OPINION 135

ACCESS TO THERAPEUTIC INNOVATIONS: ETHICAL ISSUES

NATIONAL CONSULTATIVE ETHICS COMMITTEE FOR HEALTH AND LIFE SCIENCES

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Opinion adopted by all members of the Plenary Committee present on 24 September 2020, with two abstentions.
Revised version dated 24 November 2020.

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SUMMARY

New medicines developed through biomedical research, with construction models that differ from those hitherto used in the pharmaceutical industry, now constitute high value-added therapeutic innovations.
It is highly likely that these treatments will continue to develop and that their applications will broaden, for example for many cancers and rare diseases: they will therefore be used by an increasing number of patients. However, the exorbitant prices of these innovative therapies (up to two million euros per patient) clearly raise the question of access for all patients who might need them. Furthermore, the very high prices of these treatments could compromise the financial equilibrium of the solidarity-based healthcare system that prevails in France, leading to difficult choices being made and restricting access to care for other patients.

The CCNE has examined the ethical issues raised in this context on its own initiative, focusing in particular on **the ethical challenge of ensuring that all patients have access to innovative therapies**. How can we reconcile, on the one hand, access to these very expensive treatments for all those who need them and the sustainability of the Assurance Maladie (French national health insurance system) and, on the other hand, the interests of pharmaceutical companies? How can such prices be justified, and how can fair prices be determined?

The business model of pharmaceutical companies has changed over the last twenty years, marked both by the outsourcing of research (carried out in particular by start-ups that have subsequently been bought up by the major pharmaceutical groups) and by the financialisation of the sector, leading to the pursuit of very high profits to meet the demands of shareholders. The analyses produced by pharmaceutical companies also reveal that production costs represent on average less than 5% of the total and, above all, that expenditure on research and development is lower than that allocated to marketing.

Price setting is a complex process, the result of opaque and unbalanced negotiations between the public authorities and companies in the sector.
In this opinion, the CCNE analyses the principles that should be applied to ensure that negotiations are fair, with the aim of achieving a "fair price", even if the interests of the parties involved are somewhat conflicting. How can such prices be charged without any clear justification, despite the fact that patients are effectively trapped, as most of the time they have no alternative? How can we achieve an ethic of "fair negotiation"?

The Covid-19 pandemic highlighted the importance of ethical reflection on access to therapeutic innovations.

The CCNE has put forward recommendations aimed at reconciling two objectives: optimising access to the best care for everyone and optimising the search for the lowest price in the context of negotiations. This objective can be broken down into the following three elements: (1) demanding transparency; (2) strengthening and/or extending the powers of the public authorities; (3) developing a policy of cooperation at European and even international level.

(1) The demand for transparency is ethical and democratic above and beyond its strategic economic importance. This will involve setting up a "Ségur du médicament" consultation process, bringing together all stakeholders in the sector, including representatives of society, to discuss ways of developing a policy of transparency based on the definition of explicit rules regarding cost.
Capping authorised lobbying expenses for pharmaceutical companies, as well as regulating the activities of medical sales representatives, should help to limit the effects of lobbying on the approval process for marketing authorisations in Europe, as well as on the practices of professionals with the authority to prescribe medications, who should be encouraged to develop the ethical and multidisciplinary dimension of the decision-making process for the allocation of innovative medicines.

(2) The second component of the recommendations should **strengthen the public bodies preparing the negotiations** by calling on public researchers and academics to carry out medico-economic analyses, and by developing real-life evaluation of the effectiveness of innovative and costly medicines. Patent offices also need to be given the resources and information they need (legal and regulatory provisions) to assess the effectiveness of innovations proposed by manufacturers. Finally, one recommendation addresses criticism of the current economic model, proposing the creation of an (autonomous) "public medicines office" to set up public (or mixed) entities for the production of innovative medicines on a not-for-profit and profitable basis, based on the coordination of research teams.

(3) The third component of the recommendations, **at European and international level**, is to **promote a policy of cooperation** to examine the issues surrounding the legal classification of certain innovative medicines as "global public goods", to consider the possibility of creating a European agency specialising in the economic analysis of healthcare products, or to extend the remit of the EMA and, more generally, to strengthen health sovereignty at national and European level.

PREAMBLE

Since 2011, the National Consultative Ethics Committee (CCNE) has been monitoring access to healthcare products, particularly medicines, through a series of hearings, either within a dedicated working group or during meetings of the Plenary Committee. Each stage in the development of a medicine, from initial basic research to marketing and post-marketing follow-up, raises numerous questions, including ethical ones.

The CCNE's deliberations were prompted by a series of requests from the Director General of AFSSAPS (now ANSM), and subsequently from a number of associations, including Société française d'hépatologie, Médecins du Monde, Collectif Hépatites Virales, Comede, Groupe interassociatif traitements et recherche thérapeutique and SOS Hépatites Fédération, when innovative, effective but very expensive treatments were launched. The CCNE's consideration of the accessibility of innovative medicines began with a study of the case of Sovaldi® (a medicine used to treat hepatitis C).

A working group was set up in 2016, with Jean-Pierre Kahane and Jean-Louis Vildé as rapporteurs, to address the ethical issues surrounding access to innovative medicines. Several hearings were held, but the working group's work was suspended following three successive events: the death of Jean-Pierre Kahane, the partial renewal of the CCNE's membership in September 2016, and then in December 2017, the organisation of the General Assembly for Bioethics in 2018.

The issue of access to innovative medicines was not directly addressed during the General Assembly for Bioethics. However, the importance of putting people at the heart of the healthcare system and the medicine of the future was strongly emphasised, as was respect for those who are ill or, more generally, in a vulnerable situation.
These issues call for effective vigilance and a rethinking of the relationship between the public authorities and the pharmaceutical industry, while ensuring that economic considerations and efficiency do not dominate the way in which the healthcare system is organised. In addition, the Covid-19 pandemic highlighted the importance of ethical reflection on access to therapeutic innovations.

The working group, with a modified membership, was re-established at the end of 2018, with Sophie Crozier and Florence Jusot as rapporteurs (appendix 1). A list of the hearings held since 2016 is provided in Appendix 2.

This opinion 135 of the CCNE is dedicated to Jean-Pierre Kahane, who was a member for four years and the group's rapporteur until his death in June 2017. Over and above his mathematical skills and his convictions, he demonstrated within the CCNE his great human qualities, his creativity, his ability to listen, his consideration for the relational dimension of medical practice and his youthful spirit. He was instrumental in refocusing the working group's reflection on the ethical issues raised by problems of access to medicines, particularly innovative medicines.

INTRODUCTION

Article L. 5111-1 of the French Public Health Code defines a **medicinal product** as "*any substance or combination of substances presented as possessing curative or preventive properties with regard to human or animal diseases and any substance or combination of substances that may be used in or administered to humans or animals in order to make a medical diagnosis or to restore, correct or modify their physiological functions by exerting a pharmacological, immunological or metabolic action*".
The French pharmaceutical companies association (LEEM) also states that medicinal products are industrial products subject to strict regulations governing their manufacture and use, particularly in view of their unique risk/benefit ratio.

However, medicines have a number of specific characteristics that make them different from other industrial products. They respond to an essential health need, and access to them must be guaranteed to all.
Their beneficial effect is directly aimed at combating a pathological condition or disease, on either a curative or preventive basis. They therefore play a role in improving health and preserving life. Access to essential medicines is a fundamental element of the "right to the highest attainable standard of health", as enshrined in the WHO Constitution[1]. **In reality, it is a question of defending equal access to medicines, and more generally to healthcare, as a fundamental right of each individual.**

Most commonly used medicines, which have often been around for a long time, are not very expensive, especially as most of them are classified as generics. On the other hand, **new medicines** to treat serious illnesses, particularly those for which there is no effective therapy, or to treat recently identified serious illnesses for which there is no treatment, **are marketed at very high or even exorbitant prices** (from tens of thousands to two million euros).
For example, among the first treatments to be made universally available were direct-acting antivirals for hepatitis C infection: Solvadi® (Sofosbuvir DC) and Harvoni® (Sofosbuvir DC, Ledipasvir DC). However, these highly effective medicines (treatments capable of eradicating the viral infection) with real benefits for patients (possible cure) were initially rationed in France, due to their price, and reserved for patients suffering from severe forms that could lead to liver cancer, due to the financial burden that would have been difficult to bear in treating all the patients potentially concerned.

Innovative medicines[2] also draw, and will increasingly do so, on recent sectors of research, distinct from traditional chemical or biochemical research, with technologies based on immunology, genomics, computer science and artificial intelligence.
New anti-cancer treatments based on monoclonal antibodies - for example, Keytruda® (Pembrolizumab DC) - which increase patient survival time and cause fewer side effects

[1] "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition." (Preamble to the WHO Constitution; 1946).

[2] See the INSERM ethics committee note: Rethinking Health Innovation: Towards a Plural Ethical Approach (2020), 28 p. https://inserm.hal.science/inserm-03127943/document

than traditional therapies, are also being offered by pharmaceutical companies. Similarly, immune checkpoint inhibitors (blocking proteins specific to checkpoints, enabling immune cells to attack and destroy cancer cells) have recently been developed and have revolutionised oncology.
Finally, some new medicines are tailored for individual patients, such as certain gene therapies. Gene therapy is a method of introducing nucleic acids (DNA or RNA) into the cells of an organism to correct a anomaly, such as a mutation, that is the cause of a disease[3]. In the treatment of cancer, gene therapy can modify the patient's own immune cells so that they destroy cancerous cells. For example, T lymphocytes T cells modified into cells known as CAR-T cells have produced encouraging results in cases of leukaemia and lymphoma.

