The Chief Pharmaceutical Officer in the *exploitant* company

Anne-Catherine PERROY
Lecturer at the University of Lille 2
and Associate Counsel with Simmons & Simmons

Abstract

The issue of the Chief Pharmaceutical Officer's position has long arisen but been exacerbated in the context of increasing globalization. French pharmaceutical regulation has specificities that must be remembered and explained in all their organizational consequences to the parent companies of international groups. It was in this context that the French National Agency for Medicines and Health Products Safety and the French Chamber of Pharmacists wrote to the Chairmen, Managing Directors, Chief Pharmaceutical Officers and Legal Directors of pharmaceutical companies in March 2016, with a letter headed: "Position of the Chief Pharmaceutical Officer within a pharmaceutical company". This letter provides an opportunity to examine the concept of Chief Pharmaceutical Officers and identify its effects on the organization of pharmaceutical companies' activities in France.

Keywords

Chief Pharmaceutical Officer – Pharmaceutical companies – French National Agency for Medicines and Health Products Safety– French Chamber of Pharmacists – Globalization – Pharmacovigilance

Box: What are the responsibilities of stakeholders in the medical distribution process?

Contents

In March 2016, the Director-General of the ANSM and heads of Sections B (*exploitants* and manufacturers) and C (wholesale redistributors and depositories) of the French Chamber of Pharmacists wrote to pharmaceutical companies' Chairmen, Chief Pharmaceutical Officers and Legal Directors. The letter was headed: "Position of the Chief Pharmaceutical Officer within a pharmaceutical company".

It is reproduced here in full:

> "French law places pharmaceutical responsibility in the hands of a named person, the Chief Pharmaceutical Officer. It is vital that s/he can meet that responsibility in full.
>
> In a context of increasing globalization and division of the pharmaceutical chain, the Chief Pharmaceutical Officer is a cornerstone of the French health system, ensuring that essential medicinal products are made available to patients with the necessary quality.
>
> Yet the French National Agency for Medicines and Health Products and the Chamber of Pharmacists are becoming increasingly concerned about the Chief Pharmaceutical Officer's position within pharmaceutical companies and the resulting effects on medicinal product quality.
>
> We need your help to ensure that Chief Pharmaceutical Officers can take full pharmaceutical responsibility.
>
> France's Public Health Code specifies the Chief Pharmaceutical Officer's duties, roles and responsibilities. A corporate officer (Art. R. 5124-34) with all necessary powers over the company's pharmaceutical activities, the Chief Pharmaceutical Officer's position is defined in law (Art. R. 5124-36) and should be presented in detail in the deed of appointment.
>
> In particular, s/he must be able to make independent decisions relating to the company's pharmaceutical products and activities, pursuant to the Public Health Code and current good practice, in line with our code of ethics and conduct, and in the

interests of public health and patients.

As the law states, the Chief Pharmaceutical Officer is the final decision-maker at national level and must be allowed to play his/her role in the operation of all company departments involved in pharmaceutical activities.

It is important that his/her responsibility is visible. Therefore, the Chief Pharmaceutical Officer's position must be clearly specified in the company's organizational chart with details of the hierarchical relationships, delegations to the various departments responsible for pharmaceutical operations and connections with those departments.

Notwithstanding the company's joint liability, the Chief Pharmaceutical Officer is personally liable for pharmaceutical matters, both civilly and criminally, and can face disciplinary action.

We know that we can count on you, in your company as well as in its European and international dealings, to recognize the unique position of Chief Pharmaceutical Officer, who is accountable for medicinal product quality and patient safety."

The issue of the Chief Pharmaceutical Officer's position has long arisen, particularly in *exploitant* pharmaceutical companies, but been exacerbated in the recent context of increasing globalization.

French pharmaceutical regulation presents specificities that should be remembered and explained in terms of their organizational effects on the parent companies of international groups. It was in this context that the letter above sought to support *exploitants* and their Chief Pharmaceutical Officer in this sometimes-complex educational exercise.

The letter provides an opportunity to re-examine the definitions of *exploitant* and Chief Pharmaceutical Officer (**I**) and identify the effects on the organization of pharmaceutical activities and performance of duties in France (**II**).

I. DEFINITIONS OF "EXPLOITANT" AND "CHIEF PHARMACEUTICAL OFFICER"

The legal framework surrounding medicinal products in Europe is largely outlined in European Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use (hereinafter the "Directive" or "Community code"). In France, this European framework has been transposed into the Public Health Code.

