDA) had issued a complete response letter for its Biological License Application of Bimekizumab, its latest biological product and expected blockbuster candidate.

The letter indicated that the FDA could not approve the application in its current form and that some issues had to be resolved (UCB, 2022). At this point of time, this letter, at best, delayed access to the lucrative American market and therefore had an impact on the predicted future incoming cash flows. UCB had to review its financial guidance for 2022. Coming out of the COVID-19 pandemic, this letter came as a new challenge in an already complicated situation, that, everyone would have probably preferred to avoid.

The letter could be considered a surprise as the product had already been accepted by European and Japanese authorities. Gossips and rumors started to spread focusing on the exact reason the FDA sent this letter, while other regional health authorities did not seem to have opposition. The theories ranged from reasonable scientific rationale to severely flawed conspiracy theories. In-between the rational and the obviously crazy was a complete spectrum of credible possibilities, which probably deserved considerations.

The initial objective of this work was to assess the possible biases of the FDA, which could lead to sending “scientifically unjustified” complete response letters. As the work went on, it appeared more and more clearly that the problem was not the FDA response letter, but the delaying of the cash flows from the American market. The work was therefore recentered around the factors affecting the risk to those cash flows, as those seem crucial for long-term strategic decisions in the drug manufacturing industry.

In this work, a highly complicated, movie-worth, context involving science, politics, insurances, industrial secrets and lobbying is explored. In this context, the existence of conflicts of interests (disclosed or not) between authors, organizations, publisher, and other possible stakeholders seems ubiquitous shedding doubt on much of the publicly available information.

While French is the most used language for this type of work, the English language has been chosen for one main reason: The translation of American terminology could prove difficult, as literal tradition possibly exists, but the translated terminology could have another meaning in French regulatory language. To maintain a minimum of clarity, the language of the regulatory authority considered was kept.

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List of Accronyms

FDA	Food and Drug Administration
PDUFA	Prescription Drug User Fee Act
IRA	Inflation Reduction Act
EMA	European Medecine Agency
MAGA	Make America Great Again
CRL	Complete Repsonse Letter
RTF	Refuse To File
CMC	Chemistry, Manufacturing and Controls
NDA	New Drug Application
BLA	Biological License Application
AIDS	Acquired Immune Deficiency Syndrome
US	United States
OTC	Over The Counter
CDER	Center for Drug Evaluation and rResearch
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Device and Radiological Health
VA	Veteran Administration
S-CHIP	State-Children's Health Insurance Program

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Introduction

The pharmaceutical industry is the medical industry responsible for the research, development, production and distribution of medication. For a drug to reach a specific regional market, the drug manufacturer must provide sufficient information to that market drug regulating body. Most famous drug regulation institutions are the Food and Drug Administration in the United States and the European Medicine Agency (EMA) in Europe. While the details on the amount of proof needed to obtain a marketing authorization may vary from region to region, it is generally needed to show the product is fit for its intended purpose and can be manufactured safely and consistently.

Roughly speaking, at the end of product development, drug manufacturers prepare files to send to regulatory authorities to obtain the marketing authorization. Those are known as New Drug Application (NDA), for drugs manufactured through chemical processes or Biological License Application (BLA) for drugs produced by living organisms, such as monoclonal antibodies or vaccines. Those applications are reviewed, and, if approved, the marketing authorization is granted.

The approval of the applications are crucial steps in the lifecycle of a new drug. It is the point at which the product can start generating returns on the large research and development investments. In financial terms, it is the point at which positive cash flows can be expected from the drug.

An accurate estimation of the different cash flows is needed for optimal management of a company. It is therefore crucial for a drug manufacturer to have a good view on the expected cash flows and the different factors putting those flows at risk. High risks on important cash flows should be, at the minimum known, and at best controlled to avoid unpleasant surprises.

As will be discussed in this work, one of the most important cash flows is the one coming from the drug sales on the United States market.

The first section of this document covers the basic knowledge necessary for the understanding of the discussions. This section is mainly divided into four parts:

1. The Food and drug administration and a brief history of drug regulation in the United States
2. A brief description of the general drug development process
3. A general description of the United States health care system
4. The importance of the United States market for drug manufacturer

In a second section, the information provided in section 1 is used to discuss a list of potential risks to the cash flows from the United States, and how those risks can be/were mitigated. The risks are considered from the point of view of an non-US pharmaceutical company. Among the considered risks:

1. FDA risks
2. Political risks

Disclaimer

It is not this work objective to enter a moral debate on the role of the pharmaceutical industry in different problems associated with health care industry in general, while it is recognized that completely avoiding the question is difficult. The objective is to evaluate factually the current situation and provide potentially useful information for long-term strategic decision making.

Section 1

Food and drug administration

Role and structure

The food and drug administration (FDA) is a large US federal agency, best known for its role in the regulation of medical drugs in the United States, but also regulating veterinary medicine, cosmetic products, food, tobacco and devices emitting radiations. The human drug is just a part of this large regulatory agency (FDA, 2024). The organization chart of this administration is presented on Figure 1.

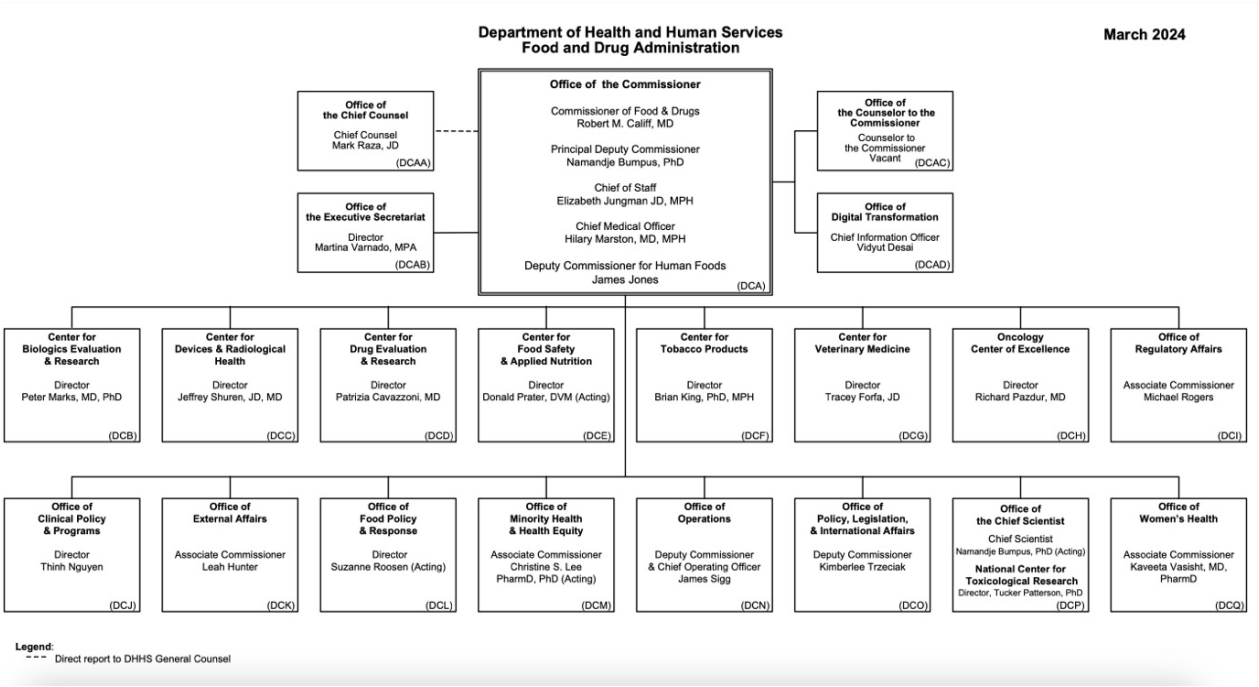

Figure 1 FDA organization chart, in March 2024 (FDA, 2024)

To highlight the importance of the FDA, it is estimated that the about 20% of all US import fall under FDA jurisdiction and that 25 cents on every dollar spent on commodities in the US is spent on an FDA regulated product (Grundke & Moser, 2019).

