

## Why Europe and France in Particular are Dependent on Asian Chemical Industry (India and China) in the Event of a New COVID Pandemic?

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### ABSTRACT

During the pandemic in Europe and mainly in France, product stock shortages of various drugs such as analgesic (paracetamol), muscle relaxants (propofol), anti-inflammatories, and various essential medical materials such as fibers to make protective masks, polypropylene for the manufacture of medical equipment, syringes, and tubes, were effective. These drugs and materials require essential basic chemical raw materials such as nitrobenzene, aniline, phenol, and polypropylene, of which China and India are the largest exporters. The purpose of this manuscript is to show that in the current state of the production capacity of these raw materials, France remains dependent on Asian nations and that in the event of a new pandemic. Stock shortages of essential drugs and medical equipment will always be feared and that the aid of Asian nations remains imperative to provide the essential chemical raw materials. Synthesis processes of these raw chemical compounds are discussed.

**Key words:** Petrochemicals raw materials, Asian manufacturers, Covid-19 pandemic, Pharmaceuticals drugs.

### 1. INTRODUCTION

Situation of the petrochemical and pharmaceutical industry in the world, at the time of the pandemic, could be summarized as follows : Eight hundred and sixty-eight is the number of reports of stock shortages of drugs of major therapeutic interest (corticosteroids, antibiotics, neuroleptics, and anticancer drugs) in France in 2018, while it was only a few dozen in 2008, [1]. These supply problems are not specific to France, this same problem occurs in other European nations. One of the major reasons for these drug stock-outs is directly attributable to the problem of the production in industrial quantities of the required active ingredients to synthesize these drugs at the global level. Petrochemical industries producing these essential raw chemical materials are concentrated mainly in Asian countries and the USA [2]. Concentration of “heavy petrochemicals” industries in Asian and North American countries partly explains the stock-outs of certain drugs in Europe and in France in particular, since the production and sale of finished drugs manufactured by the major industrial groups in the pharmaceutical industry depend essentially on the production of raw materials by oil processing plants.

We will first analyze why some pharmaceutical drugs and medical plastics devices of first need for the treatment of COVID-19 infected patients were the subject of shortage, and why producers were not able to supply the requesting countries.

In a second part, we will analyze the world production of major raw materials by petrochemical industries, which are essential for the pharmaceutical industry to synthesize drugs need during COVID-19 pandemic.

In a third part, we will discuss whether in the future, European nations will be able to overcome these problems of shortage, by relocating and reindustrializing the production of the pharmaceutical industry in Europe and in France in particular [3].

### 2. SHORTAGES OF ESSENTIAL PHARMACOLOGICAL DRUGS AND MEDICAL MATERIALS REGISTERED IN EUROPE FOR COVID-19 PANDEMIC

What have we learned from the SARS-Cov-2 pandemic which has been raging since 2019 on all continents? We will not mention in this manuscript problems related to the vaccination, we will only mention the significant shortages and stock shortages of drugs [4,5] and various medical materials registered in Europe and in France in particular. Among the main essential medicines for which supplies have sometimes been limited or even interrupted, we can cite:

- Analgesics such as paracetamol [6]
- Sedative derivatives such as propofol [7], various anesthetics or muscle relaxants such as cisatracurium and midazolam. These compounds maintain patients who require mechanical ventilation, in a state of continuous sedation during resuscitation periods
- Anti-inflammatory corticosteroids such as prednisolone, dexamethasone, or prednisone [8,9].

These supply shortages also affected essential materials, necessary for the immediate care, and protection of patients with COVID, such as disposable syringes, gloves, overcoats, hydroalcoholic gel for hand washing, and specially anti-COVID protective masks.

This finding requires that in the event of a new coronavirus pandemic, all countries have planned sufficient quantities of drugs for appropriate

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periods of time and have sufficient quantities of essential antiviral protection equipment so that all patients and hospital staff can immediately protect themselves against infection. Could France in the current state of the situation become independent from the supply constraints of essential compounds and materials, by manufacturing on its soil, both the drugs and the materials need to immediately face to a possible rebound of the pandemic.

