EHESP

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Class of: **2012 - 2013**

Defense date: **September 26th, 27th 2013**

Is the introduction of a priori control of advertising of medicinal products for healthcare professionals effective in reducing the risk of misuse and off-label prescriptions?

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Special Thanks

I gratefully dedicate this dissertation to:
My beloved family: Cris, Lou & Lenny,
My parents & parents in-law,
My brothers & sisters: Quôc, Cu Bê, Bê & Cu An
Always by my side

A special thought goes to my grandparents from here and above.

I am grateful for the support, guidance, and encouragement of my Director of Studies, Prof. Alain Ollivier.

I would also like to thank the whole academic and operational teams that have made this Executive Health MBA program so interesting and rich.

I deeply thank my professional network for their promptness in helping me disseminate the surveys, and also Gwen, Minh and Daniel for their precious help.

Finally, a special thank goes to the MBA fellows without whom this year would not have been as rich and pleasant as it was.

Contents

List of acronyms

AFAR	association française des affaires réglementaires – *French association of Regulatory affairs*
ANSM	agence de sécurité sanitaire du médicament et des produits de santé – *National Agency for Safety of Health Products*
B/R	benefit-to-risk
CEPS	comité économique des produits de santé – *economic comittee on health products*
CSP	code de la santé publique – *code of public health*
CSS	code de la sécurité sociale – *code of social security*
DDP	dispositions déontologiques professionnelles – *code of professional ethics*
IGAS	inspection générale des affaires sanitaires et sociales – *the Inspectorate General of Social Affairs*
Leem	les entreprises du médicaments - *the French pharmaceutical companies association*
MA	Marketing authorization
MED	mise en demeure – *formal notices*
NR	non remboursable – *not refundable*
SPC	summary of product characteristics
WHO	World health organization

Introduction

From Mediator to Diane 35 ...

The off-label uses of a drug have always existed: between 15 and 20% of all prescriptions are reported in the literature, even more in certain areas such as pediatrics, gerontology, or and oncology. Up to 78% of physicians have prescribed drugs for off-label uses according to a recent survey[1]. If those are sometimes justified, recent incidents have shown failures in the whole chain of the drug industry involving many actors: from manufacturers, that sell the medicine to the authorities granting the marketing authorization and reimbursement, to prescribers and pharmacists, not to mention the more or less informed patients who seek and demands results.

In addition, studies show that drugs were involved in 40% of avoidable serious adverse effects[2]. The definition of "avoidable" or “preventable” is "*would not have occurred if the treatment had been in line with management considered satisfactory*" or "*situation that deviates from procedures or outcomes expected in a normal situation and that is or would be a potential source of harm.*" If medication errors are the most common causes of these unwanted side effects, off-label uses also contribute to them. However, the figures raise the question of the poorly managed uses of the drug.

As a consequence of the IGAS report[3] (2011) following the Mediator scandal and based on proposals made during the national conference on medicines policy (*Assises du Médicament)*[4], the Drug Reform (or so-called Bertrand’s reform) emerged with Law No. 2011-2012 of 29 December 2011 on the strengthening of the safety of drugs and health products, under the drive of Xavier Bertrand, then Minister of Health, and Nora Berra, Secretary of State for Health.

Among all the provisions that concern the management of prescriptions for the proper use of drugs, there is one about the advertising of medicinal products to healthcare professionals. Indeed, since the budget for marketing and publicity represents approximately 23% of the pharmaceutical companies revenue[5], and the average yield in

[1] Haroche A. Les trois quarts des médecins prescrivent hors AMM. JIM, mars 2013 : http://www.jim.fr/print/e-docs/00/02/1A/AA/document_actu_pro.phtml

[2] Enquête Nationale sur les Événements Indésirables graves associés aux Soins - Description des résultats 2009 - Série Études et Recherche N° 110, septembre 2011 : http://www.drees.sante.gouv.fr/enquete-nationale-sur-les-evenements-indesirables-graves-associes-aux-soins-description-des-resultats-2009,9499.html