From an organizational point of view, the FDA is part of the operation division of the United States department of health and human services. The secretary of this department and the FDA commissioner of the FDA (head of the FDA) are both appointed by the president of the United States with approval of the US senate. The overall position of the FDA in the US government is presented on Figure 2.

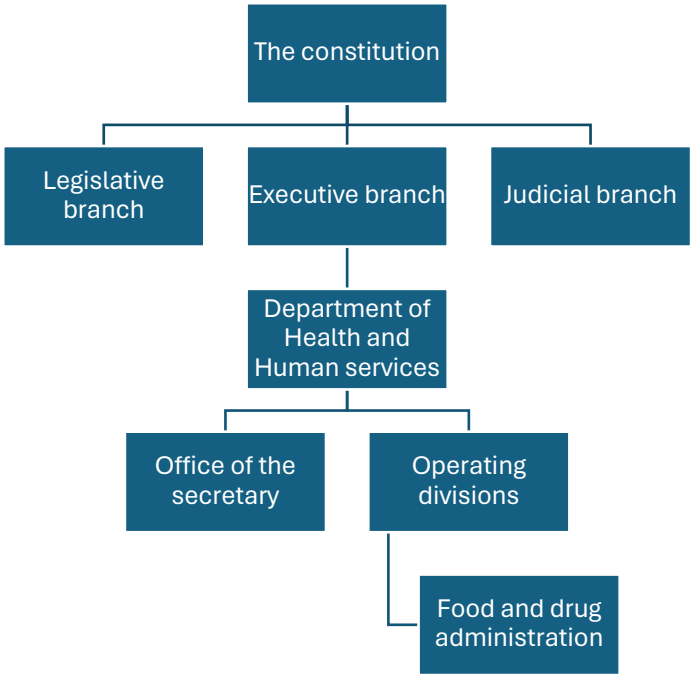

Figure 2 Position of the FDA in a simplified US government organizational chart.

History of drug regulation in the United States

Pre-FDA drug regulation in the United States

Before the 20th century, there was only limited regulation of the drugs manufacture and marketing of drugs, except for the vaccine act of 1813.

1883 - The Division of chemistry begins conducting research into the adulteration and misbranding of food and drugs on the American.

1902 - The Biological Control act is passed after the death of multiple children linked to a tetanus-contaminated anti-toxin. This Act established a board to oversee the implementation of regulations of biological products. It also mandated that all products be labeled accurately with the name of the product, the address of the manufacturer and its license number. The punishment for the violation of this law was a fine of up to $500 (1902 dollars) or up to a year in prison. While this may seem light in terms of regulation, it paved the way for further actions.

1906 - Pure Food and Drug Act which prohibits, under penalty of seizure of goods, the interstate transport of food that had been "adulterated". The Act applied similar penalties to the interstate marketing of "adulterated" drugs, in which the "standard of strength, quality, or purity" of the active ingredient was not either stated clearly on the label or listed in the United States Pharmacopeia or the National Formulary. The pure Food and Drug Act will later on give birth to the FDA.

Sulfanimide elixir, Food drug and cosmetic act

1937 - The Sulfanilamide elixir disaster led to the death of about 100 patients. The manufacturer had developed a liquid form of the product and tested of fragrance, color and taste before selling it. (Ballentine, 1981). The solvent in this liquid form was diethylene glycol, which we now use as anti-freeze and know to be highly toxic. Despite the clearly deathly effects of the drug, the only option the FDA had was to forbid the drug based on a technicality.

1938 - The Federal Food, Drug, and Cosmetic Act is signed into law. This law increased federal regulatory authority over drugs by mandating a pre-market review of the safety of all new drugs, as well as banning false therapeutic claims in drug labeling without requiring that the FDA prove fraudulent intent.

Thalidomide scandal and the Kefauver-Harris amendment

1957 - Thalidomide is first commercialized in West-Germany for multiple indications, including reduction of nausea in pregnant women. The use of Thalidomide in pregnant women led to complications in about 10 000 pregnancies, with 40% resulting in the death of the child. Babies surviving birth, were generally afflicted with severe physical deformations. In the United States, thalidomide was never marketed. During review, Frances Kelsey, a physician tasked with examining the Thalidomide file had concerns about the safety of the product.

1961 - The drug is taken off the market in Europe.

The scandal generated major changes in the way health authorities considered drug. In

1962 - The Kefauver-Harris amendment to the Food and Cosmetic act is passed. This amendment fundamentally changed the role and scope of the FDA. It prohibited drug manufacturer from marketing drugs without its explicit approval. This amendment also required manufacturer to obtain approval before starting the human experiment part of the drug development. The human experiments were split in 4 different phases that are now known as Phase I, II, and III clinical trial, and the less known phase IV trials, which are post-approval studies or the pharmaco-vigilance phase. In Europe, this led to the 1965 European directive 65/65/EEC1 and the Medicine Act in the United Kingdom in 1968.

The drug lag debate and the prescription drug user fee act

A direct consequence of the Kefauver-Harris amendment is the augmentation of the delays between submission and commercialization of new drugs on the US market. This led to a lengthy “Drug lag debate”. One “free market” side claimed that the delays in reviewing life-saving drugs cost more lives than the marketing of potentially dangerous drugs would. In addition, the regulatory costs were claimed to be a tax on patient.

In the early eighties, the AIDS epidemic and patient groups pressured the FDA to accelerate the review of the drug submission (Daemmrich, 2003).

1992 - The Prescription Drug User Fee Act (PDUFA) allows the FDA to collect fees from drug manufacturer for the review process. It is the solution found to put an end to the drug lag debate. Three types of fees are collected in the original version of the PDUFA:

1. Application fees, paid by the manufacturer for the review of each NDA or BLA
2. Establishment fees paid by the manufacturer for the facilities
3. Product fees: an annual fee for every product covered by the PDUFA

This act is renewed every 5 years. Under PDUFA I (the original 1992 act), the FDA was required to review 90% of standard applications within 12 months and to provide one of three written responses[1]:

1. Non-approvable letter: the application does not meet the quality standard of the FDA
2. Approvable letter: the filing can be approved provided some deficiencies and question are answered appropriately
3. Approval letter which grants access to market.

1999[2] - In the end of the 90's, it was estimated that about a third of American were experiencing chronic pain. This led to an increased use of opioid based pain killers. In short, this led to over-use of opioids, and opiate addiction and a severe increase in the number of deaths related to opioid overdose. (Wikipedia: Opioid crisis, 2025). It widely accepted that the main reason fo this crisis is the aggressive marketing of opioids by the pharmaceutical industry, with the most infamous being Purdue Pharma. It is laso considered that the FDA failed to enforce most basic regulatory standards. As example, After noticing a clinically unjustifiable increase in the prescription of insulin, the FDA called. For an advisory committee meeting. Out of the 10 experts invited to this meeting, 8 had connection to the pharmaceutical industry (among which Purdue pharma). The result of this meeting was a vote against the narrowing of the indication for prescription opioid. FDA missed the opportunity to kill this epidemic early on.. In addition, the two principal FDA reviewer for the extension of the use of Purdue Oxycodone took position at Purdue after leaving the FDA[3] (Kolodny, 220).