### 3. PRODUCERS OF MAJOR RAW PETROCHEMICAL MATERIALS FOR PHARMACOLOGICAL DRUG MANUFACTURING PROCESSES (PARACETAMOL, PROPOFOL, POLYPROPYLENE, AND PROPENE)

Why were pharmaceutical compounds out of stock [3] during the COVID-19 pandemic?

Let us recall the main pharmacological compounds mentioned in the first part which have been the subject of supply difficulties (Paracetamol, propofol, dexamethasone, muscle relaxants, and hydroalcoholic gel) and disposable materials (masks, gowns, and syringes) which require special plastic materials. To understand these difficulties, it is necessary to consider at the same time the manufacture processes of these compounds, their places of manufacture, manufacturers who provide for their supply, and the raw materials essential to their production. It is only by considering all of these parameters that we can better understand the difficulties that the governments of the Western countries have had to face, and which they will have to overcome in the event of new coronavirus pandemic.

For the sake of simplicity, we will take the significant examples of the production of the most used pharmaceuticals drugs during the pandemic: Paracetamol and propofol.

The manufacture of any chemical compound whether of pharmaceutical interest or used as materials comes from factories of different sizes, of different specialized capacities which are installed in different countries and which have particular production specificities.

On a global scale, we can cite the largest petrochemical groups: US and Europe:

*Unilever, Exxon, Kem Owe, Total Petrochemicals, Bayer, Dow, Chevron, BASF*, and the largest Asian groups such as *Mainland* in China and the *Jamnagar industrial site* in Gujarat, which is the largest industrial petrochemical center in India [10].

These large groups provide the essential raw materials which are then exported to specialized European factories: In Germany (BASF SE companies [Ludwigshafen], Evonik Industries [Essen], Helm AG [Hamburg], Wacker Chemie AG [Munich], and Altana AG [Wesel], in USA, there are no <9000 companies that manufacture high value-added chemical products as well as different chemical materials for different industrial applications.

The requests for essential raw materials come mainly from the major global pharmaceutical groups represented by the following big pharma in the USA and Europe [11].

- -10 are American (*J and J, Roche, Pfizer, Merck, Abbott, Amgen, Gilead, Abbevie, Bristol-Myers, and Elli-lilly*), -2 are German (*Bayer Boringher*), -2 are from the UK (*Glaxo and Astra-Zeneca*), -2 are Swiss (*Roche and Novartis*), -1 Japan (*Takeda*), and -1 French (*Sanofi*).

In recent years, Asian big pharma competing with American and European big pharma has emerged:

- In China: Ten major pharmaceutical companies [12], whose revenues are around 10 billion dollars, including the leading company *Sinopharm Group*, (271 billion US dollars) (*Shanghai*

*Pharmaceuticals, Jiangsu Hengrui Medicine; Guangzhou Baiyunshan Pharmaceutical, China Meheco, Huadong Medicine, Yunnan Baiyao, and Shanghai Fosun Pharmaceutical*) [13]

- In India: 10 pharmaceutical companies including the leading company:

*Sun Pharmaceutical Industries Ltd, Reddy's Laboratories Ltd, Divi's Laboratories, Cipla., Aurobindo Pharma, Torrent Pharmaceuticals, Lupine Ltd, and Zydus Cadila Healthcare*). The revenues of the Indian pharmaceutical industry were around 20 billion US dollars in 2019 [14].

If these global big pharma can source much-needed raw materials, they can manufacture and supply almost all of the medicine needs of the people of the planet. In this feature, one could think that given the number and production potential of these big pharma, drug stock-outs would be very low or even unlikely, except in the event of major incidents: Quality defect and technical problems.

The major problem that remains is the production of the essential raw materials required for the chemical synthesis of these molecules of therapeutic interest by these big pharma. Only a few large heavy petrochemical groups have a monopoly on the production of these basic raw materials essential to big pharma for the development of their molecules of therapeutic interest.