These new medicines, from biomedical research, **constitute therapeutic innovations with high added value**, with construction models completely different from those hitherto implemented in the classic chemical pharmaceutical industry. It is highly likely that these treatments will continue to develop and that their applications will be extended to many cancers and rare diseases, meaning that an increasing number of patients will be treated with them. However, **the prices of these innovative therapies clearly raise the question of access for all patients who might need them.** In a solidarity-based healthcare system such as the one that prevails in France, this presupposes that the Assurance Maladie will be able to bear the cost[4].
As a result, the very high prices of certain innovative treatments could undermine the financial equilibrium of healthcare systems as they currently operate, and hinder access to them for all patients who need them. While access to these treatments in the most economically vulnerable countries, particularly in the South, is already highly unequal or non-existent (apart from generic HIV and AIDS medicines), despite the fact that cancer, among other diseases, is progressing extremely rapidly in these areas, it is possible that the richer countries of the North will soon face similar difficulties.
This kind of expenditure on the healthcare system could lead to choices being made and access to care being restricted for other patients. It could also affect all taxpayers if it leads to an increase in compulsory deductions and calls into question the effectiveness of public spending. This observation is shared internationally. For example, the Institute for Clinical and Economic Review (ICER) in the United States has carried out a number of studies on the very high cost of innovative medicines: if tomorrow, 1% of patients suffering from rare diseases had access to a gene therapy costing $1 million per person, the corresponding budgetary impact would be equivalent to the amount currently spent on medicines in the United States[5].
Numerous analyses and reflections on this subject have already been produced[6] (parliamentary reports, opinions from scientific bodies, press articles, manifestos from

[3] This makes it possible, for example, to introduce a normal, functional gene (transgene) into a cell where the existing gene is altered, or to introduce RNA capable of regulating or partially blocking the expression of an altered gene. These nucleic acids are introduced into the patient's cells via a viral vector or injected directly into the cells in the form of naked DNA.
[4] "For patients, an unaffordable treatment is no more effective than one that doesn't exist," says Marc-André Gagnon (https://www.prescrire.org/Docu/DownloadDocu/PDFs/PiluledOr2015_Gagnon.pdf).
[5] Marsden G, Towse A, Pearson SD, Dreitlein B, Henshall C. (2017). Gene therapy: understanding the science, assessing the evidence, and paying for value. Boston, Institute for Clinical and Economic Review (ICER), 48 p.
[6] See in particular:

associations and institutions, appeals from healthcare professionals, etc.). Their proliferation reflects the growing collective concern about universal access to such costly therapies, both in France and internationally[7].

- Daudigny Y., Deroche C. and Guillotin V. (2018) Information report no. 569 of the Senate on early access to innovation in health products. Social Security Assessment and Control Mission and Social Affairs Committee, 127 p.

-Polton D. (2015). *Rapport sur la réforme des modalités d'évaluation des médicaments*: https://solidarites-sante.gouv.fr/IMG/pdf/rapport_polton_-_evaluation_medicaments.pdf, 168 p.

- Nuffield Council (2013). Expensive life extending-treatments: https://www.nuffieldbioethics.org/publications/expensive-life-extending-treatments, 17 p.

- National Cancer Institute (2017). *Le prix des médicaments anticancéreux*. Coll. Current situation and knowledge, 64 p.

- Court of Accounts report on the application of social security finance laws (2017), Part 3 (ch. VIII) "*La fixation du prix des médicaments : des résultats significatifs, des enjeux toujours majeurs d'efficience et de soutenabilité, un cadre d'action à fortement rééquilibrer*", 331-395.

- Haute Autorité de Santé (2020). *Plan d'action pour l'évaluation des médicaments innovants*, 6 p.

- Médecins sans Frontières (Access Campaign), UFC Que Choisir, La Ligue contre le Cancer, France Assos Santé, Prescrire, Médecins du Monde, UNEM and Aides (2018). Medicines and therapeutic progress: guaranteeing access, bringing prices under control. Civil society's contribution to the debate in France. White paper, 32 p.

[7] Belgian Advisory Committee on Bioethics (2014). *Avis n°58 relatif à la problématique du financement de médicaments onéreux*, 69 p.

American Cancer Society (2017). The costs of cancer, Atlanta (GA), 28 p. https://www.acscan.org/policy-resources/costs-cancer

The CCNE has examined the ethical issues raised by the situation described above on its own initiative, focusing in particular on the ethical challenge of ensuring that all patients have access to innovative therapies. This can be broken down into the following questions:
Why are the prices of these innovative therapies so high? How are they justified by manufacturers? By production costs? (Re-)acquisitions of patent-holding companies? Research and development costs?
How can access to innovative treatments that meet public health objectives be reconciled with maintaining sufficient financial incentives for the pharmaceutical industry, in order to guarantee support for therapeutic innovation?
Are public purchasing policies, and the procedures and requirements to be applied in negotiation, still appropriate and compatible with the long-term viability of a solidarity-based healthcare system?
Finally, will we have to choose who to treat?

The CCNE's reflection is a continuation of its earlier work, including opinion 57[8]: Technical progress, health and social model: the ethical dimension of collective choices (1998) and opinion 101:[9]: Health, ethics and money: the ethical aspects of budgetary constraints on health spending in hospitals.
In opinion 57, it was stated that "*healthcare is a field in which fundamental principles are applied, many of which are constitutional in nature or which have provided a strong framework for the laws in force in this field.*
Ethics demands that all these principles be respected. [...] *Society cannot simply assert, in parallel, the primacy of these principles on the one hand and the need to control costs on the other. It must say how these rules combine and what happens when they are applied to an individual situation."*

[8] https://www.ccne-ethique.fr/sites/default/files/publications/avis057.pdf
[9] https://www.ccne-ethique.fr/sites/default/files/publications/avis101.pdf

I. THE IMPORTANCE OF ETHICAL REFLECTION ON ACCESS TO INNOVATIVE THERAPIES

1 - The place of medicines in the healthcare system

While not all medicines require a medical prescription, many cannot be delivered to patients without one. This patient-doctor (and pharmacist)-industry triangle is unprecedented and unheard of in any other industrial sector. Access to medicines is therefore not characterised by free choice for the patient, and the freedom to prescribe is also subject to legally defined limits, taking into account "scientific knowledge" (Art. R 41127-8 of the French Public Health Code). Appendix 3 contains a diagram describing the process by which medicinal products reach the market and patients, explaining in particular the marketing authorisation (MA) process, as well as the temporary authorisation for use (ATU) for serious diseases without appropriate treatment (diagram taken from information report[10] no. 569 of the French Senate).

The desire to guarantee the best possible health for all requires **the establishment of a solidarity-based health system** that gives those who need it **access to the best care**, regardless of their ability to pay. In France, this solidarity is organised by the State and the Sécurité Sociale (social security system). Since its inception, the Assurance Maladie system has been designed to guarantee fair, affordable access to healthcare for all those who need it, and to prevent illness from impoverishing individuals or widening inequalities in living standards (or even discriminatory exclusion of certain categories of the population from access to healthcare). In this way, by disconnecting the use of healthcare from the financing of that healthcare, the Sécurité Sociale ensures solidarity between all, particularly between income groups.

This solidarity is particularly apparent when it comes to access to medicines delivered as part of the treatment for pathologies recognised as long-term conditions and to medicines delivered in hospital, for which the patient does not have to pay any co-payment (although they have had to pay the fixed contribution[11] since 2005)[12]. Collective solidarity is the key to guaranteeing fair access to healthcare for all.

2 - Recent developments in the pharmaceutical industry: unbridled financialisation

[10] See Note 5.

[11] Fixed daily rate (in hospitals) or fixed rate for the consumption of boxes of medicines, laboratory tests or even medical transport.

[12] For information, medicines accounted for €32.7 billion, or 16.06% of total Assurance Maladie expenditure in 2018 (€203.5 billion). In 2017, 10.7 million people (i.e. 17% of the insured population) benefited from full coverage of medical expenses incurred as a result of a long-term condition. According to INSEE and Assurance Maladie: see
https://www.insee.fr/fr/statistiques/4277750?sommaire=4318291
https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/prevalence/prevalence-des-ald-en-2017.php

The pharmaceutical industry is characterised by a number of specific issues that create difficulties in the production process. The development of a new medicine takes a long time, sometimes as much as 10 to 12 years before it is brought to market, not least because of the stringent requirements for evaluation through clinical trials, but also because of the high failure rate during the testing phases of medicine candidates[13]. There are also many uncertainties: how widely will it be used? How effective will it be, and for how long? The pharmaceutical industry is a high-risk industry.

Over the last few decades, and particularly over the last twenty years, the pharmaceutical industry has undergone profound changes (like other industrial sectors), epitomised by three terms: concentration, outsourcing and financialisation. These changes stem from or respond to the difficulties mentioned above.

Concentration: The exploitation of patents is no longer within the reach of small or medium-sized businesses, leading to a strong and rapid concentration of intellectual property. Between 1970 and 2018, the number of companies almost halved (from 422 to 240).[14]

Outsourcing: The big pharmaceutical companies are carrying out less and less of their own research. They are banking on the potential success of the start-ups they exploit or absorb. In reality, their research is increasingly carried out by the start-ups with the best results and the best chances of development.
This is the first level of outsourcing. Big Pharma is therefore including the investment it has made in buying start-ups in the selling price of the drugs it markets. This reorganisation of skills is also reflected in successive company takeovers[15].
The second level of outsourcing, currently booming, is the contracting of public laboratories, teams or individual researchers to carry out research of direct interest to industry. This strategy is supported by public scientific and technological institutions (EPST) and offers major tax advantages to industrial companies.
This outsourcing strategy gives rise to two distinct phases in the development of a medicine: an invention phase, for which the agility of start-ups is considered more favourable than industrial organisation, followed by a production phase, for which it is necessary to call on industrial expertise and to have a large financial base to absorb the risks and costs associated with phases 2 and 3 of clinical research, and then marketing. However, the technological breakthroughs that have characterised recent developments in medicine and the pharmaceutical industry (development of biological medicines and gene therapy, artificial intelligence, etc.), as well as the creation of niche markets (rare diseases, representing low production volumes) could change the economics of these two phases.

Financialisation: as they acquire more and more start-ups and, to a lesser extent, develop contracts with public institutions, pharmaceutical companies, consolidated into

[13] The average phase 3 success rate for a medicine was 58% in 2013-2014 (vs. 55% in 2010-2012). See: Harrison R. (2016). Phase II and phase III failures: 2013–2015. *Nat Rev Drug Discov* 15, 817–818. https://doi.org/10.1038/nrd.2016.184

[14] https://fr.statista.com/statistiques/501308/evolution-nombre-entreprises-pharmaceutiques-france/

[15] Pharmaceutical giant Roche, for example, bought cancer start-up Flatiron Health for $1.9 billion in 2018. Novartis bought AveXis (a start-up specialising in the treatment of spinal muscular atrophy) for $8.7 billion.

huge consortia, are becoming veritable financial enterprises. The dominant companies are putting in place profit strategies that respond to the interests of their shareholders and managers, whose training is often far removed from medical culture and whose practices are now marked by a financial rationale based on the promise of substantial rewards[16] as compensation for taking the risk of seeking the greatest profits.

These changes have obvious consequences for the medical directions chosen by pharmaceutical companies, associated with new business models that increasingly focus on gene and cell therapies[17].

The changes taking place in the pharmaceutical industry raise a number of questions. Are they always a source of innovation, or do they only lead to increased profits for the pharmaceutical industry? Do these profits provide the necessary incentives for innovation? In other words, are the very high costs quoted by manufacturers necessary to finance research and development costs?
Will we soon have to come to terms with the ethical question of triaging lives and rationing care and medicines, instead of reflecting on fair compensation for shareholders and manufacturers?

In addition, directing research towards therapies that could prove profitable above all else, rather than meeting the essential needs[18] of the majority of the population (for example, little research into developing new antibiotics) raises an ethical question, because the role of the pharmaceutical industry should develop in line with public health needs. How can such an imperative be reconciled with the industrial and financial reality of these companies?