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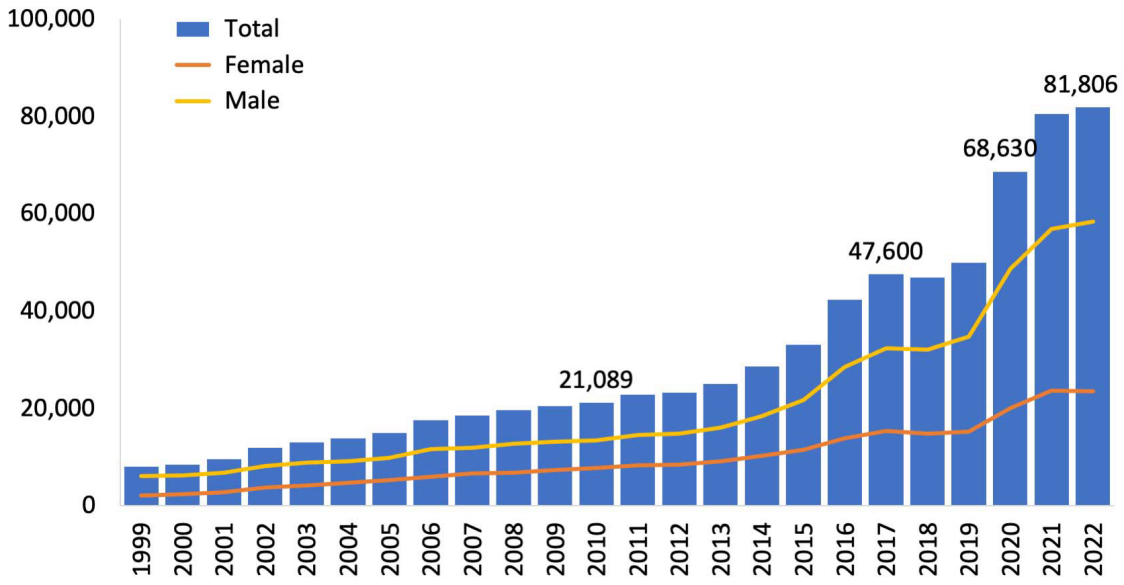
[1] The three letters were current procedure at the time of PDUFA I. The apparent confusion in the naming of the letters led to changes and to the use of Complete Response Letters.

[2] Most information relates to the late 90's as start period for the opioid cris.

[3] As suspect as it is, maybe Purdue Pharma could have been the only place to hire them after such a fiasco.



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

Figure 3 US Overdose death involving any opioid. Number Among All Ages, by sex (Wikipedia: Opioid crisis, 2025)

2009 – Staring in 2019 and going on after 2019, the cost of insulin products (for which there is a limited of provider for the United States) has almost or more than tripled. This generated scandal because insulin is a live-saving drugs that patients cannot afford not to take (see Figure 4).

2019 – COVID-19 hit the US as well as the rest of the planet, in one of the major recent health crisis.

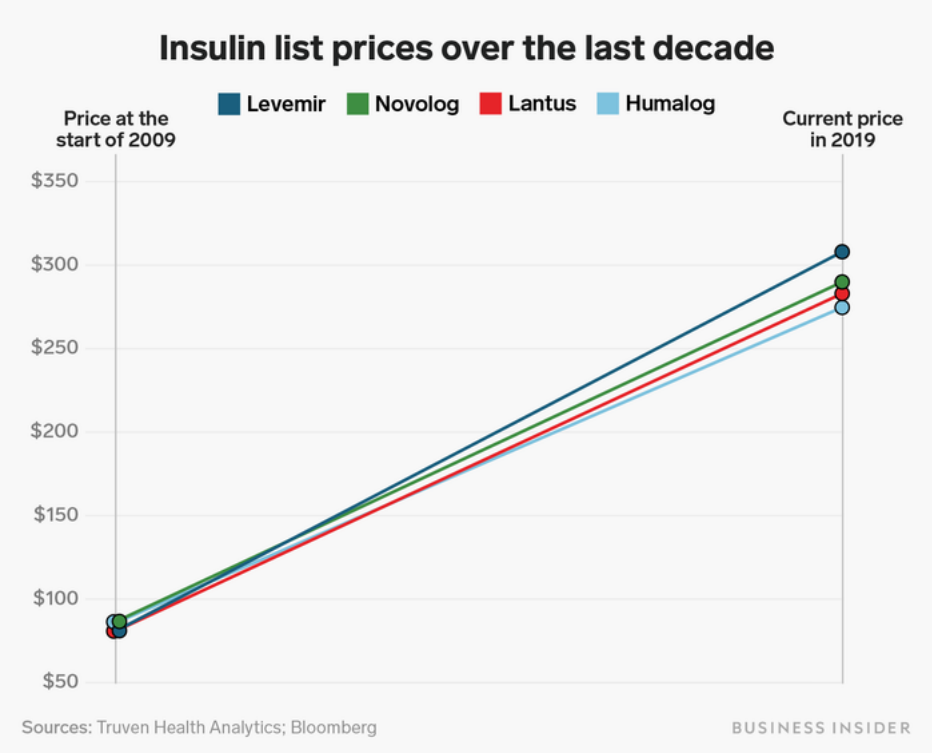


Figure 4 Insulin prices between 2009 and 2019. Prices for 10 mL

Overview of the drug development process

The drug development process is a complicated process and is not the scope of this document. However, a minimum understanding of the process is required to follow and understan the discussions.

According to the FDA website, the drug development process contains 5 steps:

1. Research and development: the laboratory works necessary to identify potential candidates.
2. Preclinical research: laboratory and animal testing to answer basic safety questions
3. Clinical research: test of safety and effectiveness on human subjects
4. FDA review: FDA review teams thoroughly examine all the submitted data related to the drug or device and make a decision to approve or not to approve it
5. Post-marketing safety monitoring: FDA monitors all drug and device safety once products are available for use by the public.

In parallel to those activities, processes to produce the drug must be developed, along with the tools necessary for the process monitoring and quality control. Those activities are known as Chemistry, Manufacturing and Control (CMC) activities.

It may not be evident from the, but this development process is takes a long time and also costs a lot of money. Debates exists on the actual cost of development of a drug, but common

estimates, considering the costs of drugs not making it to the market for any reasons are around a billion dollars.

FDA advisory committees

The FDA convenes advisory committees to provide external scientific expertise and support for the administration decision, e.g. for the evaluation of new, drugs, new indications and medical devices.

The committees are composed of individuals have in recognized expertise and technical skills in the field. Details on the composition, voting rights and conflicts of interests in advisory committee can be found in the related FDA guidance for industry, and will be further discussed in another paragraph (Food and Drug Administration, 1998)

Submission process

There are two main refusal letters a filing company can receive:

1. A refuse to file letter (RTF)
2. Complete response letters (CRL)

Refuse to file letter

Refuse to file letter (RTF) is an indication that the file, as submitted does not meet the minimum standard of quality to be reviewed. FDA does not disclose content of the RTF If the company receiving is public, the consequences of a RTF letters can be disastrous. Refuse to file letters are rare and impact about 4% of the new applications between 2008 and 2017. About 85% of the RTF were not disclosed, and in total, only about 5% of the reasons were disclosed (Harinder , Mukher, Sigelman, & Temple, 2021).

Complete response letter

The reception of CRL is also. CRL indicate that the FDA refuses to grant the marketing authorization for the product, as proposed. As for the RTF, FDA does not disclose the content of the CRL, while the EMA does. The manufacturer may communicate on the reception of the letters based on US laws requiring communication of significant event to investors. As for the RTF, the reasons are generally not accurately communicated, over-representing manufacturing issues and underrepresenting clinical safety and efficacy ones (Lurie, et al., 2015).

Importance of time

The pharmaceutical industry, as many others is relying on patents to protect innovation. The duration of the patent is 20 years. Commonly, patents are submitted when first human trials start, and, at the end of development and the marketing authorization, 8 years of that patent are already spent, leaving a limited time before the generics and biosimilar become available. There

are however, pathways and FDA process that can allow an exclusivity period up to 14 years after approval.

It is important for drug manufacturers to accelerate their development and optimize their launch activities to maximize the time spent on the maturity section of the product lifecycle curve, before the generic drugs and biosimilar[4] arrive on market (see Figure 5). As will be discussed, much of the lobbying of the pharmaceutical industry targets the minimization of development costs and development time, to reach the maturity phase sooner.