The questions then arise: What basic chemical raw materials are needed at industrial scale? What are these producing countries? What is their production capacity? Is it possible for any country to produce these materials at industrial scale?

#### 3.1. Paracetamol Case

To answer these questions, we will take the case of the industrial production of paracetamol, cited as a molecule temporarily out of stock during the pandemic in France and Europe [15].

The objective being to produce paracetamol on an industrial scale [Scheme 1], that is to say several thousand tons, what tonnages of essential raw material would be necessary? Can Europe produce these raw materials for the production of millions tons of paracetamol, a drug which was out of stock during the last COVID infection:

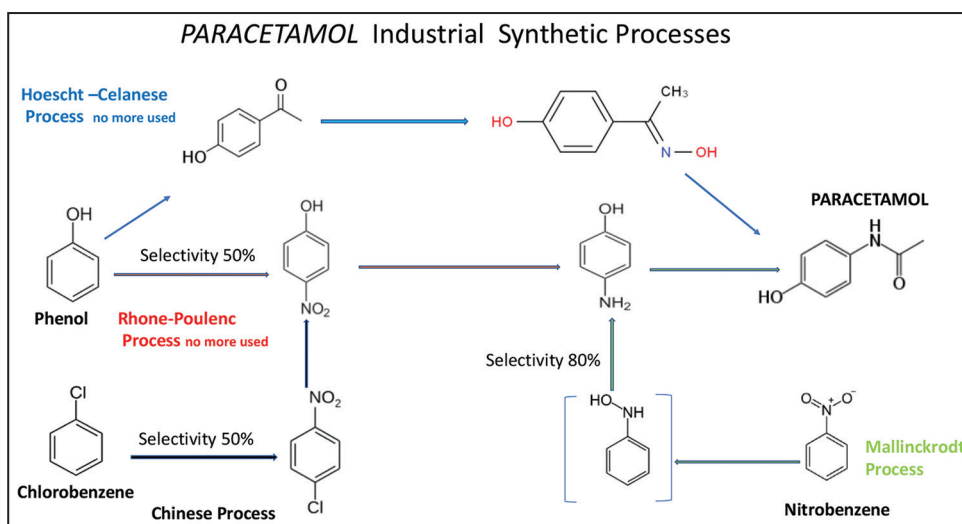
The synthesis of paracetamol requires, depending on the synthetic processes, the following chemical materials: Phenol for the *Rhône-Poulenc* and *Hoescht-Celanese* processes, and chlorobenzene for the *Chinese process*. Today, the most widely used process being the *Mallinckrodt process*, [16] which basic raw material essential is nitrobenzene.

Who are the largest nitrobenzene producers in the world?

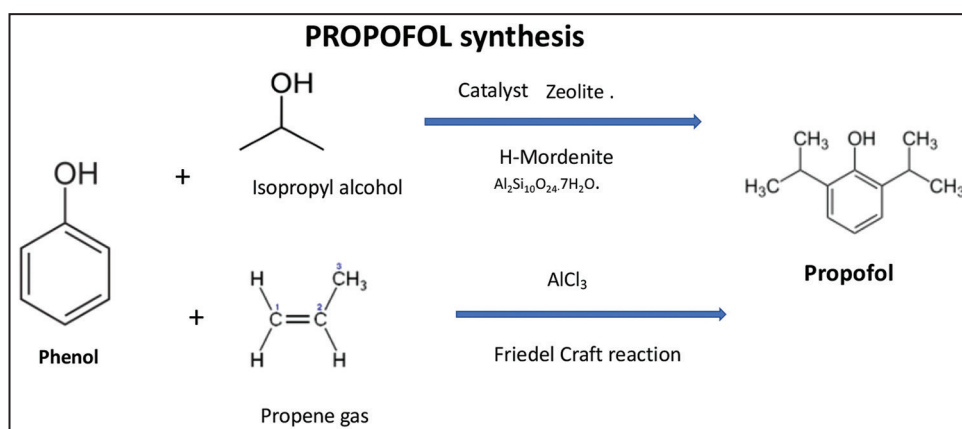
Few countries produce nitrobenzene [17,18]: The main producing countries are India, China and USA. Worldwide, the production of nitrobenzene was around 6–7 million tons.