[3] Rapport de l’IGAS RM2011-001P : enquête sur le Médiator, synthèse – janvier 2011

[4] Rapport de synthèse des assises du médicament, juin 2011 : http://www.sante.gouv.fr/rapport-de-synthese-des-assises-du-medicament.html

[5] Commission Européenne : Enquête Sectorielle dans le domaine pharmaceutique - Rapport Final 8 juillet 2009 : http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/index.html

additional sales per dollar invested in pharmaceutical advertising was 8.34 USD in 2004[6], it has been established that the promotional efforts (advertising, sales representatives, congresses, medical journals ..) could have a negative impact on medical prescriptions going against health requirements, as was the situation in the Mediator case: thus, an a priori control of advertising has been restored.

We will consider the merits of this measure regarding both the off-label prescriptions and the misuses.
An initial report from the Parliament's control task force on the implementation of the law seem to confirm this.
We will try to undertake a more detailed analysis of the situation to assess whether the measure actually had the expected positive impact on practices.

We will firstly discuss some definitions and the regulatory basis of the concept of "off-label & off-proper use" and describe briefly the legal framework of drug advertising in France. We will highlight and discuss the contributions of the Bertrand reform on advertising rules, describing how it is linked to the issue of off-label and off-proper use.
Secondly, we will measure the effectiveness of the new regulation through surveys of the drug chain actors.

[6] Arnold M (2005). All the talk about pharma ROI yields only diminishing returns. Medical Marketing & Media, 40(8):9

1 LEGAL FRAMEWORK AND DEFINITIONS

1.1 Definitions

It is important that all institutions and healthcare professionals share the same definitions so that texts emitted by the former can correctly be applied by the latter, especially when it concerns off-label use and proper use. Is the prescriber aware when he or she prescribes off-label? It seems that this is not so obvious, as the discussions at the *Assises du Médicament* have shown. Has the pharmacist got the means to know and detect off-label prescriptions? Are all the institutions themselves in tune when they recommend practices, set up pharmacovigilance systems or enact laws and policies that aim to ensure cohesive actions in the field?

If European and national law texts provide definitions for “bad” uses of drugs (misuse, off-label use, abuse,...), no definition is provided for their “good” uses such as compliance with marketing authorization or proper use. Is that so obvious that a “good” use definition is not needed? Or does it suffice to state a definition that mirrors the “negative” one?
As a reminder, here are some basic facts.

1.1.1 Misuse

This is an intentional and **inappropriate** use of a drug (or product) with regards to the authorized or prescribed dosage, route of administration, indications, or a use **not in accordance with the terms of the marketing authorization** (or registration) as well as with the **guidelines on good practices**[7,8].
Note however that this definition covers only clinical situations that expose the patient to a risk of adverse effects. It does not take into account the effects on health care cost containment.

1.1.2 Off-label

It should be noted that only a European guideline on good pharmacovigilance practices[8] provides a definition of "off-label": situations where a medicinal product is intentionally used for a medical purpose **not in accordance with the authorized product information**.

[7] Article R5121-152 du CSP modifié par Décret no 2012-1244 du 8 novembre 2012 relatif au renforcement des dispositions en matière de sécurité des médicaments à usage humain soumis à autorisation de mise sur le marché et à la pharmacovigilance
[8] EMA/876333/2011 Rev. 1

In France, the common law expression "off-label prescription" was previously cited by the Social Security Code requiring the prescriber to mention "non-refundable" (NR) on the prescription (Article L162-4 of the CSS). Since the Drug reform, the Public Health Code has introduced this term (“off-label”) to acknowledge certain uses that "not compliant" with the marketing authorization and require the prescriber to mention the words "off-label" on the prescription when applicable (Article L5121-12-1 CSP).

1.1.3 Compliance with the Marketing Authorization or “On-label”

A) Generalities[9]

Compliance with MA is not defined in any regulation.