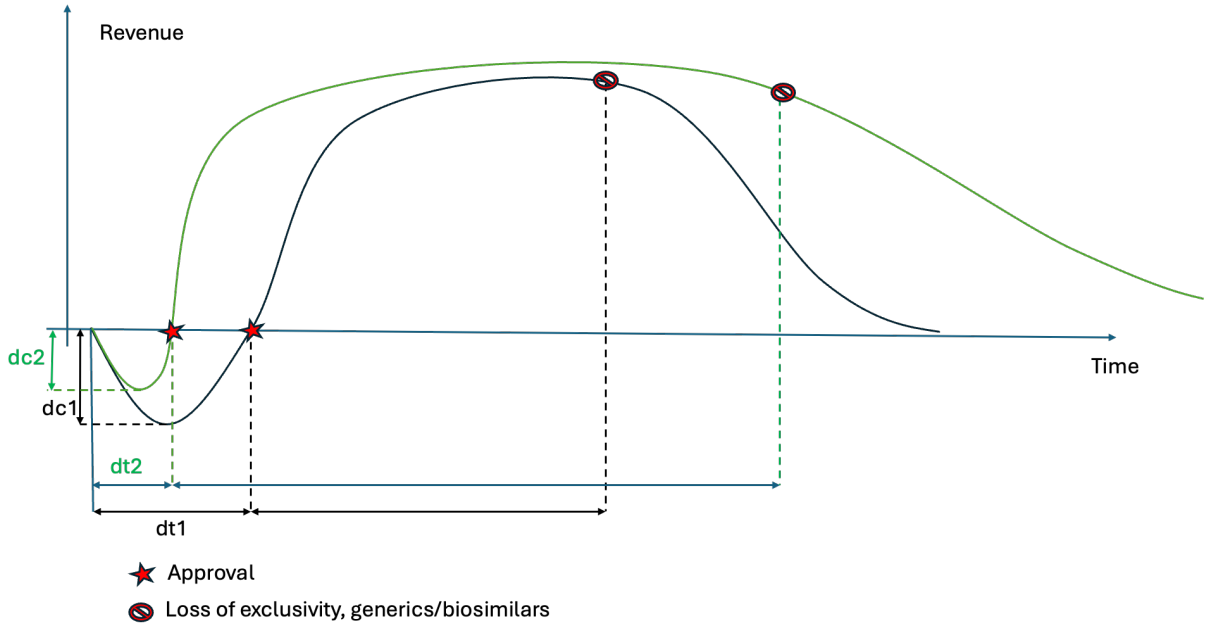


Figure 5: Lifecycle curve of two hypothetical product. Green curve is the most favorable situations. "dc" are development costs and "dt" development times

American health care system

In terms of health care systems, the United States distinguish themselves by being the only developed country without a single payer system[5]. This leads to a complex healthcare system with many intermediates and possibilities, including the government, the insurance companies, the health care provider, the employers, the patient and so on. The principal options for health insurance in the US are represented on Figure 6. These are the possibilities to receive health care.

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[4] Generics and biosimilar are "copies" of an original brand name drug. Those are less expansive products coming on the market after the expiration of the exclusivity period of the original drug.

[5] According to Wikipedia: "*A single payer is a type of universal health care in which the costs of essential health care for all residents are covered by a single public system (hence "single-payer").* (Wikipedia: Single-payer healthcare, Single-payer healthcare, 2024)

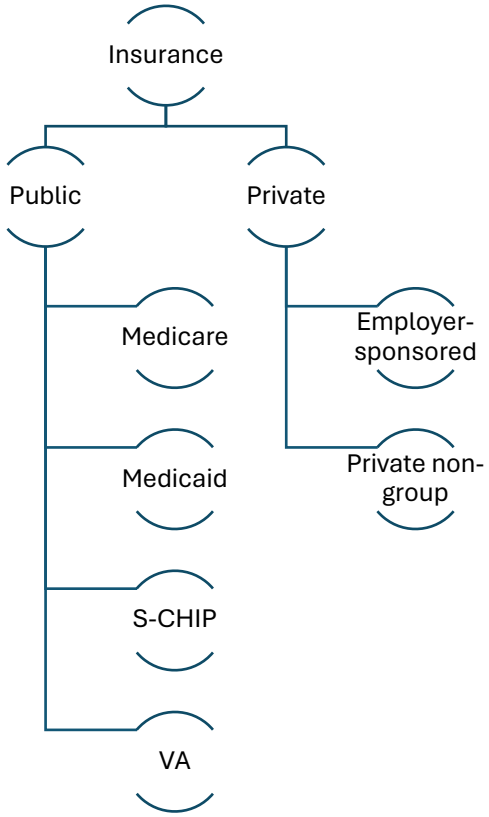

Figure 6: US health insurance options

The public insurance programs presented on Figure 6 are:

- Medicare: A federal program covering the aged over 65 and some others with specific disabilities. Medicare is managed at the federal level and is a single payer system financed through taxes, payroll taxes, shared by employer and employee, and individual contributions in some specific cases. More details are provided on Medicare in further sections as it is central to some further discussions.
- Medicaid: A state administered program designed for the low income and disabled. It must also cover poor pregnant women, elderly and disabled. It is financed through state and federal taxes. The Affordable Care Act (aka "ObamaCare") expanded the Medicaid coverage (among other things).
- S-CHIP: State Children's Health Insurance Program. This program is a state-run program for families that make too much money to qualify for Medicaid.
- VA is the Veteran Administration insurance plan. Health care is provided at very low cost to veteran in VA-owned hospitals and clinics. It is federally funded.

The private insurance programs are either employer sponsored (whether this employer is public or private) and paid by both the employer and the employee. Individual insurances are paid by individuals, e.g. self-employed individuals.

Now, in all this, where do the drug manufacturer fit in? Another graphical representation (see Figure 7) represent the money flows from and two the different stakeholders. Drugs are generally sold to wholsalers (included in the Health care provider box).

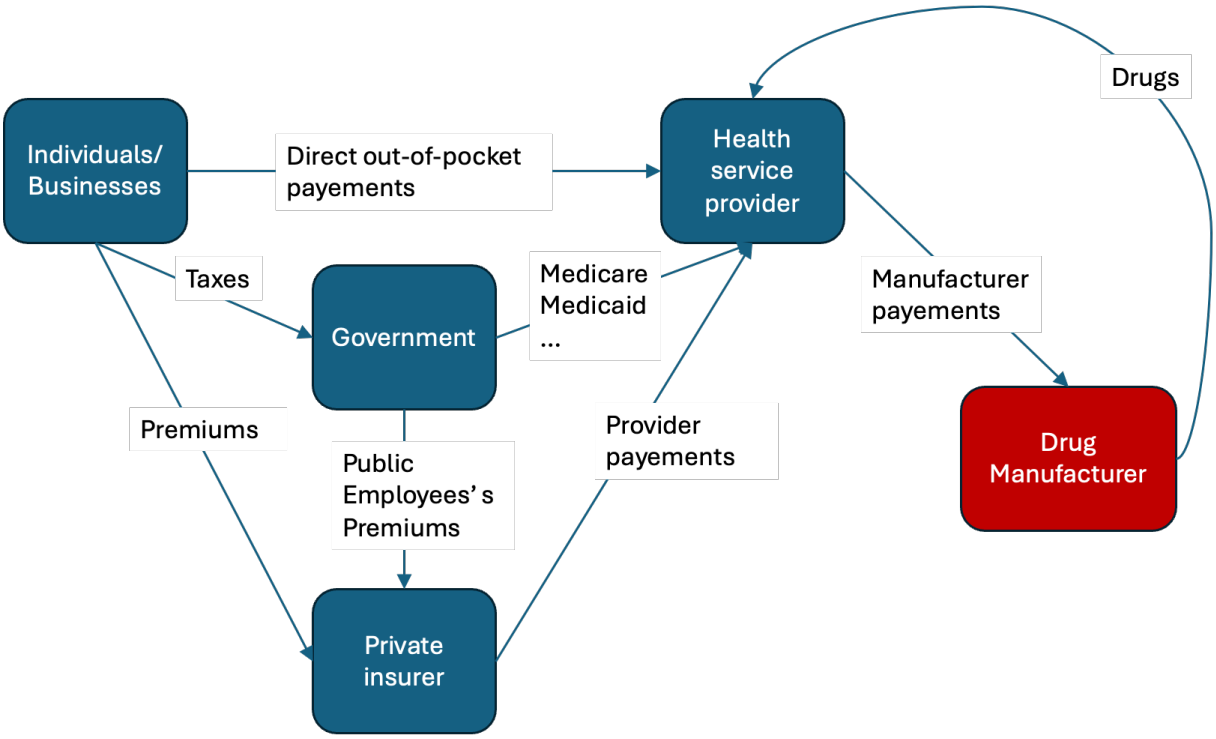

Figure 7 Simplified representation of the US health care system. Adapted from (Chua, 2006)