Finally, medicine shortages, which are becoming more and more frequent, but only rarely concern innovative and more expensive medicines, pose real problems of access to treatments that are sometimes essential to people's health.
Against this backdrop, **it would appear necessary to urgently strengthen a regulatory system that will enable public and industrial interests to be safeguarded in tandem.**

3 - Could the exorbitant price of innovative medicines be a barrier to access for the patients who need them?

The current prices of innovative therapies raise questions about the capacity of Assurance Maladie system to pay. For example, gene therapy treatment for spinal muscular atrophy (Zolgensma®) costs €1.8 million per patient per year; new direct-acting antiviral treatments for hepatitis C virus infection (Solvadi® and Harvoni®) will be offered in 2020 at prices of nearly €25,000 and €37,000 respectively for a 12-week course; treatment of cystic fibrosis (Trikafta®) is priced at around €270,000 per patient

[16] According to several of the people we interviewed, the dividends paid out by the pharmaceutical industry are higher than those paid out by the luxury goods industry.

[17] https://www.google.fr/amp/s/www.lesechos.fr/amp/1151285

[18] Research into medicines for orphan diseases is of course necessary, but generates niche innovations.

per year, which would account for just over 5% of annual medicine expenditure in France; immune checkpoint inhibitors (specific immunotherapy for certain cancers) cost around €75,000 per patient per year, which, given the potential number of people to be treated (382,000 new cases in 2018, according to Inca), would represent a considerable budgetary burden.

In an article published on 25 November 2019 in the scientific journal Nature Medicine, Alain Fischer, Mathias Dewatripont and Michel Goldman warn of the worrying rise in the prices of innovative medicines, particularly gene therapies[19]. According to Alain Fischer, these therapies represent "major advances", but will be accompanied by difficulties of access for patients and a lack of interest on the part of pharmaceutical companies in developing less profitable medicines. He also points out that a point of imbalance has been reached between fair compensation for companies and the defence of the public interest (hearing of 15 June 2020)[20].

The expected growth in spending on innovative medicines, against a backdrop of a general increase in healthcare needs as the population ages and the prevalence of obesity, diabetes and hypertension rises, necessarily raises the question of trends in healthcare spending as a whole. The impossibility of massively increasing compulsory deductions within the European framework, as well as the need to maintain other essential public expenditure, such as for education, security or environmental protection, call for increased vigilance with regard to the healthcare expenditure[21] covered by the Assurance Maladie funds, particularly with regard to the price of innovative medicines.

Very high prices also call for reflection on the value of life and health - a reflection that France is not in the habit of conducting, unlike the United Kingdom, Sweden or the Netherlands, which can refuse or cease to cover a medicine whose cost is deemed too high in relation to the therapeutic benefits obtained - as well as on the **question of the 'fair price' and its justification**: risk-taking; the Buyer's willingness to pay; best medical service; production costs.

The Covid-19 pandemic highlighted the importance of ethical reflection on access to innovative therapies and, more broadly, on **the limits of the healthcare system** in meeting new needs. Insufficient resources in the face of new health needs put a strain on the healthcare system, leading to emergency decisions to reorganise care and even to make choices in the allocation of resources[22].

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[19] See also the article by Fischer A., Dewatripont M. and Goldman M. (2020). What is the fair price of innovative therapy? Med. Sci., 36, 389-393.

[20] See also: Zafar SY, Peppercorn JM, Schrag D, Taylor DH, Goetzinger AM, Zhong X, et al. (2013) The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist. 18, 381-390. https://www.ncbi.nlm.nih.gov/pubmed/23442307 Ethics and Cancer Committee (2017). Opinion 33: Should the price of a medicine be determined by market forces and can it be set on the basis of the service rendered? 20 p.

[21] More specifically, the proportion of healthcare expenditure covered by the Assurance Maladie funds in relation to wealth creation.

[22] See the CCNE opinions published during the Covid-19 epidemic, in particular:
https://www.ccne-ethique.fr/sites/default/files/publications/reponse_ccne_-_covid-19_def.pdf
https://www.ccne-ethique.fr/sites/default/files/publications/ccne_-_reponse_a_la_saisine_cs_enjeux_ethiques_lors_du_de-confinement_-_20_mai_2020.pdf

II. THE SEARCH FOR A "FAIR PRICE" AND THE PRINCIPLES OF "FAIR NEGOTIATION"

The price of a medicine first and foremost serves to facilitate and coordinate exchange between the parties involved in supply and demand. A "fair price" should be the result of a mutually beneficial exchange between these various parties. **The search for a "fair price" is part of a negotiation between private and public players whose interests are in part divergent.** The manufacturer is a private, profit-making player whose principal objective is to make profits in order to compensate shareholders and remain dynamic in its innovation strategy in order to be supported by the financial markets. The objective of the public authorities is above all to meet a public health objective, which is to protect the health of the entire population within the limits of a defined financial envelope. The public authorities are therefore seeking to obtain the proposed innovation for patients suffering from the targeted pathologies, provided that it is deemed to be effective, while preserving their ability to cover all the care needs of other patients. Public institutions must also make their medicine purchasing decisions within budgetary constraints[23].

1 - Unjustified prices

The monopoly power of manufacturers, the huge profits they make, and the infinite willingness of buyers to pay

The TRIPS agreements (Agreements on Trade-Related Aspects of Intellectual Property Rights) signed at the World Trade Organisation (WTO, 1994) strengthened and extended the system for protecting trade-related intellectual property and gave pharmaceutical companies a monopoly (sometimes an oligopoly) that maximises profits, insofar as each new drug benefits from a twenty-year patent that can be extended by a supplementary protection certificate for a maximum of five years[24].
These patents give pharmaceutical companies greater bargaining power and higher returns than they would have obtained in a competitive market. It is only at the end of this twenty-five year period that the medicine can be made available in generic form.

Public authorities, for their part, suffer from this power imbalance, all the more so because their willingness to pay has no predetermined limit. The imperative of responding to unmet healthcare needs and the very great political and moral difficulty of refusing an innovation because of its price considerably reduce its bargaining power.

[23] The budgetary envelope for medicines is fixed and defined within the framework of the National Health Insurance Expenditure Target (ONDAM), which sets the framework for all Assurance Maladie expenditure on outpatient care, medicines and hospital care - created by the 1996 Orders - and which is set each year by the Social Security Financing Law (LFSS).
[24] French Treasury briefing note (2017). *Quelle politique pour poursuivre la diffusion des médicaments génériques*, French Treasury Department, 12 p. https://www.tresor.economie.gouv.fr/Articles/3a8c1afa-4874-456b-9fb5-d26001b7ac8d/files/dd93dd2e-2398-438a-a537-253f141ea843

This situation enables pharmaceutical manufacturers to achieve **extremely high levels of profit**, higher, for example, than those of the oil or luxury goods industries, according to several of the people we interviewed.
In a study produced by the *Journal international de bioéthique et d'éthique des sciences*[25], economists note that there is no correlation between medicine prices and the costs associated with research, development, production and marketing[26]. They argue that these costs derive solely from society's "willingness to pay" and from what the market can "absorb". The price negotiated is never based on the cost price. As a result, some prices are set without consideration for the public interest[27]. On the other hand, in 2017, the ten largest pharmaceutical companies in terms of revenues distributed €60.77 billion to their shareholders[28]. An article in the "*Pharma papers*" (part 4)[29] reveals that since 1999, pharmaceutical companies have made profits of more than €1,000 billion, 90% of which went directly to shareholders. Revenues have increased sixfold since the 1990s, while assets and dividends have increased twelvefold.

One of the reasons why pharmaceutical companies seek to focus research into therapeutic targets on the most financially profitable sectors (rare diseases, individualised therapies or so-called "niche" innovations) is that these target sectors are relatively protected from the risk of litigation in the event of unexpected adverse effects, as the patients concerned are far fewer in number and less visible in the public arena. In addition, these target sectors generate significant development costs, which are sometimes borne by start-ups before they are taken over.

The pharmaceutical industry's use of the results of public and university research

The prices of innovative medicines are high, even though the pharmaceutical industry uses the results of public research to produce certain treatments. Most of this research is financed by public funds, to which the pharmaceutical industry contributes only marginally. What's more, the pharmaceutical industry does not reimburse the State for

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[25] Trouiller P. (2018) "*L'économie morale de la disponibilité des innovations thérapeutiques pour les maladies négligées*", *Journal international de bioéthique et d'éthique des sciences*, 29, 53-67.
[26] See also:
Prasad V. De Jesus K., Mailankody S. (2017). The high price of anticancer drugs: origins, implications, barriers, solutions.
https://go.gale.com/ps/anonymous?id=GALE%7CA491968921&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=17594774&p=AONE&sw=w *in* Nature Rev. Clinical Oncology, 14.
Sinha M.S., Curfman G.D., Carrier M.A. (2018). Antitrust, Market Exclusivity, and Transparency in the Pharmaceutical Industry. *JAMA*, 319, 2271-2272.
[27] For example, the price of a product used to treat toxoplasmosis, synthesised in the 1950s using an inexpensive chemical process, rose by 5000% in the space of one day following the repurchase of the patent on the drug used: pyrimethamine, both in its original indication and for new parasitic infections. Furthermore, the price set by manufacturers is not the only determining factor in the final cost to the consumer. Taxes, wholesaler and pharmacy retailer margins, warehousing and transport costs can all add up to manufacturer prices that can be doubled. See: https://www.lemonde.fr/economie/article/2015/09/22/le-prix-d-un-medicament-contre-la-toxoplasmose-a-bondi-de-5-400-en-un-jour_4767396_3234.html
[28] https://pharmanalyses.fr/2017-une-excellente-annee-pour-les-big-pharma-et-leurs-actionnaires/
[29] *"Pharma Papers", volet 4 : comment les labos sont devenus des monstres financiers* 17 January 2019: https://multinationales.org/Pharma-Papers-volet-4-comment-les-labos-sont-devenus-des-monstres-financiers

its R&D efforts in this area. Part of this academic research is central to the discovery of molecules that go on to become innovative medicines. According to French healthcare spending data[30], €4.66 billion of public spending was devoted to health research in 2017, including €2.64 billion in universities and teaching hospitals and €2.02 billion in the public research and development budget (organisations such as Inserm, CNRS, Institut Pasteur, Institut Curie, Gustave Roussy, etc.).