In 2019, China used 40% of nitrobenzene produced by its Mainland China plant for its own internal needs. Only a few large industrial groups (BASF, Dupond Nemours, Mainland China) export nitrobenzene to drug big pharma European and American makers already mentioned. India uses a large part of its production (0.6 million tons) of nitrobenzene for the production of certain specific drugs widely prescribed in the world, such as paracetamol.

In particular, India through its company *Sri Krishna Pharamaceuticals* [19] located in Hyderabad, manufactures large quantities of paracetamol used in the world. India is one of the biggest producers of paracetamol with approximately, 22,000 tons of paracetamol per year. It is one of the world's largest exporters of paracetamol. In 2020, *Sri Krishna Pharamaceuticals* exported 1000 tons of paracetamol to Europe.



Scheme 1: Paracetamol: Industrial synthetic processes



Scheme 2: Propofol : Industrial synthetic processes

We note that with regard to paracetamol, Europe in general and France in particular are partly dependent on Indian Pharmaceutical Groups, and it should be also underlined that India is itself dependent on the world production of nitrobenzene, whose prices in the market, varies a lot.

### 3.2. Propofol Case

Propofol is a drug used in certain cases to soothe patients with COVID, who are in intensive care and who must undergo tracheal intubation. As shown on **Scheme 2**, the synthesis of propofol [20-24] requires as essential raw chemicals phenol, isopropyl alcohol, and propene gas.

### 3.3. Phenol Case

Phenol is a basic raw chemical produced mainly by different global groups: for India - (*Sigma lifesciences India, Harman Finochem India, Neulands lab India*). For China: (*Porton Fine Chem*). For USA: (*SI group*). At the European level, some European companies (Switzerland and Italy) manufacture phenol. The synthetic phenol process is given on Scheme 3. Its synthesis requires mainly as major raw chemicals: Benzene and propene [25].

World production of phenol is approximately 11 million tons per year [26].

The USA through its *Lineos group* produces about 1.17 million tons. This Lineos company is the largest phenol producing company with factories in Belgium, Germany, and the United Kingdom. Propene is also an important raw material, it is used for both phenol and propofol

synthesis. Isopropanol and propene are two compounds produced by different groups, American, Asian, and European. Isopropyl alcohol is also used in the composition of certain hydroalcoholic gels produced by INEOS, USA, used for hand washing to protect against COVID-19 infection [27].

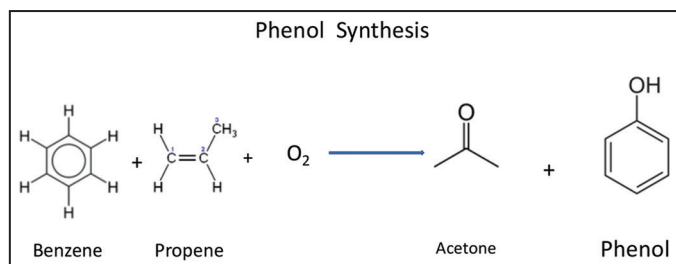
### 3.4. Polypropylene Case

To make so-called FFP2 masks that are effective in filtering viral particles, it is necessary to create polypropylene fibers which after a special treatment, give access to high-performance specific materials called “meltblown” and “spunbond.”