However, French pharmaceutical regulation presents some important specificities, not least the positions of *exploitant* (A) and Chief Pharmaceutical Officer (B).

A. Exploitant

As the *exploitant* in French law is simply a translation of the distributor in European law, it is worthwhile reiterating the legal definition of wholesale medicinal product distribution activities in Europe (**1**) before exploring the position of *exploitant* (**2**).

1. Wholesale distribution activities in Europe

At European level, there are three separate positions:

- the MA holder, responsible for product marketing, pharmacovigilance, information-advertising, batch tracking and, where necessary, recalls[1];
- the manufacturer, with authorization granted by the Member State in which the manufacturing operations under its responsibility are carried out[2];
- the distributor, responsible for wholesale distribution operations[3].

Article 1(17) of the Community code defines the wholesale distribution of medicinal products as "All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public."

As well as holding medicinal products, therefore, supply and export are considered part of wholesale medicinal product distribution. On that basis, even if an operator does not physically hold medicinal products, it is still seen as a distributor and required to meet the associated obligations, particularly authorization from the competent health authority[4]. Legally, there is supply when medicinal products are sold, even if there is no logistical involvement in the distribution chain. In principle, it is not possible to claim that there is supply in commercial law but not in pharmaceutical law.

This is confirmed by whereas 6 of Directive 2011/62/EU of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, which introduced the concept of medicinal product broker in Europe to cover all links in the supply chain, even those unrelated to holding, handling, buying or selling medicinal products[5].

[1]Directive, Art. 6. 1a
[2]Directive, Art. 40 et seq
[3]Directive, Art. 76 et seq
[4]Directive, Art. 77. Therefore, not having storage and distribution premises, and so not physically holding medicinal products, does not exempt the operator from distribution authorization, which is designed to ensure that it and any subcontractors meet the obligations related to that activity.
[5]Whereas 6 of Directive 2011/62/EU states: "Persons procuring, holding, storing, supplying or exporting medicinal products are only entitled to pursue their activities if they meet the requirements for obtaining a wholesale

As an agent, the broker does not own the products, hence its activity is not defined as buying or selling but simply "in relation to the sale or purchase of medicinal products"[6] to facilitate its completion by a third party.

Article 1 of the aforementioned Community code states that wholesale distribution activities "are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned."

Therefore, the wholesale distributor of medicinal products can have two types of customers, depending on whether they are in direct contact with patients. Only the distributors supplying companies or sites with direct links to the public are subject to the public service obligations defined in Article 1, 18° of the Community code as "the obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question."[7]

2. *Exploitation* activities in French law

France has acknowledged the two categories of wholesale distributors defined at Community level by creating two separate positions alongside that of export wholesale distributor:

- the wholesale redistributor, defined as "the company buying and storing medicinal products […] in view of their wholesale distribution on an 'as is' basis"[8]; and
- the *exploitant*, a status entailing specific obligations for the marketing manager.

Therefore, the French legal framework does not recognize the status of simple distributor. Either the operator is an *exploitant* with all the associated obligations or a wholesale redistributor.

An operator that wants to market a particular medicinal product from and in France will necessarily have *exploitant* status — given the associated public service obligations[9], wholesale redistributor authorization, which is also limited to a specified distribution area, is not appropriate for an operator that intends to distribute a product in France.

Exploitant status has no European foundation and this French particularity, which may

distribution authorisation in accordance with Directive 2001/83/EC. However, today's distribution network for medicinal products is increasingly complex and involves many players who are not necessarily wholesale distributors as referred to in that Directive. In order to ensure the reliability of the supply chain, legislation in relation to medicinal products should address all actors in the supply chain. This includes not only wholesale distributors, whether or not they physically handle the medicinal products, but also brokers who are involved in the sale or purchase of medicinal products without selling or purchasing those products themselves, and without owning and physically handling the medicinal products."

[6]Remember that Article 1, 17a, of the Community code transposed into Article L. 5124-19 of the Public Health Code defines the brokering of medicinal products as "All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person."