Is the public funding body capitalising too little on its discoveries? In its inter-association White Paper, the Ligue contre le cancer asks[31]: "Medicines and therapeutic progress: guaranteeing access, bringing prices under control": *"According to Novartis, the company spent over one billion dollars to bring Kymriah® to market, but what about investment in public research? The NGO Patients for Affordable drugs has calculated that the NIH (National Institute of Health) alone has poured US$200 million into research on CAR-T therapies. Is this public funding paid for by citizens taken into account in the cost of research, and in the definition of prices? Wouldn't medicines be paid for twice, firstly through support for research, and secondly when they are on the market and prescribed to patients?"* [32]

Finally, while the results of public research are the fruit of public spending, some innovations may have been made possible through charitable funding. For example, 60% of the development of Janssen's *Bedaquiline* was funded by charity. However, the treatment is marketed at prices that are prohibitively expensive for the countries that need it. Zolgensma®, for its part, was marketed at €2 million per injection, having been developed as a result of research and financial contributions from Inserm and the Téléthon (public and charity money).

R&D costs not always correlated with medical services actually rendered

While medicine prices do not always correlate accurately with research and development costs, neither do they always correlate with the quality of medical service rendered[33]. Indeed, in most industrialized countries over the last ten years, the proportion of medicines with significant added value, i.e. products considered to represent a major therapeutic advance (level I of the French scale of improvement in medical service rendered, ASMR) is less than 5%, while that of products with no added value (ASMR level V) is around 40%[34]. When there are therapeutic benefits, they are often limited: between 2002 and 2014, the 71 anticancer medicines marketed for solid

[30] DREES, Healthcare spending in 2017 Health accounts results, colll. "Panoramas of DREES Santé", 2018.

[31] See reference 5

[32] The President of the United States himself raised this issue in November 2019. His administration is suing Gilead Sciences over the sale of anti-HIV medicines (Truvada® and Descovy®, as part of PrEP, a strategy known as "pre-exposure prophylaxis") that can cost up to $20,000/year/patient, accusing it of making billions of dollars in profits from taxpayer-funded medical research, without nevertheless reimbursing them. See: Victor D (2019). Trump administration sues Gilead, Maker of HIV-Prevention drugs. https://www.nytimes.com/2019/11/07/business/gilead-truvada-hiv-lawsuit.html

[33] Lavaud S. (2019). *Nouveaux médicaments : apportent-ils vraiment un bénéfice ?*. Medscape. 01/08/2019. https://francais.medscape.com/voirarticle/3605137

[34] Haute Autorité de santé (2015) Activity Report 2015, https://www.has-sante.fr

tumours increased median survival by around two months only [35]. Nevertheless, whatever the absolute value, manufacturers claim that R&D costs have more than doubled over the same periods[36].

2 - The pitfalls of defining a "fair price"

The prices of certain therapeutic innovations can seem unfair, as well as making them potentially inaccessible. On this last point, less than 10% of pharmaceutical companies take accessibility criteria into account for the medicines they market[37].
However, it appears illusory to attempt to define a "fair price" in a "deontological" or "essentialist" way[38,39].
Innovations are partly protected by industrial secrecy, and the costs involved in producing and marketing them are difficult to observe, as in the case of any industrial production.
Above all, the reality of the pharmaceutical market responds to a series of private interests which do not subscribe to moralistic reasoning, interests which also play an integral part in encouraging pharmacological innovation.

A more "contractualist" definition could envisage a "fair price" as the result of an equitable price-setting process that places an equitable burden on consumers.
From this perspective, the "fair price" is no longer based on the quality of the actors, nor on the properties of the good, but on the characteristics of the procedure. It should be the result of a balanced negotiation.
This power imbalance between the State and the pharmaceutical industry, which undermines the possibility of balanced negotiations or makes them impossible, raises major ethical questions.
How can such prices be charged without any clear justification, despite the fact that patients are effectively trapped, as most of the time they have no alternative? Why is it so difficult to obtain a "fair price"? How can we achieve an ethic of "fair negotiation"?

3 - The need for fair negotiation

This quest and demand for fair negotiation is not the result of an "anti-liberal" stance that would deny the freedom of trade and industry, but of the desire to preserve a public good, health, which is a "resource of freedom" for every individual.
The challenge is to preserve the freedom of the pharmaceutical industries and the best possible access to their innovations, for which the public authorities are the sole buyers.

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[35] https://www.prescrire.org/fr/3/31/49931/0/PositionDetails.aspx

[36] Schüler P, Buckly B. Re-Engineering Clinical Trials - Best practices for streamlining the development process Elsevier, 2015, XiX-Xxi.

[37] Access to medicine index (2016). Access to medicine Foundation, 192 p. The Netherlands.

[38] By way of example, a team of Oxford researchers looked at the cost of producing sofosbuvir and estimated that Sovaldi® costs €74 for three doses of treatment, 756 times less than the price charged by the laboratory. See: Hill A., Khoo S., Fortunak J., Simmons B., Ford N. (2014) Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries. *Clinical Infectious Diseases*, 58, 928–936, https://doi.org/10.1093/cid/ciu012

[39] Le Pen C. (2018) Existe-t-il un « juste prix » du médicament ? Revue française des affaires sociales, 3-2018, 15-25.

The aim is to create the conditions for fair negotiations between government and industry, so that these negotiations can lead to prices that ensure the financing of innovation and, above all, meet clear public health needs.

Historically, the alliance between the State and the pharmaceutical industry has been based on the shared desire for effective collaboration, recognising industrial interests without compromising the imperative of seeking the common good and meeting public health needs.
At the start of the First World War (1914-1918), many products were in short supply, as France was heavily dependent on Germany for its medicines. It had not built up a powerful chemical industry capable of developing, producing and marketing the active substances needed for modern medicine.
Although there was a real awareness of this at the start of the First World War, it was not until the law of 1941 that the legislative framework was radically changed and the pharmaceutical industry truly established itself within modern pharmacy[40]. Finally, social insurance schemes have progressively strengthened the growth of the pharmaceutical industry. At the end of the 1930s, when nearly six million employees were insured, 11,000 specialities were recognised by the Assurance Maladie.

The State gradually came to recognise the essential role played by the pharmaceutical industry and **eventually offloaded the task of producing medicines onto private companies** that were better placed to meet public health needs.
Reconciling the two goals of economic liberalism and respect for the principles of the welfare state has therefore always been desirable, and it has proved possible to put it into practice. Today, however, it is under threat.
The current trend in total Assurance Maladie expenditure on out-patient care, medicines and hospital treatment (governed by the ONDAM) is raising fears that the cost of access to innovation will force the Sécurité Sociale to reduce its coverage of other types of care, thereby jeopardising the principles of universality and solidarity on which it is based.
Up until now, access to innovative treatments has not hindered access to other medicines, thanks to the rise in generic medicines made possible by the entry into the public domain of blockbusters (i.e. medicines that are widely used and the delisting of many medicines deemed to be ineffective). Despite this, the constraints on the Assurance Maladie budget justify the introduction of criteria for selecting treatments, including those for rare diseases, which should benefit the entire population. These criteria should not be used by practitioners on a case-by-case basis to treat their patients, but **should apply to all patients concerned**.
Since the issue is to make trade-offs between different treatments, these criteria are comparative: they involve judging the benefits provided by a new treatment compared with the standard treatment.

A prerequisite for any negotiations on the price of an innovation is its effectiveness. Only treatments that have been shown to be more effective than the standard treatment are considered. Reimbursement of medicines is therefore conditional on their ASMR level, i.e. the progress made in terms of medical service rendered, a criterion designed to measure not only therapeutic efficacy and side effects, but also taking into account the existence of alternative therapies, the severity of the disease in question, and the public health interest.

[40] In 1933, the French Academy of Medicine issued an opinion stressing the urgent need to give the pharmaceutical industry legal status. See: Bonnemain H. et Bonnemain B. (2002) *Les relations entre l'industrie pharmaceutique et les pouvoirs publics en France au cours des deux derniers siècles : de la liberté à la liberté surveillée*. *Revue d'histoire de la pharmacie*, no. 334, 239-256. https://doi.org/10.3406/pharm.2002.5360

This condition justifies considering the **accessibility of therapeutic innovations to all**, regardless of their cost, to be **an ethical requirement**. It therefore makes it legitimate for every patient to expect to benefit from the best treatment. It also explains why public funding can only be envisaged for new treatments that offer real benefits, whether in terms of survival or quality of life.
This is the criterion that has so far guided the approach in France, which chooses to include a new innovative treatment in its basket of reimbursed goods as soon as it has a major or significant ASMR, even if its cost is high or very high. This is particularly the case in the absence of an alternative therapeutic strategy, where the absence of the necessary treatment is considered a loss of opportunity. The price is then negotiated after the reimbursement decision.

One criterion often put forward to judge which treatments should be covered for the population as a whole is efficiency. This involves striking a balance between the benefits provided in relation to the standard strategy and the costs. Furthermore, this calculation between benefits and costs is made not at the level of the patient, but at the level of the community. In the latter case, such an approach would presuppose that it is possible to aggregate the treatment needs of all patients (after making them more or less commensurable) and to define the best distribution between these needs, without exceeding a given overall cost.
At patient level, benefits are calculated by taking into account gains in survival and quality of life. The most commonly used unit for measuring benefits is the QALY, or Quality Adjusted Life Year. The costs are calculated by taking into account not only the price of the innovative medicine, but also the subsequent healthcare expenditure saved thanks to the therapeutic benefits of the treatment, and the daily allowances and productivity losses avoided if the treatment makes it possible to reduce exclusion or disengagement from the labour market[41].
Despite the desire to respect the right to effective treatment, this criterion requires that the expected benefit on average for the patients concerned by the new treatment is deemed sufficient in relation to the sacrifice required of the community.

This efficiency criterion is widely used in national healthcare systems with a Beveridgian[42] tradition, such as in the United Kingdom, Sweden and the Netherlands, where the level of cost-effectiveness determines the decision on whether a medicine is covered by the public system and therefore whether it is placed on the market.
In the United Kingdom, for example, the National Institute for Health and Care Excellence recommends that treatments with an additional cost exceeding £20,000 or £30,000[43] per life-year adjusted for additional quality of life should not be covered, although exceptions are made for the treatment of cancers, rare diseases and

[41] In practice, this involves calculating an incremental ratio in relation to the standard treatment, which is equal to the ratio between the additional cost and the additional benefit, known as the Cost/Effectiveness ratio. The idea behind this criterion is that the additional therapeutic benefit of a new treatment alone cannot guide the public decision. Its additional cost must also be taken into account, so as not to take a decision that would lead to an exorbitant sacrifice of resources that could have been used elsewhere in the healthcare system and that could have provided a greater therapeutic benefit.

[42] The Beveridgian system was defined in 1942 in the United Kingdom by William Beveridge and concerns the British compulsory health insurance scheme.