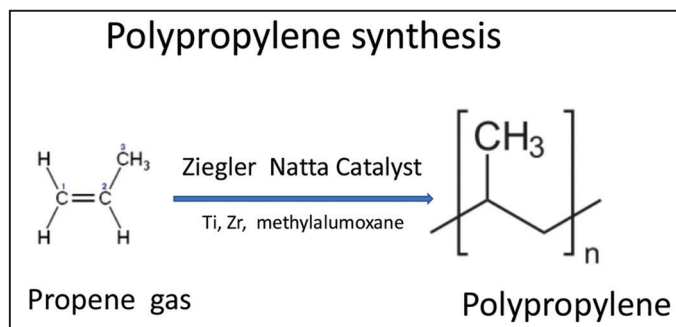
Polypropylene is the essential raw material for the manufacture of these fibers. Its synthetic process is given on **Scheme 4**. Polypropylene is mainly produced by China (20 million tons), Asia (18 million tons), Europe (11 million tons), and the USA (8 million tons). China and India are also the biggest consumers of polypropylene [28].

This polymer is used in many sectors of economic life (car, electronics, etc.), and for the manufacture of plastic materials, syringes, and materials essential for hospital care. This polymer requires as basic raw chemical propene (monomer) which is then polymerized according to well-known industrial processes. Propene is obtained either from 1-propanol [**Scheme 5**] or by metathesis from the mixture of ethylene and 2-butene [29].

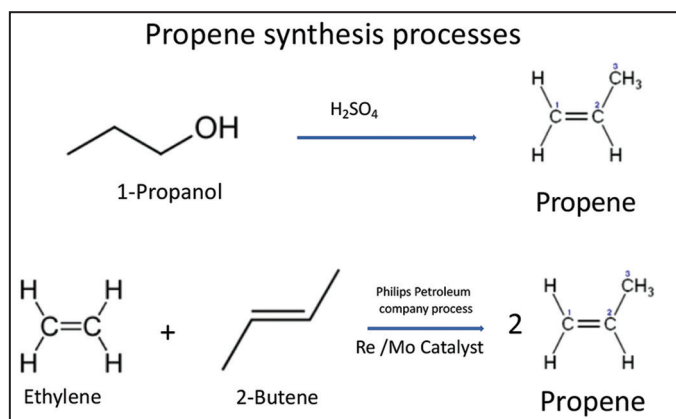
Paracetamol, propofol, FFP2 masks, and materials for single medical use (syringe, tubes, pipettes, etc.), whose manufacture requires raw



Scheme 3: Phenol : Industrial synthetic process



Scheme 4: Polypropylene :Industrial synthetic process



Scheme 5: Propene industrial processes

chemicals from heavy petrochemicals, have been subject to stock shortages during the COVID pandemic. As shown these raw chemicals and materials essential to their manufacture are mainly produced by China, India, and the USA, which partly explains the supply difficulties encountered by European countries.

#### 4. RELOCATION OF CHEMICAL AND PHARMACOLOGICAL INDUSTRY IN EUROPE TO PREVENT DRUGS AND MEDICAL MATERIALS SHORTAGES

Can Europe and France protect itself against shortages of pharmacological drugs or certain materials whose needs could prove crucial during possible new pandemics?

The answer to this question is not simple on the scale of France. Is the relocation of the French chemical industry on French soil possible? Is the establishment of new factories that manufacture toxic and dangerous chemical materials desirable? The recent incidents that have occurred with the AZF and Lubrizol factories in France are not very encouraging for these relocations or establishments. Which French regions that would welcome without hesitation factories producing toxic and dangerous chemicals but essential, if France wants to regain

relative independence from Asian and North American nations in the production of pharmaceutical compounds and certain essential medical materials?