Medicare

The Medicare is a federal health care systems providing health coverage for US citizens over 65 years old, which represents about million patients, as well as some other patients with specific disabilities. Medicare is the country's biggest insurance program as it covers almost all retired Americans. The Medicare program has four different parts, covering different categories of health care. Those parts are represented on

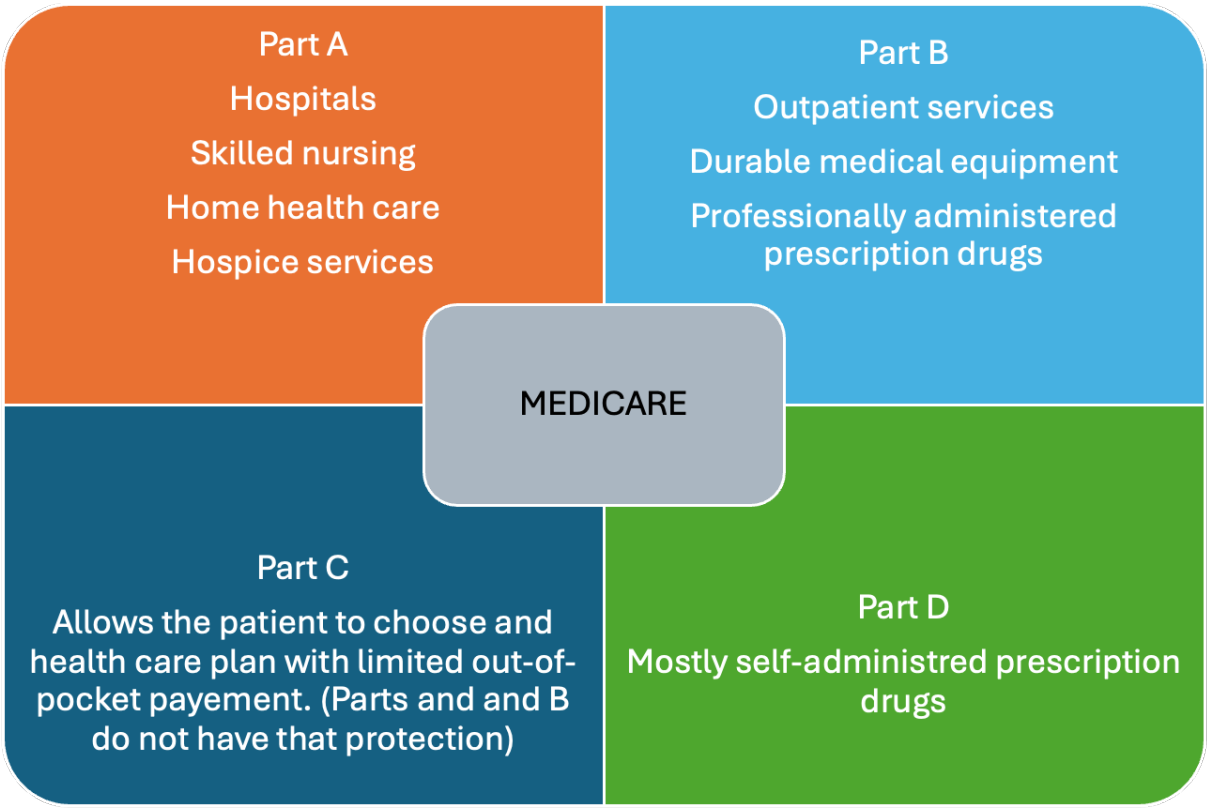

Figure 8: Coverage offered by the different part of Medicare (adapted form (Wikipedia: Medicare (United States), 2024)

Importance of the United States market

Approval of a new drug is a key step in a pharmaceutical product lifecycle. It is the point at which a drug can start generating returns. Usually, approval is first sought on the markets that can provide the most important returns. Those are markets countries in rich regions of the world such as:

- The United States
- Europe (region under EMA regulation)
- Japan

In addition, those three countries have at least partially harmonized their requirements, making the set-up of submissions easier.

In terms of population, the region of Europe under EMA regulation is larger than the US, and both are larger than Japan. Which would make Europe, the a priori, main target for a marketing authorization, followed by the United States and finally, Japan.

However, generally the drugs are allowed on the European market after the Us market for multiple reasons

1. Review times are slightly higher in Europe (about 60 days)

2. The FDA grants the marketing for the 50 states simultaneously, while the CHMP provides an opinion to the European commission. Sixty days later, the European commission's grants the authorization to start negotiations which each member state. In term of delays, the US market is more interesting.
3. Because of the particularities of the US health care system, the prices than can be asked on the US market are much higher than the ones possible in Europe. Prices set in the US could be presented as benchmark prices for negotiation with the Europeans countries. (Joppi, Bertele, Vannini, Garattini, & Banzi, 2020)

Prices of drugs in the US

A recent report from the Rand corporation (Mulcahy, et al., 2021) highlighted the differences between the prices in the US and other well-off countries.

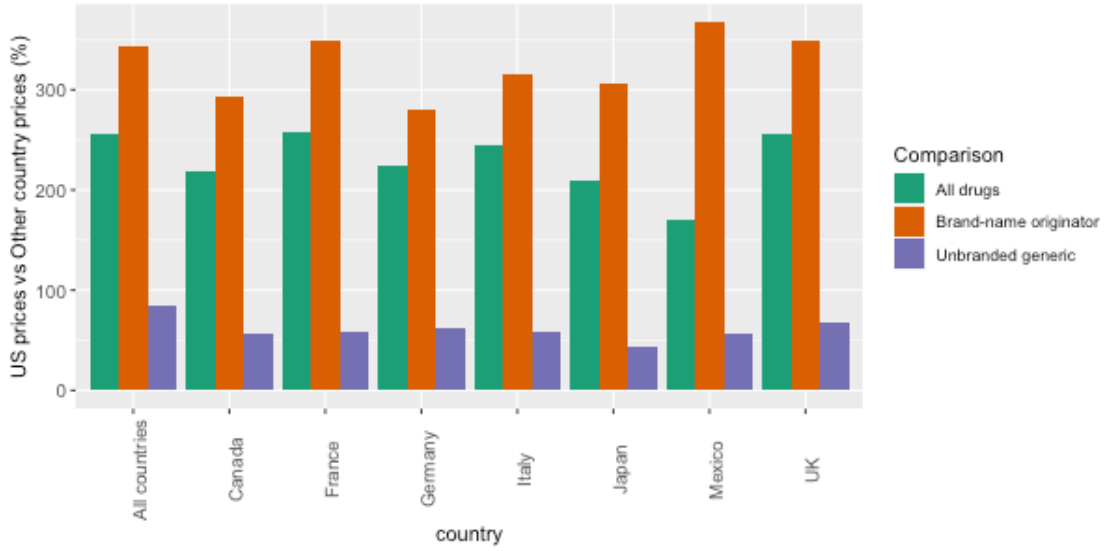

Figure 9: Us prices relative to comparative countries (reproduced from)

The authors recognize that differences in the absolute numbers can appear when methodological aspects of the analysis are change, nevertheless, all methodologies tested led to the same conclusion, Americans pay more for their prescription drugs. For all drugs combined, the same report indicates that, while accounting for about 24% of the volume of drug sold, the US market accounts for 58.4% of the share of sales. It is also stated that it is not linked to American consuming larger number of drugs, nor different types of drugs.