[43] 1 pound sterling = 1.10 euro.

paediatric care[44]. While the use of such a threshold value for treatment decisions may seem sacrificial, it does have the virtue of setting a limit on the acceptability of prices to manufacturers, who tend to align themselves with this limit when proposing innovative treatments.
Conversely, France remains firmly committed to the patient's right to the best possible treatment to improve his or her life expectancy. However, the Commission for Economic and Public Health Evaluation (CEEPS) of the French National Authority for Health (HAS) gives its opinion on the efficiency of new treatments, before the list price[45] is set by the Economic Committee for Health Products (CEPS), even if this opinion counts for little in negotiations today, according to the people we interviewed.

The Polton report[46] proposes, among other things, the introduction of temporary reimbursement schemes based on certain criteria and the inclusion of medico-economic evaluation criteria in price-setting criteria.
In addition to price negotiation, this efficiency criterion has already been used in France to select the patients who should be given the quickest access to an innovative medicine, when its availability was not sufficient to immediately treat all the patients who could have benefited from it. In 1945, streptomycin was used to treat tuberculosis, and in January 1996, protease inhibitors were used to treat HIV infection. These highly innovative medicines were used immediately to treat severe or advanced forms of the disease, before availability was rapidly extended.
The prioritisation of certain patients may nevertheless remain ethically questionable, even if it is accepted in very specific circumstances and on a temporary basis, which has been the case with direct-acting antivirals for HCV infection[47].

Although the National Institute for Clinical Excellence (NICE) sometimes circumvents the QALY[48] system in order to offer treatment to patients who would not have benefited if the threshold had been applied[49], it does follow a policy of rationing based on a "triage of lives". These are economic-political trade-offs that answer the following questions: who should we treat (save) when we can't treat everyone? How many people - and which ones - can we tolerate being deprived of treatment in order to preserve our collective public health objectives? [50]
For example, Kadcyla®, produced by Roche, is a breast cancer treatment for patients whose condition no longer improves with other medicines. It is one of the most expensive drugs on the market: £90,000 per patient, for a one-year course of treatment. The price of this treatment was deemed "unaffordable" in relation to the

[44] https://www.has-sante.fr/upload/docs/application/pdf/2014-12/valeurs_de_reference_vf.pdf
[45] The public price displayed on the box of the medicine.
[46] See Note 5.
[47] Sovaldi, a treatment for HCV infection that has been available since 2014, was initially made available for patients with forms of the disease that were already advanced in terms of fibrosis or extra-hepatic manifestations. Since January 2017, it has been used for all patients infected with HCV, regardless of their symptoms.
[48] https://halshs.archives-ouvertes.fr/halshs-01789639/document
[49] This is the case, for example, for end-of-life treatments, for which the threshold value is regularly raised to £50,000; moreover, since 2010, innovative anti-cancer medicines have had a specific envelope (Cancer Drugs Fund) and since 2012 orphan and ultra-orphan medicines have been the subject of regulatory treatment giving them a positive recommendation by NICE for ICERs (incremental cost effectiveness ratio) of up to £100,000 per QALY (increased to £300,000 per QALY in May 2017).
[50] See the work of Frédérique Leichter-Flack (Sciences Po, Paris), who was consulted by the opinion's rapporteurs.

expected therapeutic benefit, since it would cost £166,000 for one year of healthy life. This is a form of rationing: a treatment that is undeniably clinically effective (even if the aim is not to cure, but to prolong survival and improve quality of life compared with the standard treatment) is refused on the grounds that it is too expensive. This naturally runs counter to the idea that "health is priceless" and the feeling that any medication needed should be paid for by the community[51]. However, is the idea that "health is priceless" necessarily ethical, insofar as very high healthcare expenditure could lead to the sacrifice of other expenditure that is also necessary for the health of the population?[52]

While the use of the efficiency criterion and a threshold value may therefore give rise to fears of prioritising patients in terms of access to care, which is ethically questionable, it seems to be a way of strengthening the United Kingdom's negotiating power vis-à-vis manufacturers and thus achieving a more balanced negotiation process, provided that the threat of non-acceptance of the requested price is credible.

At first sight, there is an incompatibility, or at least a tension, between the efficiency criterion and the requirement to give every patient access to therapeutic innovations.

The criterion of efficiency is based on the ethics of a distribution that benefits the community as a whole (even if it may appear to harm certain individuals), while the requirement of the best treatment for all refers to an ethic founded on the unique nature of each human life and the need to preserve it to the greatest possible extent.

However, these two approaches may prove impractical, especially when it comes to innovative therapies, given the financial resources available to the Assurance Maladie. The additional healthcare costs that would be generated by any new medicine need to be taken into account, given the size of the population concerned.

Setting the price of medicines must therefore take account of several considerations: the first is purely ethical, relating to every patient's right to the best possible treatment; the second is economic and political: the public authorities' desire to encourage innovation and sustain pharmaceutical activity in France; and the third is budgetary: the sustainability of healthcare funding. It is therefore clear that the public authorities are not 'pure' negotiators, concerned only with the interests of patients, and that the activities of pharmaceutical companies also have a decisive impact on them.

The two approaches described above (one in search of a balance between treatment costs and needs, the other concerned with providing the best care for all) are both conceivable, each inspired by different ethical principles. Nevertheless, the CCNE prefers the second approach, in the light of the French tradition of solidarity, which is probably more appropriate for reconciling the optimal provision of the best care for each individual with the optimal price to be achieved for overall funding. All the measures proposed below are designed to make it possible to negotiate in a way that achieves

[51] The National Consultative Ethics Committee (CCNE) stated in its opinion of 13 March 2020 that "the individual value of each person must be recognised as absolute".

[52] It should be noted that the product was ultimately accepted by NICE in 2017, following a new price proposal from the manufacturer. Although the amount of the discount granted by Roche is indicated as being confidential, it is estimated that Roche had to grant a discount of between 60% and 70% to win the NHS contract. See http://www.ipubli.inserm.fr/bitstream/handle/10608/9687/MS_2017_12_1121.html?sequence=8&isAllowed=y; https://www.pseudo-sciences.org/Comment-gerer-les-traitements-onereux

these two objectives[53]. To achieve this, it seems essential to question the mechanisms that lead to the very high prices of therapeutic innovations.

[53] If France were to experience mass demand for an expensive innovation, a different rationale would of course apply, based on the use of legal tools such as compulsory licensing.

III. HOW CAN WE RECONCILE ACCESS TO INNOVATIVE TREATMENTS FOR ALL WITH THE FINANCING OF INNOVATION, TAKING INTO ACCOUNT THE INTERNATIONAL CONTEXT OF NEGOTIATIONS?

The financial quantification of human life remains an ethical pitfall that must be avoided. So how can we achieve a more equal balance of power between the State and the pharmaceutical industry without resorting to the negotiating levers used by the United Kingdom, for example, based on the potentially effective threat of non-reimbursement or rationing of certain treatments?

1 - Medicine price setting: regrettably opaque, despite an ethical requirement for transparency

Research and development costs

Manufacturers justify the cost of the medicines they put on the market by citing high research and development costs. In reality, these costs are unobservable, due to the lack of data availability (business secrecy) and transparency regarding the objective costs involved in the calculation. The methodology of studies advancing some probable figures is highly debated[54].
According to Olivier Maguet (Médecins sans Frontières), "*there is no objective information available to put a figure on the cost of researching and developing a medicine*", and the benchmark used by the pharmaceutical industry to assess these costs (the work of Tufts University in Boston) is "*not based on any methodology*"[55].
The analyses produced by manufacturers reveal that production costs represent on average less than 5% of the total and, above all, that **expenditure on research and development is lower than that on marketing**. For information, Sanofi's expenditure on research and development amounted to around €5.9 billion in 2018 (or 17.1% of revenues), compared with €9.9 billion on commercial expenses and overheads. In 2018, Novartis incurred research and development costs equivalent to €8.2 billion, compared with around €14 billion for commercial and general operations.[56]

[54] Light D, Warburton R. (2011) Demythologizing the high costs of pharmaceutical research. Biosocieties, 6, 34-50.
[55] By way of example, Gilead's own research and development expenditure is actually in the region of €746 million, according to a US Senate report based on the company's internal documents. Although Gilead spent the equivalent of €9.32 billion in 2011 to acquire the laboratory that designed the treatment, it earned more than €25 billion from its hepatitis C business between January 2014 and December 2015.
Excluding pharmaceutical marketing costs, which can account for up to 25% of the total, the final cost is more likely to be well under half of the figure given. See a US Senate report on the price of Sovaldi®:https://www.finance.senate.gov/imo/media/doc/1%20The%20Price%20of%20Sovaldi%20and%20Its%20Impact%20on%20the%20U.S.%20Health%20Care%20System%20(Full%20Report).pdf
[56]https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/common/docs/investors/Sanofi-DDR2018-FR-PDF-e-accessible_03.pdf
https://www.novartis.com/sites/www.novartis.com/files/novartis-annual-report-2018-en.pdf

Insofar as research and development expenditure is unobservable, but lower than marketing costs, it is questionable whether it should be used as an argument to justify the exorbitant prices of certain innovative therapies. Even if defining a justified price as part of a fair negotiation remains a difficult objective to achieve, the lack of transparency and the difficulty of accurately assessing these research and development costs risk making it unattainable.

List prices, real prices and the European price guarantee: the fog of negotiations

To organise the negotiation process with the pharmaceutical industry, the French government has agreed a number of rules with manufacturers (see appendix 4). **This French price-setting model differs from those developed in other countries** at either European or international level, where price-setting systems are heterogeneous. Germany, the United Kingdom and the United States, for example, have introduced a number of rules of their own, reflecting unique political and economic traditions, which result in significantly different price levels and power relationships with the pharmaceutical industry.[57]

These French regulatory provisions are currently proving inadequate, as they do not allow price levels to be set to which the State can agree, taking into account the ONDAM, in a context where an increase in compulsory levies does not seem feasible.
These rules are sometimes even inflationary, i.e. they contribute to increasing the price of innovative medicines. The inadequacies and inefficiencies of these rules jeopardise the State's original objective, defined when the first founding framework agreement between LEEM and CEPS was signed in January 1994. This agreement was based on the desire to reconcile industrial and economic imperatives with the need to control Assurance Maladie expenditure and ensure the predictability of public policies.
We must identify the shortcomings of these provisions, which underpin the balance of power between the State and Big Pharma.

The State, through the CEPS[58], negotiates a so-called "list" price. This is the public price displayed on the box of the medicine. At the same time, it negotiates confidential discounts, known as "secret discounts[59]", based on sales volumes, to reduce the final cost borne by the Assurance Maladie. There is therefore a difference between the "list price" and the "real price" (after discounts), which runs counter to the principle of transparency that applies to public procurement. Furthermore, France has no precise information on the prices actually charged in other European countries, whereas manufacturers are very familiar with negotiated prices in different countries.