A few ways to improve the situation of the therapeutic chemical industry in France can be envisaged:

- Many patents fell in the 2000s, giving possibilities for the manufacture of generic drugs. Unfortunately, laboratories producing these compounds have had to lower their prices, and in fact massively outsource their production to low-cost countries. For example, out of 206 pharmaceutical treatments authorized in France between 2012 and 2016, 16 are developed by French factories, 65 in Germany, 57 in the United Kingdom, and the rest are developed in Asia. In addition to lower production costs, the environmental standards required for the production of these molecules at the factory level, the quality of the products is less drastic in Asian countries than in Europe
- Another reason for the deindustrialization of the pharmaceutical industry remains the high taxation, the cost of labor, and the environmental standards which have led to the relocation of production sites by the creation of subsidiaries abroad of French groups in the French chemical industry. Today 62% of industrial employment in the French Chemical Industry is abroad, compared to 52% in the United Kingdom, 32% in Germany, 26% in Italy, and 10% in Spain [31]. It is legitimate for pharmaceutical business leaders to seek above all to protect their interests and the sustainability of their companies by relocating them [30,31].

To improve this situation, it might be necessary to:

- Act on some of these tax levers to lower the tax burden
- Rethinking the establishment of “clean chemical plants” on the national territory [32]
- Review the introduction of taxes on the import of certain pharmaceutical products
- To renegotiate some of the agreements of the world trade organization for essential health products in the event of a new pandemic.

#### 5. CONCLUSION

To return to our initial point, if a new COVID pandemic was to arise, based on the information from the previous pandemic, would we be protected from the risks of stock shortages of essential products, as was the case during this first pandemic?

Today, based on our experience, we could anticipate certain shortcomings such as FFP2 masks or hydroalcoholic gel, but if the needs for anesthetic, sedative, analgesic or anti-inflammatory drugs, or any other pharmaceutical product were to become significant, we would not be safe from shortages. Indeed, if for certain sectors, industrial reindustrialization is possible, cosmetics, agri-food, household appliances, furniture, and relocations are possible, for the pharmaceutical industry, the task is more difficult and our independence will be more difficult to acquire, and probably will stay for several years.

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#### COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals performed by any of these authors.