Because of multiple reasons, among which the weak bargaining position generated by the US health care system, the US market is seen as a gold by pharmaceutical industries and other intermediaries.

The inflation reduction act

The inflation reduction act (IRA) was passed by the Biden administration. It aims at reducing inflation and has two main panel. One panel concern reducing energy prices and transitioning towards renewable energies. The second concerns the cost of health care. Numerous publications have already been devoted to the subject (Drozdowsky & Kachinsky-Bye, 2023; Shah, Meyers, Kirby, & Chen, Navigating the Inflation Reduction Act's Impact on Drug Pricing and Innovation, 2023; Shah, Meyers, Kirby, Chen, & Van Couwenberghe, The Inflation Reduction Act's Ripple Effects on the US Health Care Ecosystem, 2024). As has been seen in th history section, major changes in the health regulation is often associated with major crises. The IRA may be the major change triggered by the COVID-19/Opioid/Insulin[6] crises. A short summary is proposed in the next paragraphs.

Drug Prices negotiations

Under the IRA, Medicare is now allowed to negotiate drug prices directly with pharmaceutical, biopharmaceutical and biotechnology companies. To be eligible for negotiation, the drug must:

1. Be in the top of the list
2. Lack a generic or biosimilar (note that authorized generics[7] are not taken into considerations, otherwise, the loophole would be too obvious)
3. Have been on the market for a certain number of years (7 for the small molecules, 11 for the biologics)

The number of drugs opened for negotiation is also expected to increase with time, from 10 drugs in 2026 to 15 in 2027 and 2028 and 20 in 2029. In addition, manufacturer would not be able to walk away from negotiations without risking their license on the product under negotiation and other products on the US market.

Medicare drug rebates

Another provision on the drug prices is the Medicare Inflation Rebate. This provision states that the manufacturer, selling drugs covered Medicare part D should pay a rebate to the government if the prices of the drugs has increase faster than the inflation.

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[6] The Inflation Reduction Act alos caps the cost of insulin.

[7] Authorized generics are generic drugs which is the same as the brand name, as it is manufactured by, or with permission of the Brand name company. It is sold under the same license as the brand name drug. (Latwal & Chandra, 2021)

Section 2

This section proposes to describe the different solutions that were found by the pharmaceutical industry to mitigate risks, and list the risks that needs or will need to be considered. Itappears that the pharmaceutical industry and its lobbyist have done very good work far upstream to reduce risks and that most probably solutions are already in place.

Consequences of the prescription drug user fee act

As described, the Kefauver-Harris amendment was a real change, which led to delays in approval. This delay did not only delay access to the drug for the patient, but also delayed marketing authorization and therefore the cash flows. The 1992 PDUFA lead to faster NDA and BLA approval, which was its target.

There is however a catch:

1. The act, as well as other congressional decisions, led to the FDA being funded at about 70% by the industry it is supposed to regulate.
2. This puts the FDA in a weak bargaining position for the discussions for the renewal of the act, which takes place every five years.

Each successive PDUFA, lead to changes in scope of the fees, evidentiary standards, approval path (creation of more and more type of faster alternative development paths) and so on. A detailed account of the different changes can be found in the literature (Mitchell, Trivedi, & Bach, 2022).

Among the changes, the scope of the fees has been broadened to cover other type of activities, such as the post-approval monitoring or activities related to the review of pre-clinical. Also, between PDUFA I and 2021, the fees associated with a application went from $179,000 to more than $2,875,000. This is however balanced by the reduction of the evidentiary standard. Indeed, PDUFA II reduced the number of required phase III trials, from two, to one. Median expense related to a phase III trial is reported around $19 million, ranging from $2 million to $347 million (Mullard, 2018). In addition, the duration of a phase III trial lasts between 1 to 4 years (Abbvie, 2024)[8]. The observed increase in user fees is a minor detail compared to the gain

[8] This reference is the Website of Abbvie, a major drug manufacturer. This website may have an interest, for strategic purpose in communicating inflated duration for clinical trials. However, even if those estimates are cut in hals, the gain is still significant.

generated by the reduction of necessary evidence to gain approval from two to one phase III trial.

Political stability

On one hand, most of the potentially significant decision that would affect the pharmaceutical industry in general is likely going to com have a political origin. A certain level of stability in the regulation is needed for long term decision making. On the other hand, drug development takes about 8-12 years. Which is equivalent to 2-3 presidential term, and possibly 6 possibilities of changes in the senate and the congress. It is therefore worthwhile to have influence on both parties and to maintain a certain predictability of the political decision.

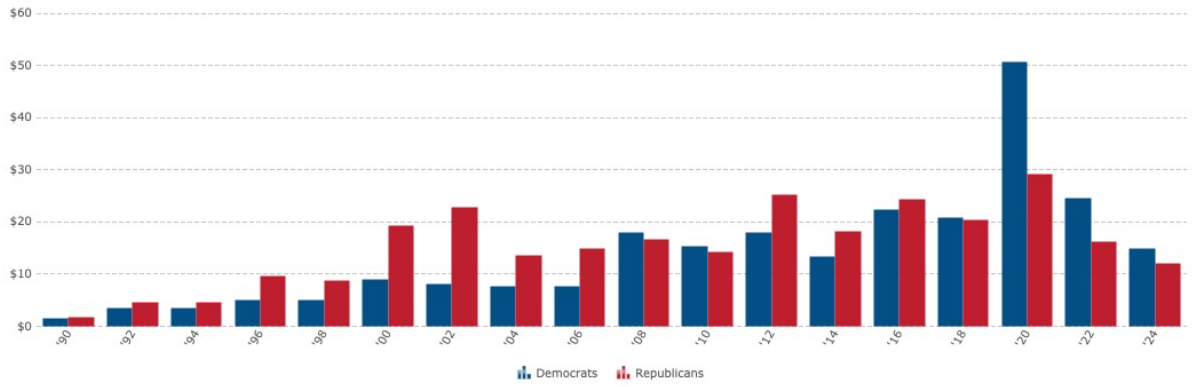

Figure 10: Overall contribution of the pharmaceutical industry of affiliated organization to political parties (Opensecrets: Pharmaceuticals / Health Products Summary, 2024).

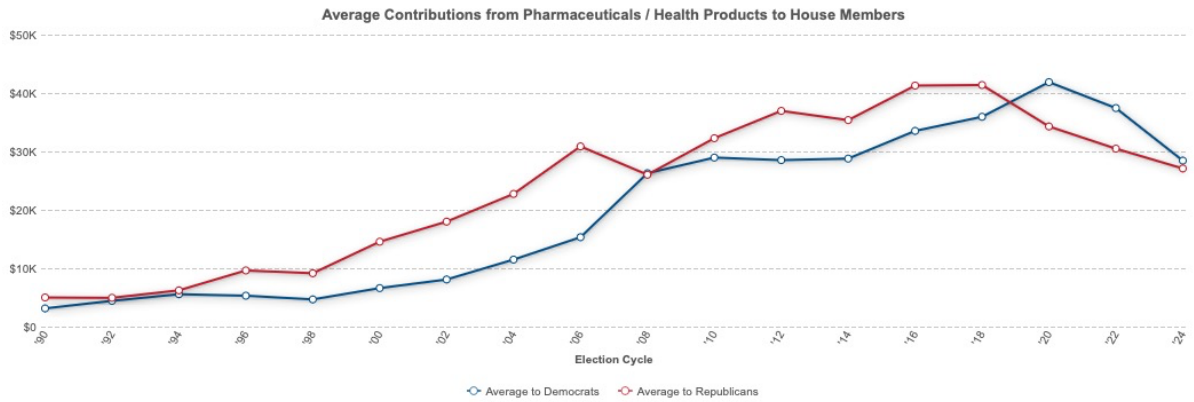

Figure 11 Average contribution from pharmaceuticals/Health product to house members (Opensecrets: Pharmaceuticals / Health Products Summary, 2024)