[7]See whereas 38 and Article 81 of the Community code

[8]Public Health Code, Art. R. 5124-2 5°

[9]Article R. 5124-59 of the Public Health Code defines wholesale redistributors' public service obligations. Wholesale redistributors that fail to meet these obligations are liable to penalties, both criminal (Art. L. 5423-5, Public Health Code) and administrative (Art. L. 5423- 8, Public Health Code).

hinder the holder's freedom of establishment in the European Union, has attracted the European Commission's attention since it was created. Yet France has been able to maintain the status by assuring the European authorities that it would not require a holder established in another Member State to move to France in order to operate there legally[10].

Although the ANSM has recognized, therefore, that *exploitation* of a medicinal product in France could be provided by a company based in another Member State and with wholesale distributor authorization granted by this Member State when the Public Health Code's provisions are met[11], if the operator is established in France, it must be authorized as an *exploitant* and meet the requirements pertaining to that status in French law.

In Article R. 5124-2 3° of the Public Health Code, *exploitant* is understood to mean:

> "The company or organization providing the *exploitation* of medicinal products […]
>
> *Exploitation* includes wholesaling or free distribution, advertising, information, pharmacovigilance, batch tracking and, where necessary, batch recall as well as any corresponding storage operations."

The status places significant obligations on the operator, the marketing manager, which are very similar to those placed on the MA holder by Directive 2001/83/EC of 6 November 2001. Pharmacovigilance, information, medicinal product advertising and batch tracking in particular are activities associated, in France, with *exploitant* status. The aforementioned article states that "*exploitation* is provided by the MA holder, or by another company or organization on its behalf, or by both, in which case each one carries out one or more categories of operations constituting the *exploitation* of medicinal products."

It is interesting to note that in relation to European MAs in centralized procedures and for which the European holder appoints local representatives in the country, the ANSM's correspondence clearly implies that if the local representative is based in France, it must be an *exploitant*.

In relation to pharmacovigilance, the *exploitant*'s obligations are outlined in Articles R. 5121-162 to R. 5121-177 of the Public Health Code, which emphasize the need to manage proactively the pharmacovigilance of medicinal products that it places on the French market[12].

In organizational terms and pursuant to Article R. 5121-164 of the Public Health Code, all *exploitants* must employ the services of a doctor or pharmacist living and working in

[10]If the holder meets its own obligations in relation to information, advertising and pharmacovigilance, and the manufacturer oversees batch tracking and, where necessary, recalls, France should not require the presence of an *exploitant* in the territory.

[11]The company must be able to offer French patients the same quality undertakings and services as a French *exploitant*, e.g. no extra costs, access to documents in French and a 24/7 pharmacovigilance service.

[12]LEEM has published a document entitled *Le système qualité de l'exploitant*. It summarizes the regulatory texts and the documents / deliverables required to meet these obligations. The documents / deliverables that the *exploitant* must be able to produce in the event of an inspection covering the recording, processing, assessment and follow-up of adverse reactions include: management procedure (recording and processing accurate, verifiable information, analysis/assessment); procedure for managing cases reported by external partners (co-marketing, copromotion, etc.); procedure for detecting cases reported in the literature; procedure for detecting cases reported on websites; procedure for interfacing with departments that are potentially sources of pharmacovigilance cases: medical information, marketing, market access/business intelligence, medical affairs, quality complaints, clinical trials, legal affairs; procedure for detecting signals and analyzing trends with evaluation of the relevance of amending the SPC; procedure for monitoring data in EudraVigilance and providing appropriate information to the competent authorities in the event of a signal; procedure for reconciling pharmacovigilance cases.

France to manage pharmacovigilance[13]. Although this can be an outside figure[14], pharmacists working in France must be registered with the Chamber of Pharmacists[15] and, as required by the code, practice within a duly authorized pharmaceutical site.

This figure, whose name and position will be provided to the ANSM when s/he is appointed, will be required to cooperate with the EU-QPPV[16] (European qualified person for pharmacovigilance in the European Union), forming strong working relationships with the Chief Pharmaceutical Officer[17].

In France, medical information and medicinal product advertising are activities legally associated with *exploitant* status under the Chief Pharmaceutical Officer's responsibility. These activities are vital in that they contribute to correct use of the medicinal product and essential components of pharmacovigilance management.

Finally, Article R. 5124-2 of the Public Health Code stresses that *exploitation* includes batch tracking. Therefore, the *exploitant* must implement internal procedures and a solid contractual structure to ensure compliance with applicable batch tracking guidelines, particularly for the ANSM. In its document entitled *Le système qualité de l'exploitant*, LEEM identifies the documents / deliverables that the *exploitant* must be able to produce in the event of an inspection and lists the documents required for batch tracking and traceability, batch recalls and managing quality complaints.