We therefore propose to shed some light on this concept.

Above all, it is perhaps useful to recall the foundations of marketing authorization for a drug.

The MA is the marketing authorization of a drug.

It is granted by the competent authorities when the dossier submitted by the pharmaceutical company has met the scientific criteria of quality, safety, and efficacy.

In the context of an application for a Community MA, usually reserved for new therapies or destined for several Member States, the competent authorities are represented by the EMA (European Medicines Agency). When the application is limited to the French national territory, it is then assessed by the ANSM.

Regardless of the procedure, the previously described criteria are rigorously evaluated on the basis of reports including the results of preclinical testing, clinical trials, and industrial development.

To obtain a marketing authorization, the new drug must show a benefit-to-risk ratio at least equivalent to existing products on the market.

The MA is a certified copy (text of the decision) accompanied by appendices essential to the daily practice of healthcare professionals as well as the use of the drug by the patient:

- The Summary of Product Characteristics (SPC) is the basis of information for healthcare professionals: it contains all the information necessary for safe and effective use of the medication; it is the legal reference document;
- The patient leaflet with the essential information of the SPC in a more accessible vocabulary;

[9] Source ANSM: http://ansm.sante.fr/Activites/Autorisations-de-Mise-sur-le-Marche-AMM/Definition-et-modalite-des-AMM/%28offset%29/0

- The labeling that displays the statements to be included on the outer packaging and the immediate packaging.

By extension, the term MA is used to designate the information mentioned in the SPC.

B) Sections of the SPC: prescription basis

The SCP is a summary of all relevant data on which the MA is founded. The wording of the various topics is the result of a rigorous review by health authorities of the indications, dosages, and properties specified by the laboratory on the basis of preclinical, clinical trials and pharmaceutical tests that have been conducted.

The SPC strictly defines the use conditions of a drug.

It includes the following sections:

1. NAME OF THE MEDICINAL PRODUCT
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
3. PHARMACEUTICAL FORM
4. CLINICAL PARTICULARS

4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and precautions for use
4.5 Interaction with other medicinal products and other forms of interaction
4.6 Fertility, pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
5.2 Pharmacokinetic properties
5.3 Preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
6.2 Incompatibilities
6.3 Shelf life
6.4 Special precautions for storage
6.5 Nature and contents of container
6.6 Special precautions for disposal and handling

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10. DATE OF REVISION OF THE TEXT
11. DOSIMETRY
12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Older MA suffered from a lack of well-conducted clinical studies and were therefore rather based on experience, literature review and expert consultation: the SPC wording was (and is still) broad or vague[10].

In contrast, more recent molecules obtained their MA on more rigorous scientific criteria that meet high methodological requirements[11]: the resulting information is very precise.

In any case, a prescription complies with the MA if **all conditions of use defined in the SPC are respected**, notably those described in sections 4 and 5.

C) In practice: how to prescribe accordingly to the MA vs off-label[12,13]

A prescription "off-label" is a prescription that does not comply with the use recommendations described in the MA. “Off-label” is also not only limited to the use of a drug for an unapproved disease.

The SPC is the cornerstone between assessment and information intended for use by healthcare professionals; any deviation from the recommendations of the SPC may cause an adverse effect, as defined by the Public Health Code, namely "a noxious and unintended response to a drug or product mentioned in Article R. 5121-150 CSP. "(See appendix-1 for more detailed information on sections of the SPC and the implications in terms of prescription)

[10] A program of re-assessment of old MA has been initiated since 2011.