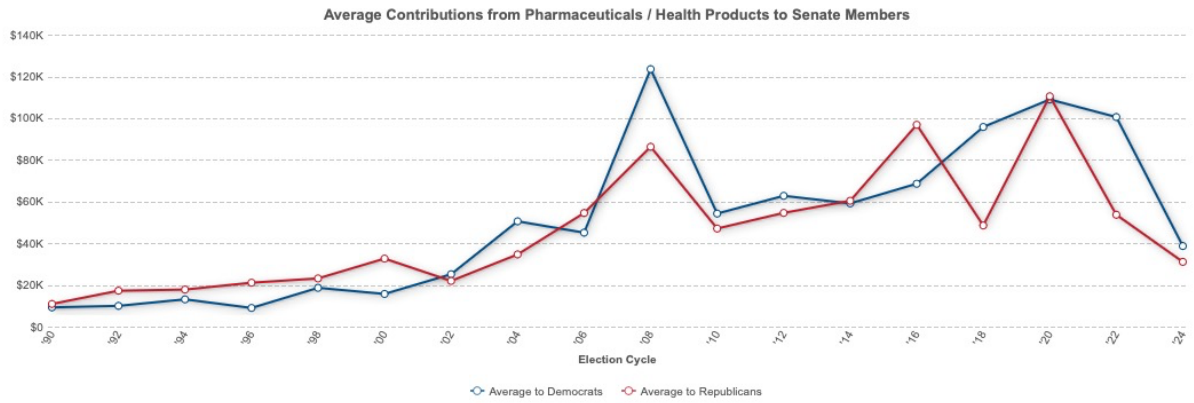

Figure 12: Average contribution from pharmaceuticals/Health product to senate members (Opensecrets: Pharmaceuticals / Health Products Summary, 2024)

An unpredictable candidate could, for instance decide that PDUFA is not renewed, and FDA is financed through public funding and decide to cap drug pricing, which would probably be a huge blow to the industry.

The predictability of the candidate may be the reason the industry favored the democratic candidates in 2020. During Donald Trump's term (from 2016 to 2020), the FDA had different 5 different commissioners. That is more than any term from any previous presidency and not an indicator of consistency or continuity.

Considering the current presidential election, Joe Biden is far in front of former republican candidate Nicky Haley, herself in front of Donald Trump.

Other prominent MAGA figures have very low pharmaceutical industry funding (Marjorie Taylor Green: $3886, Matt Gaetz: $4499) compared to the top 30 beneficiaries (> $100,000, each).

All this indicates that the US market is far from an hostile environment for drug manufacturer. These are however global numbers. A single manufacturer still must be aware of potential existing risks, specific to its own situation. For instance, the manufacturer could be located outside the US, leading to risks of regulatory protectionism. The product could have specificities making the access to the market difficult.

Regulatory protectionism

Tariffs and quotas are ways to protect a domestic market from what can be viewed as excessive import of goods from abroad. However, those are relatively controlled by international law. Another way to protect a domestic market from imports is by regulatory protectionism.

Regulatory protectionisms[9] is the use of regulatory policy to discriminate against foreign firms in a way that is not necessary to achieve a legitimate non-protectionist objective. In their 2013 paper, Watson & James indicate that regulatory protectionism has been a growing problem in the United States (Watson & James, 2013). The authors provide examples, in case studies, which mostly concerns food, tobacco and motor vehicles. No cases about pharmaceutical drug are presented. However, food and tobacco, as pharmaceutical drugs are regulated by the FDA. Not only is regulatory protectionism suspected form the example here above, it is also embedded in the Food Drug and Cosmetic act. Section 801(a) of this act states that for domestic product, FDA needs to prove a violation to deny access to the US market. In the case of imports, the FDA has the authority to refuse shipment that only appears to violate a certain us product standard. This leaves quite a room for FDA protectionist action. As shown by Figure 13, this room is being used as control and refusal appear to significantly increase when the US economy weakens (Grundke & Moser, 2019). Again, the complete scope of the FDA should not be forgotten, and most of those inspection and refusal concern food product.

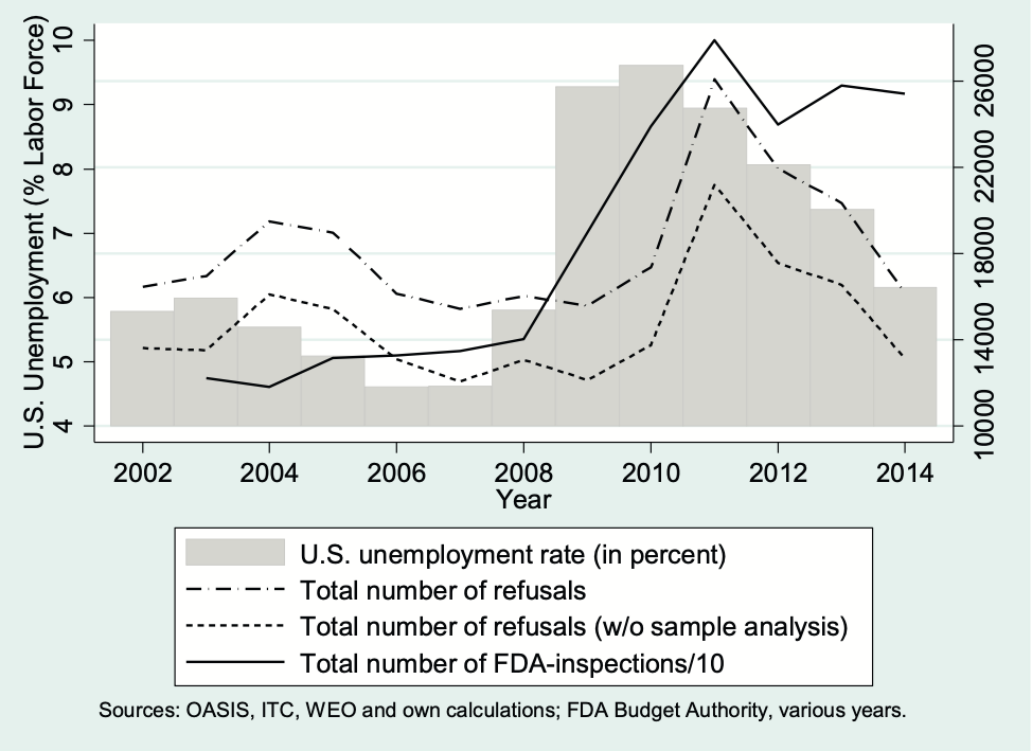

Figure 13: US unemployment rate, import refusal and FDA inspection (Grundke & Moser, 2019)

[9] Protectionism is defined as a form of political privilege that grants a competitive advantage to domestic producer over their foreign counterpart.

Advisory committees

Advisory committees are expected to be independent from the FDA, and therefore free from the administration inherent biases[10]. In her 2014 paper, Genevieve Pham Kanter discussed the financial conflicts of interest in FDA advisory committees. One of the paper's conclusions is that committee members who serve on advisory board for sponsoring firm a particularly strong pro-sponsor bias. This would make sense, not only in the hypothesis of a financial conflict, but also simply if we consider those expert stick to their initial opinion. The paper also indicates a strong sponsor-favorable bias from voting members with strong financial ties to the sponsor[11] (Pham-Kanter, 2014). This information does not seem to imply a risk to the manufacturer.

However, it should be noted that, according to the United States Code, non-US citizens cannot be appointed to FDA advisory committees. (US Congress).