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[57] Institut Montaigne (2019). *Médicaments innovants : prévenir pour mieux guérir*, Institut Montaigne report
https://www.institutmontaigne.org/publications/medicaments-innovants-prevenir-pour-mieux-guerir#
WHO (2017). Medicines reimbursement policies in Europe
https://www.euro.who.int/__data/assets/pdf_file/0011/376625/pharmaceutical-reimbursement-eng.pdf

[58] CEPS (2019). Activity report for 2018, 192 p.

[59] These may include so-called conventional discounts, which correspond to risk-sharing contracts (economic risks or those linked to the performance of the drugs), price/volume agreements (in the event that a contractually-defined revenue threshold is exceeded), so-called "cap" clauses, so-called "first box" discounts, daily treatment cost (DTC) or dosage clauses, and so on.

However, the negotiation rules agreed by the French government require them to comply with what is known as the "international referencing system for list prices", which applies to more than 50 countries worldwide, and to accept prices that are consistent with these. This international referencing system is used by manufacturers to impose the highest possible prices on the administrative authorities of the countries with which they negotiate. France must comply with a highly restrictive referencing system for medicines defined as therapeutic innovations: the "European price guarantee".
Under this rule, the French government is obliged to bring the French price for therapeutic innovations into line with prices in Spain, the United Kingdom, Germany and Italy. It is strategic for manufacturers to ensure that the price is as high as possible in France.
In a report published in 2017, the Court of Accounts stated that "*the European price guarantee amounts to creating a situation of rent for the industry: the systematic renewal of this system reflects the renewed consent of the public authorities, in their relationship with pharmaceutical companies, to the granting and maintenance of high list prices for innovative medicines*"[60].

These discounts are therefore the result of negotiations between the State and each of the manufacturers, but they contribute significantly to the opacity of the price negotiation process. The allocation of public spending therefore becomes impossible for the taxpayer to discern. Furthermore, these discounts do not always actually reduce Sécurité Sociale spending. In fact, their existence leads the State to accept extremely high list prices, in the knowledge that it will not pay them in full. However, these high prices create an anchoring effect, leading to increasingly high price authorisations. Ultimately, therefore, it has not been established that the Sécurité Sociale is unable to obtain a lower price[61].
Even if encouraging greater transparency does not systematically lead to price reductions, it is a democratic and ethical requirement that must be met in a context of budgetary constraints and considerable expenditure.

A political commitment to transparency that lacks clarity and firmness

The political commitment to transparency in the negotiations that lead to the setting of medicine prices has not been sufficiently expressed or assumed. It is regrettable to note the existence of contradictory directives providing for, on the one hand, the tightening of industrial secrecy and, on the other, the demand for transparency.[62]

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[60] Court of Accounts (2017). Report on the application of social security financing laws, 729 p.

[61] The Court of Accounts also mentions, in the above-mentioned report (note 51), taking the example of medicines offering little or no innovation: "*the example of multiple sclerosis treatments is illustrative of the pricing advantages granted to several medicines with minor (IV) or no (V) ASMR*". According to the Court's estimate, "*strict application of the rule of using the cheapest 'comparator' to set prices could lead to savings of up to €80 million on multiple sclerosis treatments, compared with current discounts of around €30 million*". Finally, "*in reality, they entail additional costs for the Assurance Maladie and for insured persons*", which the report describes in detail. "*The current compromise between the public authorities and pharmaceutical companies, based on the granting of high prices accompanied by discounts that reduce the net cost - including for medicines that are not very or not at all innovative - appears in part to be ill-suited to the challenges of ensuring the efficiency of Assurance Maladie expenditure*".

[62] On 21 June 2018, the European Parliament adopted a draft bill transposing a June 2016 European directive aimed at protecting companies against the theft of their industrial secrets or their disclosure to

France signed a resolution adopted by the 72nd annual assembly of the World Health Organisation (WHO), in May 2019 in Geneva, to improve the transparency of markets for medicines, vaccines and other health products, but the Constitutional Council invalidated the provisions on the transparency of public contributions to research and development adopted by parliamentarians as part of the Social Security Financing Law (LFSS) 2020, in its decision no. 2019-795 DC, even though a consensus had been reached on this issue. The amendment, based on proposals put forward by health associations and patients, required pharmaceutical companies to make public "*the amount of public investment in research and development from which they have benefited for the development of a medicine*". The Constitutional Council's decision therefore makes the system even more opaque.

In addition, an "anti-gifts" law was passed in December 2011[63], setting up an anti-corruption mechanism based in particular on the creation of a public database, Transparence Santé, with the aim of making relations between manufacturers and healthcare professionals more ethical, in other words reducing the opacity that still too often characterises their relations. Unfortunately, the application of this law has never been evaluated.

Finally, pharmaceutical companies lobby extensively within the European Union (EU). A report by Corporate Europe Observatory[64], which analyses the work of lobbies on the basis of the EU's transparency register, shows that the ten biggest spenders on lobbying[65] spend between €14.6 million and €16.3 million per year - more than they spend on research and development.

One might wonder about the impact of this expenditure on the cost of innovative therapies, on prescription volumes and on the desire to control them. It should be possible to identify hospital prescriptions per prescriber, using the registration number in the shared directory of healthcare professionals (RPPS), which is compulsory but not widely used[66]. Checks on the appropriateness of prescriptions in hospitals, carried out by the ARS, should be made more widespread and more frequent. It would also be appropriate for doctors to show a willingness to take the general interest into account as part of a fair approach to prescription.

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competitors or the general public. While the director of the NGO Transparency International declared: "*in our opinion, transparency should become the rule and secrecy the exception*", it would seem that the opposite is favoured by recent developments in European legislation. See: https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:32016L0943&from=FR

[63] It stipulates that "illegal" gifts are now prohibited, while those that are "acceptable" must be declared from €10 upwards. See: Law 2011-2012 of 29 December 2011 on improving the safety of medicines and health products, https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000025053440?r=kxFhpwI6ne

[64] Tansey R. (2019). High prices, poor access: the EU medicines market and Big Pharma, What is Big Pharma fighting for in Brussels? Corporate Europe Observatory, 33 p.
https://corporateeurope.org/sites/default/files/2019-05/High%20Prices%2C%20Poor%20Access_Full%20report.pdf

[65] (Novartis, Merck KGaA, GlaxoSmithKline (GSK), Amgen, Roche, Johnson & Johnson (J&J), Sanofi, Pfizer and MSD Europe (Merck & Co group), in descending order)

[66] In 2015, the Assurance Maladie conducted a study on a sample of almost 11.6 million expenditure statements corresponding to prescriptions for medicines, transport and sick leave, issued by hospital prescribers. The rate of prescriptions including the RPPS registration number was only 5.3% for medicines.
Report on the application of social security funding laws (2016). *Rapport sur l'application des lois de financement de la sécurité sociale* (2016). Court of Accounts, Section 7 "*La maîtrise des prescriptions à l'hôpital : mieux responsabiliser le corps médical*". See:
https://www.ccomptes.fr/sites/default/files/EzPublish/20160920-rapport-securite-sociale-2016-maitrise-prescriptions-hopital.pdf

2 - Meeting public health needs: maintaining access to therapeutic innovation for all

How can inflationary medicine policies be avoided?

When controlling expenditure on medicines reimbursed by the Assurance Maladie within the framework of the ONDAM is not enough to keep spending under control, the State has one final tool at its disposal to try and reduce the invoice generated by high prices. Introduced by the 1999 LFSS, this consists of a compensation mechanism to regulate medicine expenditure retrospectively. Voted on with each annual funding law, it allows a marginal part of the sums collected to be re-invoiced to manufacturers the following year, above a certain threshold of revenues invoiced to the Assurance Maladie, and taking into account changes in these revenues by comparing them with changes in the ONDAM[67].
As with discounts, these safeguard clauses have no effect on the inflationary trend fuelled by high list prices.
Finally, the creation of the pharmaceutical innovation financing fund (FFIP), introduced by Article 95 of the 2017 LFSS was intended to "smooth out spending on innovative and expensive medicines".
Despite not being effectively resourced, its very creation offered pharmaceutical companies a new source of funding for medicines that would ease the constraints on pricing and, for the State, amounted to accounting cosmetics rather than a genuine regulatory tool.
Recently abolished, according to the Social Security Accounts Commission, the fact that a large part of the cost of retroceded medicines was charged to this fund actually reduced the increase in expenditure covered by the ONDAM, which went from an annual increase of 6% to 1.8%. The so-called retroceded medicine envelope increased by more than 140% between 2010 and 2016.

The issue of awarding patents without therapeutic innovation

The price of medicines is higher when they are covered by a patent. Some highly questionable practices by pharmaceutical companies involve the successive renewal of patents without any actual innovation, in order to prolong revenues (evergreening)[68].
As an example of evergreening practices, the drugs Isoniazid (marketed in 1952) and Rifapentine (marketed in 1988), used to treat tuberculosis, were reintegrated into the development of paediatric and preventive treatments by Sanofi who, in 2013, applied for patents on this combination (even though the clinical trials had been financed by Unitaid and it was not possible to classify these products as innovative as they derived from the re-use of old drugs).
Several African countries approved these patents because their legislation did not lay down sufficiently precise conditions regarding patentability for them to be refused, since

[67] This procedure is known as the "safeguard clause", or "compensation rate", or "L rate". For example, in response to the explosion in spending on new treatments for hepatitis C, the 2015 LFSS introduced a specific safeguard clause based on revenues from hepatitis C medicines (known as the "W rate").
[68] Take insulin, for example:
https://www.lemonde.fr/sciences/article/2015/04/13/evergreening-strategie-a-but-lucratif_4615100_1650684.html

the patentability assessment was not based on substantive criteria. In Nigeria and South Africa, a very large number of people suffer from tuberculosis, yet these countries have approved Sanofi's patents, which make this combination of drugs unavailable in their territories until 2035 (switch to generics).
On the other hand, some countries have set up highly efficient patent offices, such as Egypt, where Gilead's patent application for Sofosbuvir was rejected[69].

Ultimately, **it is necessary to adapt the system for protecting intellectual and industrial property to the needs and challenges of public health**: (a) by reducing royalties for patents with minimal innovative value, (b) by allowing the use of compulsory licensing where necessary, (c) by combating evergreening practices, and (d) with a view to enhancing the notion of global public good[70].

Can we continue to accept exorbitant prices for innovative medicines produced by industries that benefit from strong state support?