## 7. REFERENCES

- D. Jasserand, J. F. Dulère, (2021) *Drug Shortages: What Way Out? Pénuries de Médicaments: Quelle Issue?* South Korea: IESF.
- Encyclopedia Britannica, (2022) *Petrochemical Chemical Compound*. Edinburgh, Scotland: Encyclopedia Britannica. Available from: <https://www.britannica.com/science>
- Medecine Shortages in France Exacerbated by COVID, (2022) Which Products are Affected and Why? Available from: <https://www.connexionfrance.com>
- R. A. Siemieniuk, J. J. Bartoszko, L. Ge, D. Zeraatkar, A. Izcovich, E. Kum, H. Pardo-Hernandez, A. Qasim, J. P. D. Martinez, B. Rochwerg, F. Lamontagne, M. A. Han, Q. Liu, A. Agarwal, T. Agoritsas, D. K. Chu, R. Couban, E. Cusano, A. Darzi, T. Devji, B. Fang, C. Fang, S. A. Flottorp, F. Foroutan, M. Ghadimi, D. Heels-Ansdell, K. Honarmand, L. Hou, X. Hou, Q. Ibrahim, A. Khamis, B. Lam, M. Loeb, M. Marcucci, S. L. McLeod, S. Motaghi, S. Murthy, R. A. Mustafa, J. D. Neary, G. Rada, I. B. Riaz, B. Sadeghirad, N. Sekercioglu, L. Sheng, A. Sreekanta, C. Switzer, B. Tendal, L. Thabane, G. Tomlinson, T. Turner, P. O. Vandvik, R. W. Vernooij, A. Viteri-García, Y. Wang, L. Yao, Z. Ye, G. H. Guyatt, R. Brignardello-Petersen, (2020) Drug treatments for covid-19: Living systematic review and network meta-analysis, *BMJ*, **30**: m2980.
- G. Li, E. De Clercq, (2020) Therapeutic options for the 2019 novel coronavirus (2019-nCoV), *Nature Reviews Drug Discovery*, **19**(3): 149-150.
- Paracetamol, (2022) Information Centre Designed. Available from: <https://www.pharmweb.net>
- P. Picard, M. R. Tramèr, (2000) Prevention of pain on injection with Propofol: A quantitative systematic review, *Anesthesia and Analgesia*, **90**: 963-969.
- Corticosteroids, (2021) COVID-19 Treatment. Available from: <https://www.covid19treatmentguidelines.nih.gov>
- Use of Dexamethasone and Other Corticosteroids in Covid-19, (2019) Available from: <https://www.hcsp.fr>
- K. Baxter. World's 10 Largest Petrochemicals Companies-oil and Gas, (2009) <https://www.oilandmiddleeast.com>
- M. Christel, The 50 Largest Pharmaceutical Companies by Sales, (2021) <https://www.seekingalpha.com>
- W. Zhang, Top 10 chinese pharma companies (2020) Available from: <https://www.pharmaboardroom.com>; <https://www.statista.com>
- Sinopharm, (2022) Available from: <https://www.sinopharm.com>
- Statistics about Health, Pharma and Medtech in India, (2019) Available from: <https://www.statista.com>
- Analysis of Drug Sales in France in 2013. (2014) *National Agency for the Safety of Medicines and Health Products in France. Paracetamol Sales*. New Delhi: ASNM.
- Mallinckrodt Acetamiphen Manufacturing Process Changes, (1987) The Pink Sheet. Available from: <https://www.pharaminelligence.informa.com>
- L. Fernández, (2022) U.S. Nitrobenzene Production. Available from: <https://www.statista.com>
- Installed Capacity of Nitrobenzene in India. (2021) Available from: <https://www.statista.com>
- Sri Krishna Pharma, (2022) Specialises in the Bulk Manufacture of APIs, DC Granules. Paracetamol Tablet-India MART. Available from: <https://www.srikrishnapharma.com>; <https://www.indiamart.com>
- A. J. Kolka, J. Napolitano, G. Ecke, (1956) The ortho-alkylation of phenol, *The Journal of Organic Chemistry*, **21**: 712-713.
- G. G. Ecke, A. J. Kolka, (1954) Patent US 2,831,898 A Phenol Alkylation Process. RPX Insight. Available from: <https://www.insight.rpxcorp.com>
- T. J. Kealy, D. D. Coffman, (1961) Thermal addition reactions of monocyclic phenols with ethylene, *The Journal of Organic Chemistry*, **26**(4): 987-992.
- B. E. Firth, T. J. Rosen, (1984) Patent US 4447657A. Preparation of Ortho-Alkylated Phenols 1984-04-20 Universal Oil Products. Available from: <https://www.patents.google.com>
- R. Mougeot, P. Jubault, J. Legros, T. Poisson, (2021) Continuous flow synthesis of Propofol. *Molecules*, **26**: 1783.
- Phenol Industrial Production Data. (2009) *Données Sur la Production Industrielle de Phénol*. 8<sup>th</sup> ed. Florida: Phénol-Produit SCF-Société Chimique de France. Available from: <https://www.new.societechimiquedefrance.fr>
- Global Phenol Market, (2022) Available from: <https://www.statista.com>
- Hydroalcoholic Gels Shortage in France. (2020) Coronavirus: France Caps Price of Hand Gel, Manufacturers Struggle to Meet Demand. Available from: <https://www.rfi.fr/RFIFrance>
- Global Production Capacity of Propylene 2018-2030-Statista, (2022) Available from: <https://www.statista.com>
- Propylene-Study: Market, Analysis, Trends Chemicals, (2013) Ceresana. Available from: <https://www.ceresana.com>
- Industrie, Médicaments. Pourquoi Relocaliser Nos Productions (2020) Why Relocate Our Production? Available from: <https://www.capital.fr> [Last accessed on 2020 Jul 21].
- La France, Championne Des Délocalisations, (2020) France, Champion of Outsourcing Available from: <https://www.latribune.fr> [Last accessed on 2020 Nov 20].
- Covid-19 Hastens French Push to Bring Home Medicines Manufacture, (2020) Financial Times. The World 2020. Available from: <https://www.ft.com>

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