It would make sense that, if a bias exists in the FDA advisory committees, it would be pro-American, as on average, one should probably expect American citizen to have pro-American interests. Considering both from historic US economic protectionism and potentially biased advisory committees, a risk appears for non-US companies.

It appears however that:

- The number of advisory committee advice required by the FDA has been dropping in the last few years
- The FDA tends to be more favorable to approval than the advisory committees.

Nature of the product

The nature of the drug or product that the manufacturer proposes to the FDA can have a major influence on the risks. Three situations are proposed:

- Birth control
- Novelty medical devices. (Jarvie & Haberkorn, 2023)
- Target population
- Type of product

Case of birth control

This type of health care has been under constant popular and political pressure. From its submission and approval in 1999, levonorgestrel (commonly known as plan B or morning after

[10] In all logic, FDA should be considered biased against the pharmaceutical industry. After all, the administration is born from the need of a minimum control of the manufacturer, as they were no longer trustworthy when it came to patient interest. As will be discussed later, this logic may no longer hold.

[11] Members with strong financial ties the sponsor may be allowed to vote under certain conditions.

pill) is approved as a prescription drug by the FDA. In 2001 From this date on, a seeming never ending series of petition and lawsuits have been filed for the over-the-counter access to the drug. In 2013, the drug is made available OTC for everyone, without age limitations (until further notice). This whole process took 14 years, with the generic drug appearing on the market in 2009 (Sifferlin, 2013).

In a more recent case, a federal judge in Texas ordered a hold on the FDA approval of mifepristone, an abortion medication. Another federal judge ruled against this first hold request, leading to a complicated legal battle likely to end in front of the conservative supreme court (Jarvie & Haberkorn, 2023).

Novelty drug device

In a 2015 paper, it is hypothesized that the FDA is biased against new technology. This is valid especially in the world of medical devices. When a device is proposed, the FDA assign the device to a class. The class defines the level of validation that is required.

1. Class I medical devices can go right to market so long as the manufacturer observes certain quality manufacturing practices.
2. Class II devices must go through a modest FDA review to determine whether the device is in fact "substantially equivalent" to existing devices. In a sense, this is similar to a generic drug pathway. The manufacturer doesn't have to re-prove the fundamental safety and effectiveness of the device type.
3. Class III devices must be proven safe and effective through a much more rigorous premarket approval process that requires substantial clinical trials.

According to Thompson, when a device is new (in the sense that no such devices has been previously approved by the FDA) it is automatically assigned a class III. The issue is that the De Novo process[12] can be time consuming. One of the worst case example is the one of a device treating mosquito bite related itches with transcutaneous piezoelectric stimulator. IN this case, the De Novo process too 48 months, which is only the anegncy review time, and does not include file preparation by the applicant.

Target population

As discussed earlier, Medicare is the federal plan created to provide insurance to, mostly, retired Americans. In its healthcare part, the IRA gives more negotiation power to Medicare. One

[12] The De Novo process is the FDA process by which a reclassification of a class III medical device to a class I or II device (FDA.gov, 2024)

should consider the risk to the cash flows for drugs targeting American citizens covered by Medicare.

Drug types

The different provisions in the IRA have consequences on the type of product that may be impacted. The most impacted product will likely be small molecule. Not only will short molecule be subject 4 years before the biologic, but the small molecules are also generally self-administered (under the form of pills or tablets), while biologics are still most commonly injectables that have to be administered by health care professionals. This makes them covered by Medicare part B, which is not impacted by the IRA rebates.

Review time (again)

The successive PDUFA have almost obtained full control over the review time (not the review outcome). According to PDUFA I, 90 % of standard reviews should be performed in 12 months. According to PDUFA II, this time is reduced to 10 months. One should ensure that one does not end up in the 10% of delayed submission. As discussed earlier, having a too novel technology may be a problem. In his 2002 paper, Daniel Carpenter studied the factors affecting review time. Among those, two factor pop-up. The representation of the disease to the public, measured as the number and size of support or patient groups. This can explain the multiplication of disease awareness day/week/month, getting diseases the public to one disease or another could apparently increase popular pressure on the FDA and accelerate the review.

Conclusions

The topic considered in this work started as the analysis of the potential FDA biases when it comes to drug application approval. It was triggered by the turmoil generated by the reception of a complete response letter by UCB in 2022. This topic shifted to the evaluation of risks to the cash flows from the United States market, as the cash flows were perceived as the true problem-generating factor after the complete response letter reception.

This document quickly goes through FDA history and a description of the US health care system, as all is needed to start to obtain a better view of this highly complex situation.

It appeared quite rapidly that the pharmaceutical lobbyist worked a lot to defend the interests of their clients, and did it well. Successive renewal of the prescription drug user fee act tended to serve the industry's interest. While this almost guarantees stability for the industry, individual factor can still be considered.

Going through the history of the FDA and health care in the US in general, one cannot help but notice that every important health crisis was met with an important change in regulations.

In that sense, the Biden's administration Inflation Reduction act may be the reaction to the multiple crises that took place this century, from the opioid epidemic to COVID-19, through the insulin pricing scandal. On this last point, the pharmaceutical may have stretched its luck too far, as for the first time, the inflation reduction act significantly tackles the drug pricing issue, which will directly impact the manufacturer. It is likely that the industry will adapt, and that a solution will be found to this new challenge.

As last point, the 2024 election is coming. As it appears, the industry would not be happy with a possible second Trump term. His unpredictable behavior is not good for the long-term needs of this industry.

Last word

It was explicitly written in the introduction that the aim of this work was not to enter the debate on whether “Big Pharma” is evil or not. However, this work gives a relatively bad image of the pharmaceutical industry.

Because the FDA reacts mostly to scandals and popular pressure, most of the drugs cited were involve in some sort of scandal. No mention was done of life changing medicine. As example: HIV patients can now be on single dose therapy and transmission of the virus to the foetus, or through sexual intercourse can be avoided. The 5-year survival of leukemia patients has gone from 34% in the 70’s to about 70% and up to 90% of certain categories of leukemia and patients in 2010. Those are the cases popping to mind when writing those lines, but there are most likely many others.

Because part of this work focuses on actions aiming at the correction of abuses (e.g. through the Inflation reduction Act), it does not mention what works correctly. It should be remembered that the overall life expectancy increases, and that pharmaceutical research is partially responsible.

Because this work focuses on the cash flows from a specific market and on the returns from prescription drugs, it is oriented around the benefits the manufacturing company can expect from a drug. What this work does not discuss is the economic benefit of the drug for society. A society filled with sick persons can obviously not be a healthy one.

There are obviously some issues to solve and some abuse to stop in the practices of some pharmaceutical groups. There are also medical needs to meet and patients to help.

An overall and objective evaluation of the situation would be a very complicated work, as it would require the considerations of all aspects of a very complicated system, that is in constant change and adaptation. System in which data is confidential, and in which business interests and political ones can be considered to taint almost all available information.

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Summary

Reception of letters denying access to the American market can be very damaging for a pharmaceutical company. Indeed, such a letter, at best, delays important cash flows and therefore impacts the ability to finance other projects and to meet shareholders expectations. This work, after covering the basic necessary knowledge, considers the sources of risks to the cash flows from the lucrative US market.
As the discussions moves forward, it appears that money, time and politics are at the heart of every potential problem.

Résumé

La réception de lettres refusant l'accès au marché américain peut être très dommageable pour une entreprise pharmaceutique. En effet, une telle lettre, au mieux, retarde d'importants flux de trésorerie et impacte donc la capacité à financer d'autres projets et à répondre aux attentes des actionnaires. Ce travail, après avoir couvert les connaissances de base nécessaires, examine les sources de risques pour les flux de trésorerie du lucratif marché américain. Au fur et à mesure discussions avancent, il semble que l'argent, le temps et la politique soient au cœur de tous les problèmes potentiels.

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