Therefore, if the *exploitant*, the holder's local representative in France, is a wholesale medicinal product distributor, it has very extensive obligations compared to the wholesale distributor defined at Community level and remains responsible for marketing the products in France.

B. The Chief Pharmaceutical Officer

The presence of a Chief Pharmaceutical Officer is required in all pharmaceutical companies, irrespective of their activities.

The role is defined in Article R. 5124-36 of the Public Health Code, which states:

> "In view of public health guidelines, the Chief Pharmaceutical Officer defined in Article R. 5124-34 has the following duties insofar as they correspond to the activities of the company or organization where s/he works:
>
> 1° S/he organizes and oversees all the pharmaceutical operations of the company or organization, particularly manufacturing, advertising, information, pharmacovigilance, batch tracking and recall, the distribution, importing and exporting of medicinal products, devices, objects or related items as well as the corresponding storage operations […]."

Therefore, the Chief Pharmaceutical Officer is responsible for organizing and overseeing

[13]Pursuant to Article 104 of the Directive, the competent national authority may require the appointment of a figure responsible for pharmacovigilance matters at national level.
[14]Question / answer document produced by the ANSM following publication of Decree 2012-1244 of 8 November 2012 on increased safety measures for medicinal products for human use requiring MA and pharmacovigilance.
[15]See Article L. 4221-1 of the Public Health Code, which specifies the conditions for working as a pharmacist in France.
[16]According to Article 104.3 of the Community code: "As part of the pharmacovigilance system, the marketing authorisation holder shall: (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance."
[17]Although the person responsible for pharmacovigilance in France can also be the EU-QPPV, there can be no confusion between French and European pharmacovigilance procedures, with each one to be applied separately.

all the company's pharmaceutical activities and involved at all levels of the medicinal product lifecycle.

The Chief Pharmaceutical Officer must be clearly separate from the qualified person mentioned by the Directive amongst the manufacturing authorization holder's obligations[18]. The Chief Pharmaceutical Officer must be involved, not only in any manufacturing activities, but also in all pharmaceutical activities when they relate to his/her roles and responsibilities.

As the ANSM and the Chamber of Pharmacists highlighted in their letter, the Chief Pharmaceutical Officer is the cornerstone of the French pharmaceutical system, ensuring that medicinal products with the necessary quality and appropriate safety profile are made available to patients.

The Public Health Code defines the Chief Pharmaceutical Officer's position, roles and responsibilities.

S/he must be a corporate officer[19] and as such have appropriate powers over the company's pharmaceutical activities. His/her roles, as defined by the Public Health Code[20], must be outlined in full in the deed of appointment.

In particular, the Chief Pharmaceutical Officer must be able to make independent decisions on the company's pharmaceutical products and activities, pursuant to the Public Health Code and applicable good practice.

Although it does not specify his/her hierarchical superiority, the Public Health Code attempts to ensure, not least with the Chief Pharmaceutical Officer's legally required position within the company, respect for this key principle of independence, remembering that pursuant to Article R. 5124-36 of the Public Health Code, the Chief Pharmaceutical Officer must inform the ANSM if s/he feels hindered in the performance of his/her duties[21].

Pursuant to Article L. 5124-4 of the Public Health Code, the Chief Pharmaceutical Officer must "personally perform" his/her role. Therefore, s/he is personally liable, even in criminal terms, for meeting his/her obligations[22]. If a pharmaceutical obligation is not met, liability may fall (as interpreted by the court) on either or both the company and/or the company directors, including the Chairman and Chief Pharmaceutical Officer in his/her role as Chief Pharmaceutical Officer and director.

However, as the Chief Pharmaceutical Officer cannot physically carry out all pharmaceutical operations alone, the law demands procedures to organize the activities and requires the Chief Pharmaceutical Officer to be assisted and, where necessary, replaced[23].