The pharmaceutical industry benefits greatly from the research tax credit (CIR)[71]. The objectives of the CIR (to promote innovation, scientific employment and investment in research) are, in part, being abused by certain large groups. Sanofi, for example, receives around half a billion euros a year in research tax credits. The company makes profits of over €6 billion a year, yet cuts its R&D workforce by an average of 700 people a year and its R&D expenditure by €85 million[72]. It would appear that the emphasis on economic considerations in the development of the relationship with the pharmaceutical industry is not justified on either health and social or economic grounds.
To explain the State's consent to a contractual and regulatory framework that is conducive to maintaining an imbalance in its relationship with the pharmaceutical industry that is to its disadvantage[73], the Court of Accounts states that "*taking into account investments made in the European Union represents a significant concession to the pharmaceutical industry, on the grounds of this being in the national industrial interest*".
The aim is to "*take into account companies' commitments in terms of new investment and job creation or maintenance when setting medicine prices*". Is this desire to divert the Assurance Maladie from its primary objectives, in favour of industrial strategies designed to combat unemployment and promote innovation in the country, always ethical or economically justified? Beneficiary companies should be required to justify the expenditure made with the budget allocated under the CIR scheme.

How can negotiation with the pharmaceutical industry be improved?

The major agencies that play an important role in the medicine pricing process do not seem to have sufficient resources or the full range of skills needed to carry out large-

[69] At the same time, the Egyptian company Pharco has developed Sofosbuvir production to meet the needs of the whole of Africa (interview with Pauline Londeix).
[70] This has been achieved, in particular, in the fight against AIDS, by breaking Gilead's patent on Truvada®.
[71] https://www.lemonde.fr/les-decodeurs/article/2016/09/06/qui-profite-du-credit-d-impot-recherche_4993109_4355770.html
[72] https://www.senat.fr/compte-rendu-commissions/20150316/ce_cir.html
[73] This is all the more important given that the State regularly invests in the creation of start-ups, via funds allocated by the Public Investment Bank.

scale, high-quality medico-economic assessments to even out the balance of power with the pharmaceutical industry during negotiations. These negotiations are always a meeting of two bureaucratic structures. That set up by the pharmaceutical industry, known as "market access", is specialised and trained in dialogue with the regulatory authorities, separate from the medical side and the business units. Each of these manages a portfolio of products, by organ or by disease. They have their own sales specialists, most of whom are pharmacists or doctors with international training, including seminars. The negotiator for France, on the other hand, is a small team from the CEPS, made up of a few pharmacists or economists, who divide up areas such as hospitals, towns and cities, temporary authorisations for use (ATU), and so on.
As a result, the two sides of the negotiation are not evenly balanced. Furthermore, from the point of view of the HAS, whose Transparency Commission[74] advises the CEPS negotiators, the lack of robustness of the data available to it to assess the efficacy and added value of medicines presented as innovative makes the assessment all the more complex.

Finally, the manufacturers fuel their medico-economic evaluations by formulating hypotheses based on various observational data, other trials and epidemiological data. Although these figures, validated by the CEESP[75], are used in CEPS calculations to define average costs, these medico-economic evaluation reports are clearly underused[76].

While setting a threshold beyond which reimbursement would be compromised runs counter to the ethical principles of equity in the accessibility of innovative therapies, incorporating this parameter as a negotiating factor could be an opportune course of action. It is important to be able to construct reliable representations, so as to be able to quantify and accept the benefits of the products offered by manufacturers. High prices will be much more readily accepted if it appears that the therapeutic benefits are commensurate with the costs involved. Therefore, despite the scientific rigour employed within the institutions involved in the therapeutic or economic evaluation of medicines (and therefore in the negotiation process), "*it has to be said that the rapid pace of innovation and the issues surrounding early access to medicines mean that the current methods of evaluation are being called into question*"[77].

Is the French model of medicine evaluation and pricing still appropriate in the current international context of innovation?

3 - Civil society and the pharmaceutical industry: the risk of a real crisis of confidence

The question of how to prioritise human lives is increasingly raised on a daily basis by doctors, when they are short of staff, resources or equipment, when budgetary austerity policies or the failure to anticipate stock shortages force them to choose who to treat

[74] Independent scientific body made up of twenty-one experts with voting rights (doctors, pharmacists, clinicians, specialists in methodology and epidemiology, members of patient and user associations).
[75] Commission for Economic and Public Health Evaluation, housed at the HAS.
[76] According to the vice-chairman of the CEPS.
[77] http://www.senat.fr/rap/r17-569/r17-569_mono.html

and who to continue treating[78]. These situations are increasingly publicised in the media and known to the general public.
The very high prices charged by pharmaceutical companies are already leading to painful and ethically unacceptable situations. The inability of the Assurance Maladie system to bear the costs of covering all the patients who could benefit from certain innovative and expensive medicines means that doctors and pharmacists have to make choices about which patients to treat.
Multidisciplinary committees exist in public hospitals, in conjunction with the hospital pharmacy, to discuss the allocation of these new treatments. These decisions raise difficult ethical dilemmas because they involve choosing, from among several patients, the one or more who could derive the most benefit from a medicine, or choosing which diseases might be a higher priority for treatment than others. The criteria that lead to these choices are difficult to establish, and would undoubtedly benefit from being discussed either upstream, in particular with patient representatives and/or associations, or in hospital committees, with in-depth ethical reflection on the prioritisation of these choices in hospitals.
The limited choices imposed by the excessively high prices of certain innovative medicines for the Assurance Maladie system **could ultimately lead to a real crisis of confidence between civil society and the pharmaceutical industry**.

Some very expensive gene therapies, for example, are no longer accessible in Belgium, creating particularly difficult situations for families who are forced to rely on public charity and participatory funding to provide treatment for their sick relatives. Two Belgian children with type 4 mucopolysaccharidosis in need of a protein substitute, who were included in a clinical trial phase, had their treatment halted after the laboratories announced their price (€500,000/year/patient). In countries where Zolgensma® is not available (because it is far too expensive for the countries concerned), Novartis draws lots to select 100 children out of all those who need it, and delivers the treatment free of charge.

The problem of stock shortages: a regrettable example of the failure to reconcile industrial interests with the public interest.

This crisis of confidence can also be explained by the fact that **the profits of the pharmaceutical industry do not always seem to be in proportion to the quality of the services it provides**. Indeed, there are regular failings, notably the recent increase in stock shortages. A Senate report[79] shows that stock shortages increased by more than 40% in 2018. Since 2008, they have increased 20-fold. This exponential increase concerns both hospital and outpatient medicine[80].

[78] Leichter-Flack F. (2015), *Qui vivra, qui mourra. Quand on ne peut pas sauver tout le monde*, Albin Michel, 208 p.

[79] https://www.senat.fr/questions/base/2019/qSEQ190208709.html

[80] The medicines that are out of stock may belong to very different therapeutic classes: anticancer medicines (22%), anti-infectives (22%), anaesthetics (18%), central nervous system medicines (intended in particular for the treatment of epilepsy or Parkinson's disease), as well as blood-derived medicinal products are the most frequently affected by a stock or supply shortage. Of all the reports of medicines of major therapeutic interest in short supply or out of stock made to the ANSM in 2017, 26 concerned vaccines. According to LEEM, the average length of stock-outs in 2017 was around 14 weeks, with a median of 7.5 weeks.

The recurrence and worsening of the difficulties affecting major anti-cancer medicines, most of which are old but essential to the treatment of malignant diseases, is a cause for concern for the French National Cancer Institute (Inca), which in early 2020 alerted the Ministry of Solidarity and Health to the urgent need for an action plan[81]. According to Inca, around forty essential cancer medicines have been subject to major pressure or even repeated shortages over the past year.

The complexity of the production chain appears to be at the root of recent medicine shortages. "*The globalisation of production and the reduction in the number of local sites undermines the process and reduces flexibility with regard to the markets. From the active ingredient to the finished product delivered to the patient, market disruptions do not allow rapid corrections to be made to avoid stock shortages*", acknowledges the French National Academy of Pharmacy[82].
Over the last 20-25 years, for essentially economic reasons, a very large number of production operations have been relocated to Asia. China has thus become the main supplier of active ingredients and intermediate raw materials used in the composition of many medicines.
The large number of stock shortages and supply tensions is not confined to France; a comparable situation can be observed at European and international level[83].

Initial lessons from the Covid-19 crisis
The Covid-19 health crisis in the spring of 2020 served to reinforce the pressure on essential medicines, the basic components of which are produced mainly in Asia. It also highlighted the fact that the pharmaceutical industries, when it came to producing non-innovative medicines or drugs that already existed, were not very reactive when it came to making up the supply shortfall. On the other hand, the development of a vaccine mobilised a large part of the pharmaceutical industry, making it possible to envisage large-scale production in the short term using highly innovative techniques (mRNA-type vaccines).
The health crisis has brought into sharp focus the issue of 'triage' in terms of resource allocation, whether for an intensive care bed or access to a vaccine.
This health crisis, on a global scale, has also demonstrated the indisputable effectiveness of industrial research and, at the same time, the fragility of the notion of a global public good, particularly where vaccines are concerned: the rapid mobilisation of governments to raise funds for research and development, but current uncertainties over the unit price of the future vaccine; the opportunistic response of a pharmaceutical company in defining the scope of its market; uncertainty over whether low-income countries will be able to obtain the vaccine.

[81] Joint note from the Inca chair and the ANSM general management sent to the Minister for Solidarity and Health on 29 January 2018, setting out proposals "*targeting the current situation of increasing tensions in the supply of cancer medicines*".
[82] https://www.acadpharm.org/dos_public/DULIERE_Complexite_de_supply_chain_en_pharmacie_V2.pdf
[83] At European level, a survey carried out in 2016 in 21 countries by the Pharmaceutical Group of the European Union showed that pharmacies in all 21 countries had been affected by shortages during the previous 12 months. At global level, the work carried out since 2011 by the International Pharmaceutical Federation (FIP) tends to show that the phenomenon affects all countries in the world - as evidenced by the resolution adopted by the World Health Organisation (WHO) on the subject in May 2016. Finally, an own-initiative report on medicine shortages has just been submitted to the European Parliament by MEP Nathalie Colin-Oesterlé.

Towards the need to define new economic models

Scientific and medical progress is accelerating at a spectacular rate, but the considerable increase in the cost of certain therapies is seriously affecting the possibility - now or in the future - that everyone will be able to benefit from them.
The CCNE is therefore proposing that **thought be given, at national and European level, to the creation of not-for-profit medicine production entities**, which presupposes that "the objectives of the company are not restricted to the interests of the shareholders, but take into account other parameters relating to the services rendered to society in general". (Fischer *et al*. 2020). The example of the Drugs for Neglected Diseases initiative (DNDi) foundation, which manufactures medicines for orphan diseases with no profits beyond those needed to maintain the viability of the company, makes it possible not only to develop medicines for very rare diseases, but also to compete with for-profit pharmaceutical companies.
Other alternatives of this type are currently being developed around the world, notably in Brazil and Thailand for non-innovative medicines. In Belgium and Israel, for example, hospitals and/or public research institutes are producing innovative CAR-T cell medicines at prices and costs far lower than those charged by the pharmaceutical industry (price charged to patients equivalent to €8,500 vs. €170,000 corresponding to the selling price in Europe when production is industrial). In Bangalore, India, the Indian government is funding the development of public structures capable of producing gene therapies to combat thalassaemia. The Etablissement Français du Sang has also set up a platform for the preparation of advanced therapy medicinal products in Burgundy-Franche-Comté, which meets European standards and is currently involved in the production of CAR-T cells[84].
Some therapeutic innovations could therefore be produced by this type of public structure, whose governance would also have to be modified, modelled on that of benefit corporations[85]. On the other hand, when it comes to less innovative medicines, it is up to the pharmaceutical industry to find ways of avoiding shortages.