---

[18]Directive, Art. 48.
[19]Public Health Code, Art. R. 5124-34.
[20]Public Health Code, Art. R. 5124-36.
[21]Article R. 5124-36 of the Public Health Code states: "In the event of disagreement over the application of public health guidelines between a management, administrative or supervisory body and the Chief Pharmaceutical Officer, s/he informs the Director-General of the French National Agency for Medicines and Health Products or […]."
[22] Public Health Code, Art. L. 5124-2, paragraph 2.
[23]The law details three specific types of pharmacist as well as the Chief Pharmaceutical Officer: delegated pharmacists on each pharmaceutical site of a company that has several sites; assistant pharmacists acting under the Chief Pharmaceutical Officer's supervision and authority (Public Health Code, Art. L. 5124-2, paragraph 3. [for delegated pharmacists] and R. 5124-36, 5° [for assistant pharmacists]); and temporary pharmacists appointed to replace the pharmacists whose presence is required by the Public Health Code and the Chief Pharmaceutical Officer

The law expressly stipulates various categories of pharmacists to help the Chief Pharmaceutical Officer carry out pharmaceutical activities. Yet as the Chief Pharmaceutical Officer must organize and oversee all the company's pharmaceutical activities[24], such pharmacists remain under his/her supervision and authority. That is also the case in France of the delegated pharmacovigilance manager supervised by the Chief Pharmaceutical Officer, who is ultimately responsible for pharmacovigilance.

Therefore, although the Chief Pharmaceutical Officer can delegate some of his/her activities within the internal structure that s/he creates, in the event of legal proceedings, the delegation is unlikely to transfer liability from the Chief Pharmaceutical Officer to the delegate when French law has specifically given the former full responsibility for the duties defined in Article R. 5124-36 of the Public Health Code to avoid diluting responsibilities within the company.

The same reasoning applies to subcontracting the *exploitation* activity, which the Chief Pharmaceutical Officer is authorized to introduce under his/her responsibility.

Any delegation or subcontracting must be freely decided and organized by the Chief Pharmaceutical Officer under his/her responsibility, with him/her managing and monitoring said activities. In the event of an inspection, s/he must be able to prove that all necessary resources to quality control the pharmaceutical activities are allocated and used, which will necessarily imply implementing a specific structure within the *exploitant* site as well as strong working relationships between the Chief Pharmaceutical Officer and all parties involved.

in particular (Public Health Code, Art. R. 5124-23) on a short-term basis.
[24]Public Health Code, Art. R. 5124-36, 1°.

II. ORGANIZATION OF *EXPLOITATION* ACTIVITIES

As it is responsible for medicinal product marketing in France, the *exploitant* must ensure that all the pharmaceutical activities associated with the products under its responsibility are performed in compliance with applicable provisions.

In addition to its civil liability[25], penalties apply if the *exploitant* fails to meet its obligations, remembering that the regulatory framework of actions that the ANSM can take in response to deviations from applicable health product guidelines was amended by Ministerial Order 2013-1183 of 19 December 2013, which was implemented on 1 February 2014.

As well as the health policy measures involving a specific product or company activity (alteration, suspension, ban, etc.) that the ANSM can take when a pharmaceutical obligation is breached[26], it can also issue orders against an operator, requiring it to follow the applicable regulations, with details posted on the ANSM website[27]. It can also take disciplinary measures against the Chief Pharmaceutical Officer and any other pharmacist with the competent section of the Chamber of Pharmacists, which can go so far as definitive removal of the right to practice.

Alongside the criminal penalties, many of which are associated with pharmaceutical obligations, the ANSM's Director-General may decide to issue a financial penalty, combined where necessary with a daily fine, and post the decision on the ANSM website[28]. This new power was created by Act 2011-2012 of 29 December 2011 on increasing the safety of medicinal and health products. The financial penalties reflect the company's total revenue, or that generated by the relevant product or group of products, and the type of breach[29].

Beyond these risks of penalties, it is of course patients' interests that drive the *exploitant* responsible for medicinal products and its Chief Pharmaceutical Officer to implement a specific structure safeguarding quality, safety and efficacy. In particular, that requires them to manage any subcontractors (A), but also to maintain close relationships with the various links in the pharmaceutical chain (B).

A. Subcontracting of *exploitation* activities

Article R. 5124-47 of the Public Health Code states:

> "The companies and organizations outlined in Article **R. 5124-2** may not subcontract any of the activities defined in the same article or any of the operations outlined in Article **R. 5124-40**, with the following exceptions: […]
>
> 4° *Exploitants* of medicinal products other than those designed to be tested on man, and the generators, kits and precursors mentioned in 3° of Article L. 4211-1, may subcontract all or part of the operations constituting pharmacovigilance to a third party

[25] The *exploitant* stated on the labelling is responsible for any quality issues involving the medicinal products. Remember that the medicinal product's secondary packaging or, if there is no secondary packaging, the packaging in direct contact with the product, must show the holder's name and address and the name of its representative. The patient information leaflet must also show the holder's name and address and the name of its representative in the Member State (Article 59 of the Directive). In France, therefore, both the packaging and patient information leaflet mention the holder and *exploitant*.

[26] Public Health Code, Art. L. 5312-1, L. 5312-1-1, L. 5312-2 and L. 5312-3.

[27] Public Health Code, Art. L. 5312-4-3.

[28] Public Health Code, Art. L. 5312-4-1, L. 5471-1, R. 5312-2 and R. 5471-1.

[29] The figure used does not include VAT or exports. It refers to the revenue generated in France.

within a written contract that specifies, pursuant to the good practice outlined in Article R. 5121-179, their respective obligations; […]."

In principle, therefore, pharmaceutical companies and sites cannot subcontract any of their pharmaceutical activities. Exceptionally, *exploitants* "may subcontract all or part of the operations constituting pharmacovigilance to a third party within a written contract." Amongst the *exploitant*'s obligations, then, only pharmacovigilance activities can currently be subcontracted[30].

The subcontracted pharmacovigilance activities must be fully defined and quality controlled, with a contract between the *exploitant* and subcontractor clearly presenting each party's obligations and the *exploitant* remaining responsible for the subcontracted activities in dealings with both the regulatory authorities and third parties.

As previously mentioned, Article R. 5124-2 of the Public Health Code states that "*exploitation* is provided by the MA holder […] or by another company or organization on its behalf, or by both, in which case each one carries out one or more categories of operations constituting the *exploitation* of medicinal products." In any case, as they both have major pharmaceutical obligations, the *exploitant* and MA holder are required to organize the practical division of their activities in a contract. Yet this should be seen, particularly by the *exploitant*, as a subcontracting contract whose execution by its co-contractor is monitored. Although each entity's role will be clearly defined in the contract, the holder and *exploitant* will each remain responsible for all the obligations associated with their legal status in dealings with the authorities and third parties.

Therefore, even when subcontracting is legally possible and the co-contractor is, in application of the regulations and beyond the contract, responsible for the subcontracted activities, the *exploitant* will remain liable for all the obligations specified by the Public Health Code. It is required to manage all subcontracted activities effectively, which implies auditing the subcontractor.

B. Relationships with other links in the pharmaceutical chain

As a result, the *exploitant* must, in view of its legally defined obligations, maintain close relationships with the holder (**1**) and the parties involved in manufacturing and distributing its medicinal products (**2**).

1. Links between the *exploitant* and holder

As they both have major pharmaceutical obligations, the *exploitant* and MA holder are required to organize the division of their activities in a contract. As they are two separate legal entities, a contract remains necessary even if both companies belong to the same group, which is often the case when MAs are held by the parent company.

The contract should in particular ensure that the holder fulfils its duties, which is a condition of the *exploitant*'s successful management of its own obligations. It should clearly state not only the co-contractors' respective responsibilities but also the relevant documents required from the holder, particularly relative to the MA dossier and pharmacovigilance.

[30]It should, however, be stressed that other French provisions recognize the possibility for an *exploitant* to subcontract pharmaceutical sales to specialist service providers that are not pharmaceutical sites. This practice is also clearly and formally recognized by the authorities. Nevertheless, these subcontractors must have an 'ISO certificate' pursuant to the Promotional Information Charter (and its guidelines) issued by a certifying body.

The *exploitant* is responsible for product quality, which is necessarily and fundamentally dependent on the product's dossier. Therefore, it is essential that the *exploitant* is familiar with the dossier and any changes thereto[31].

For pharmacovigilance, RMP (risk management plans), PSMF (pharmacovigilance system master files) and PSUR (periodic safety update reports) must be provided to the *exploitant*'s Chief Pharmaceutical Officers, with regular communication on events affecting the products available in France at any stage and in any area. Although the *exploitant*'s Chief Pharmaceutical Officer is responsible for all the products made available in the country, s/he must have thorough knowledge of events that may affect them in other markets[32].

Very different situations can arise, depending on the company size and location of the holder. The situation is still not very clear, particularly within international groups that may struggle to understand the unique position of the *exploitant* and its Chief Pharmaceutical Officer. The EU-QPPV should not act as the only point of contact for the authorities and the parent company should avoid treating the Chief Pharmaceutical Officer as the qualified person defined at Community level, who is allocated only to the manufacturing site.