While, from an ethical point of view, this structural change may make it possible to reconcile the two stated objectives of providing the best treatment for everyone and achieving the best balance of care to ensure the sustainability of the system, it also entails a major cultural shift that could be accompanied by new legislative measures.

[84] https://www.reseau-chu.org/article/car-t-cells-vers-une-nouvelle-immunotherapie-pour-combattre-le-cancer-du-sang-et-de-la-moelle/
[85] The Italian company Chiesi is the only European company to currently have this status in the pharmaceutical sector. See: https://www.chiesi.fr/b-corp

CCNE RECOMMENDATIONS

The proposed recommendations aim to reconcile two objectives: optimising access to the best care for everyone and optimising the search for the lowest price in negotiations.

1. Demand transparency

- The demand for transparency is ethical and democratic above and beyond its strategic economic importance. Set up a "Ségur du médicament" consultation process, bringing together all stakeholders in the sector, including representatives of society, to discuss ways of developing a policy of transparency based on the definition of explicit cost rules.

- Cap authorised lobbying expenses for pharmaceutical companies in order to limit their impact on marketing authorisations in Europe and on prescription practices. Adopt the legislative and regulatory means to verify compliance with this cap, and impose sanctions if necessary.
  Evaluate the application of the anti-gift law and strengthen it by seeking to increase the separation of prescribers and manufacturers to the greatest possible extent

- Evaluate and monitor the work carried out by medical sales representatives and its impact on prescription practices. Make publication of the schedule of visits compulsory.
  Develop fair prescription policies within hospitals, in collaboration with clinicians, pharmacists, biologists and IT departments, and strengthen the multidisciplinary committees that decide on the allocation of innovative and expensive medicines by developing the ethical dimension of decision-making processes, particularly that of distributive justice.

2. Strengthen and/or broaden the powers of public authorities

- Strengthen the public bodies that prepare the negotiations by calling on public researchers and leading figures from the academic world, based on their skills and specialities (economic and scientific), to carry out medico-economic analyses.

- Develop real-life evaluation of the effectiveness of expensive innovative medicines.

- Consolidate patent offices so that they have the human resources (legal skills, training) and information they need (legal and regulatory provisions) to assess the effectiveness of innovations proposed by manufacturers.

- Create an (autonomous) "public medicines office" to set up public (or mixed) entities for the production of innovative medicines on a not-for-profit and profitable basis, based on the coordination of research teams.

3. Develop a policy of cooperation at European or international level

- Reflect on:

- The issues surrounding the legal classification of certain innovative medicines as "global public goods".
- The possibility of creating a European agency specialising in the economic analysis of healthcare products, or extending the remit of the EMA.
- Strengthening health sovereignty at national and European level. The construction of a "Europe of Health" must involve the adoption of a common geostrategy, in terms of both health planning and production.

APPENDICES

Appendix 1: Group members

Mounira Amor-Guéret
Jean-François Bach
Christiane Basset
Monique Canto-Sperber
Sophie Crozier (rapporteur)
Jean-François Delfraissy
Pierre Delmas-Goyon
Pierre-Henri Duée
Anne Durandy-Torre
Corinne Imbert
Florence Jusot (rapporteur)
Francis Puech
Dominique Quinio
Anne-Marie Taburet (AP-HP, external expert)
Bertrand Weil (CCNE, honorary member)

Louise Bacquet (CCNE, editorial assistance)
Lina Bognard (Paris 5 student)

Appendix 2: Hearings held

2016

François Chast: Head of Clinical Pharmacy, University Hospitals, Paris Centre

Jean-Paul Vernant: Emeritus Professor of Haematology, Pitié-Salpêtrière University Hospital

2017

Olivier Maguet: Director of "Médecins du Monde";

Maurice-Pierre Planel: Deputy Director General for Health, former Chairman of the Economic Committee for Health Products (CEPS);

Jean-Patrick Sales: Vice-Chairman of the Economic Committee for Health Products (CEPS) and head of the Medicines Section;

Michel Joly: Chairman of the pharmaceutical company Gilead France;

Philippe Bonnard: Medical Director, Oncology, Janssen Inc (a Belgian pharmaceutical company and subsidiary of Johnson & Johnson);

Laurent Degos: former President of the College of the French National Authority for Health (HAS);

Nicolas Revel: Director of the National Health Insurance Fund for Salaried Workers (CNAMTS);

Emmanuel Jammes: Delegate/Society and Health Policy Mission at Ligue contre le cancer and **Théo Brigand**: Advocacy and Ethics, Ligue contre le cancer;

Grégoire Moutel: Member of the Inserm Ethics Committee and former member of the Ethics Committee of the French National Cancer Institute (INCA).

Magali Leo: Head of Advocacy at Renaloo and **Adeline Toullier**: Director of Advocacy at AIDES

Yann Mazens: Health Products and Technologies Project Manager at the National Union of Approved Associations of Health System Users (UNAASS - FranceAssosSanté);

2019

Jerome Wittwer: member of the Board of Directors of the College of Health Economists and member of the health chair at Paris-Dauphine University;

Anne-Marie Broca: General Inspector of Social Affairs, President of the High Council for the Future of Health Insurance (HCAAM):

Isabelle Andrieux-Meyer: Head of Clinical Development, HIV & Hepatitis C Initiative, DND*i* (Drugs for Neglected Diseases initiative - Geneva*);*

Christian Saout: former President of the AIDES association, member of the college of the French National Authority for Health (HAS);

Hervé Chneiweiss: Chairman of the INSERM Ethics Committee

2020

Jean-Patrick Sales: Vice-Chairman of the Economic Committee for Health Products (CEPS) and head of the Medicines Section;

Eric Baseilhac: Director of Economic and International Affairs at LEEM (French Pharmaceutical Companies Association);

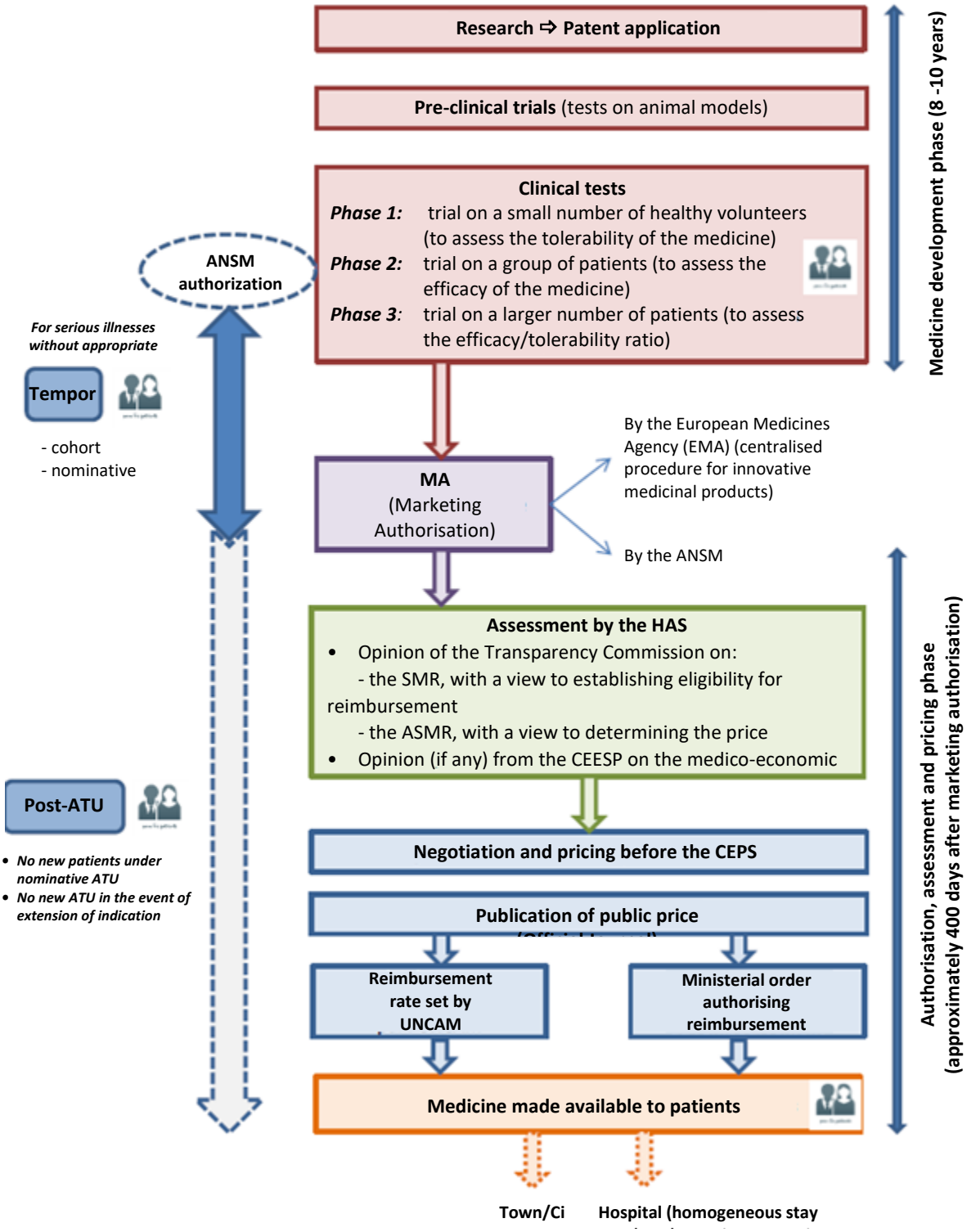
Laurence Tiennot-Herment: President of AFM-Telethon;

Alain Fischer: Professor at the Collège de France;
Pauline Londeix and **Jerome Martin**: Observatory for transparency in medicines policies (OTMeds)
Jean Mieg de Boofzheim: Master II student "Medico-economic evaluation and market access" at Paris Dauphine University;

In addition to the hearings carried out, two interviews were conducted: one with Didier Tabuteau (Council of State) and the other with Louis Schweitzer (senior civil servant).

Appendix 3: Routes to market and patient access for medicinal products (Senate Information Report, n°569 2018)

Routes to market and patient access for medicinal products



Appendix 4: Setting and regulating medicine prices in France (France stratégie; 2014)

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NATIONAL CONSULTATIVE ETHICS COMMITTEE FOR HEALTH AND LIFE SCIENCES