It is essential that the Chief Pharmaceutical Officer strives to increase and maintain his/her independence, not only via his/her formal positioning in the company's organizational chart, but more importantly via communication and maintained visibility, both internally within the company and externally in dealings with the partners and authorities.

The essential role of the *exploitant*'s Chief Pharmaceutical Officer in the supply chain should be presented in the contract between it and the holder. In the complex context of globalization, the Chief Pharmaceutical Officer must endeavour to understand his/her partners and track the product flows from raw material suppliers to patients via the manufacturing and distribution sites. Particularly in the event of anomalies leading to a batch recall, all the stakeholders in product manufacturing will be contacted and the entire flow examined to find the cause and inform all the partners, involving all links in the distribution chain.

Therefore, although the batch recall decision can be made by either the holder or *exploitant*, the Chief Pharmaceutical Officer must always be the final decision-maker in

[31]In strictly regulatory terms, MA decisions, at least modules 1 and 2 of the dossiers, variation timescales and copies of authorities' letters should be requested from the holder. For variations, the information channels should be clearly outlined in the contract or specifications. They should state that when the holder receives information from the authorities, it is forwarded to the *exploitant* promptly. If the variation changes the packaging articles, the *exploitant* must be informed of the introduction of changes (timescale, date of availability, etc.). If the variation amends the SPC, the *exploitant* must be able to update its own documentation, particularly promotional documents.

[32]Therefore, Article R. 5124-36 of the Public Health Code states that it "ensures, in the case of medicinal products designed to be marketed in the European Union, that the safety measures outlined in Article R. 5121-138-1 are shown on the packaging in the conditions stipulated in Articles R. 5121-138- 1 to R. 5121-138-4 of the Public Health Code." Note that pursuant to Article L. 5124-6 of the Public Health Code, a medicinal product *exploitant* that decides to suspend or terminate its market availability or becomes aware of information that may lead to its market availability being suspended or terminated must inform the ANSM, giving reasons for its action. Therefore, a unilateral decision by the parent company may put the *exploitant*'s Chief Pharmaceutical Officer in a difficult position. Similarly, pursuant to Article L. 5121- 9-2 of the Public Health Code, the *exploitant* must inform "the ANSM immediately of any ban or restriction required by the competent authority of any country in which the medicinal product for human use is marketed and any other new information of such a nature as to influence assessment of the medicinal product's benefits and risks." Here too, poor communication between the holder and *exploitant* may prevent the Chief Pharmaceutical Officer meeting its own obligations.

the batch recall process in France. That fact should be stated in the contracts and specifications.

The contract should also address the possibility of the *exploitant* auditing all its partners, direct or indirect, or at least the distribution of audit reports produced by the holder.

2. Links between the *exploitant* and manufacturers and distributors

To fulfil its duties relating to the tracking and withdrawal of medicinal products, the *exploitant* must be able to quality control and intervene at every stage in the manufacturing and distribution chain. As it is responsible for marketing medicinal products in France, the *exploitant* must ensure that the entire distribution chain is compliant with all applicable provisions and all pharmaceutical activities associated with the products under its responsibility are undertaken correctly. Therefore, the *exploitant* must be able to quality control its products' manufacturing and distribution.

In relation to manufacturing, Article R. 5124-55 of the Public Health Code states that incidents occurring during manufacturing or distribution and potentially presenting a health risk must be reported immediately by the *exploitant*.

We also stress that:

- Pursuant to Article L. 5124-6 of the Public Health Code, the *exploitant* must inform the ANSM if it decides to suspend or discontinue marketing a medicinal product;
- Pursuant to Article L. 5121-9-2 of the same code, the *exploitant* must also inform the ANSM immediately of any ban or restriction imposed by a competent authority of a country in which the medicinal product is distributed as well as any information likely to affect assessment of the benefit / risk ratio.

In addition, pursuant to French good manufacturing practice (GMP):

- the *exploitant* must be able to identify where a specific batch of medicinal products was released[33];
- the *exploitant* must examine, as the holder and manufacturer, the results of the quality review and assess the necessary preventive and corrective actions[34].

The *exploitant* must implement a process to manage product quality reviews. If the *exploitant*, holder and manufacturer are separate entities, there must be a contract and/or specifications between these operators to define their respective obligations in the quality review and organize the sharing of information.

The contractual organization should enable the *exploitant* to meet all the above obligations and so exclude its liability.

Therefore, the *exploitant* must be bound contractually with the manufacturer(s) of the medicinal products for which it provides the *exploitation*. Only this organization enables it to meet its obligations and prove that it has done so, particularly in the event of inspections by the regulatory authority. The necessary contract between the *exploitant* and MA holder could possibly include the contract(s) binding the holder to the relevant

[33]Point 4.2 of GMP.
[34]Point 1.11 of GMP.

manufacturer(s) in its annex.

In application of Article R. 5124-2 3° of the Public Health Code, the *exploitant* is notably responsible for medicinal product wholesaling, which is consistent with earlier analysis of the French *exploitant* as a unique French translation of the European distributor.

As Article R. 5121-5 of the Public Health Code states, pharmaceutical companies and sites must follow the applicable good practice irrespective of their activities. Good distribution practice (GDP) applies to all links in the pharmaceutical chain and to *exploitants* in particular[35].

Similarly, Article R. 5124-48 of the Public Health Code requires pharmaceutical companies and sites to "take the necessary steps to ensure that medicinal products and other pharmaceutical products are transported and delivered in conditions maintaining their preservation, integrity and safety."

Being responsible for the transport and delivery of its medicinal products, and required, more generally, to comply with GDP, the *exploitant* must manage — and demonstrate that it is managing — any distribution operations carried out by a third party. That requires a contract / specifications between the *exploitant* and third party and audits of the latter by the *exploitant*[36].

A contract will be essential to enable the *exploitant* to ensure that its own obligations are met, in direct relation to the distributor's activity and alongside the primary obligations of appropriate and continued supply[37], action against falsifications[38], retaining records of each transaction[39], and tracking and, where necessary, recalling the products that it is responsible for marketing[40].

Therefore, it is essential that the exploitant is, at least indirectly, bound by contract with its products' manufacturers and depositories. Otherwise it cannot be sure to manage these operators' activities, which have the potential to impact directly the quality, safety and tracking of the medicinal products that, as *exploitant* and in the same way as the holder, it is responsible for marketing[41].

In conclusion, therefore, in the strict line of the letter reprinted at the start of this analysis, the Chief Pharmaceutical Officer, *exploitant* and authorities should continue their dialogue with parent companies on the specific roles and responsibilities of both the

[35]Article 2 of the Decision of 20 February 2014 on GDP and amending the Order of 30 June 2000 states: "These good wholesale distribution practices for medicinal products for human use apply to the pharmaceutical sites defined in Article R. 5124-2 of the Public Health Code, particularly manufacturers, importers, *exploitants* responsible for wholesale distribution operations, depositaries, wholesale redistributors and any other pharmaceutical site with wholesale medicinal product distribution activities in or from the country. Some provisions in this guide also apply to the medicinal product brokerage activities provided as defined in Article L. 5124-19 of the Public Health Code".

[36]It should also be stressed that Article R. 5124-62 of the Public Health Code states that depositaries "carry on their activities in the conditions outlined by a written contract that determines, pursuant to the good practices stipulated by Article L. 5121-5 applicable to these activities, the respective obligations of the depositary and *exploitant*, manufacturer or importer acting on its behalf." Therefore, a written contract must be agreed between the depositary and *exploitant*, with specifications detailing their respective obligations. This follows the earlier obligations to stipulate contractually the activities subcontracted by the *exploitant*, as the depositary may be seen as the *exploitant*'s subcontractor for storage and distribution activities.

[37]Public Health Code, Art. R. 5124-48-1.

[38]Public Health Code, Art. R. 5124-48-2.

[39]Public Health Code, Art. R. 5124-58.

[40]Public Health Code, Art. R. 5124-60.

[41]In this sense, LEEM, in its *exploitant* guide, lists the documentation that an *exploitant* must have in relation to the control of its pharmaceutical contracts.

French *exploitant* and Chief Pharmaceutical Officer, reiterating in particular the key principle of independence and unique powers, notwithstanding organized delegation and subcontracting.

Whilst incurring his/her personal liability, the Chief Pharmaceutical Officer also incurs the company's liability. The exchanges should stress this individual and joint responsibility for the management of pharmaceutical activities, with failures leading to risks, not least to the quality, safety or efficacy of medicinal products, but also in terms of the company's civil and criminal liability, policing measures on the products and/or site, and commercial risks to reputation and image.