[11] Types of scientifically accepted studies, from the highest to the lowest level of evidence:
Randomized controlled trials with indisputable results (methodological)
Non-randomized controlled trials well conducted
Non-controlled prospective trials well conducted (eg cohort studies)
Case-studies: controlled trials with bias
Retrospective studies and clinical cases (group of patients)
Any study strongly biased

[12] Source: EMA – how to prepare and review summaries of product characteristics (SmPCs) for human medicines
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000357.jsp&mid=WC0b01ac05806361e1#section1

[13] Cours de pharmacologie clinique : www.chups.jussieu.fr/polys/pharmaco/poly/Pharmaco.pdf

It can be (non-exhaustive list):

- A non-approved disease (e.g. anorectic instead of diabetes)
- A non-validated stage of a disease (e.g. cancer stage 2 instead of stage 3)
- A non-approved combination with another molecule (e.g. combination therapy instead of monotherapy)
- A patient population other those approved (e.g. children instead of adult patients; in first-line instead of patients refractory to first-line treatment; contra-indicated population)
- A posology (e.g. 4 mg / day instead of 2 mg / day)
- A treatment period (e.g. one month instead of 15 days)
- A route of administration (e.g. intravenous injection instead of sublingual)

1.1.4 Proper use

Again, there is no regulatory definition for "proper use" of a drug.
The Public Health Code changed by the drug reform mentions "proper use" several times, particularly in the determination of public health goals, but without actually defining it.
In clinical practice, the proper use of a drug may be defined as the use of the right drug in the right dosage, for the time required for a given patient who will tolerate it correctly.
In the context of cost containment, one can also add an economic criterion, which is to use the cheapest drug for an equivalent therapeutic effect.
There are also off-label drug uses that result directly from prescription recommendations issued by health authorities or that benefit from special arrangements made by those authorities (RTU and other coverage of medical expenses).
These practices fall into the "proper use" mentioned in Article L. 5121-14-3 of the Public Health Code, which states: "*The company that markets a medicinal product contributes to the **proper use** of the latter by ensuring **in particular** that the medicine is prescribed according to its marketing authorization referred to in Article L. 5121-8 and, should the following exist, its temporary use recommendations referred to in Article L. 5121-12-1, its temporary use authorization referred to in Article L. 5121-12, its registration referred to in Articles L. 5121-13 or L. 5121-14-1[14], and its authorization referred to in Article L. 5121-9-1[15] or its parallel import authorization referred to in Article L. 5121-17*. "

This text provides no exclusive definition of proper use but makes precise **therapeutic situations in which off-label uses are acceptable**.

[14] Homeopathic drugs
[15] Import License for a medicinal product that is not approved in France

Thus, the proper use of a drug is not necessarily limited to the strict compliance and/or framework of the MA.

If the SPC is an enforceable standard[16], **other standards** may restrict or enlarge the **conditions for use and the expenses coverage**:

- The Transparency Commission Advice
- The therapeutic strategies recommended by the HAS
- The temporary therapeutic protocols (PTT) soon replaced by temporary recommendations for use (RTU)
- The proper use contracts for expensive drugs charged off diagnosis-related group (DRG)
- Article L. 162-17-2-1 of the Social Security Code (special clause covering off-label uses in the scope of RTU, rare diseases or chronic diseases)
- The recommendations of the ANSM, the HAS, HCSP
- The enforceable medical references (RMO) and recommendations for good practice (RBP)
- Consensus conferences
- The recommendations of medical societies ...

In the simplest clinical situations, the SPC alone is enough to respond to a given pathological situation.

However, the SPC may sometimes be limited in clinical practice.

We should recall that the information in the SPC results at the time a drugs hits the market, from clinical trials. However, the information is limited[17] by:

- Sampling: Selected patients may not be exactly representative of the patients who could benefit from the treatment (the target population is not the population reached)
- Combinations not studied because not planned (drugs, food, sun ...)
- The existence of rare genetic backgrounds, not encountered during the trials
- The presence of comorbidities, which was an exclusion criteria during the trials
- The size of the trials: on a limited number of patients (hundreds to thousands), the chance to observe a serious but rare adverse event is statistically extremely small. However, the emergence of these effects can be enhanced with the number of patients exposed once the product is on the market.

[16] Note that the information of the SPC is fully or partially included in the Vidal (French PDR) dictionary based on the commercial policy of the laboratory

[17] Dangoumau Jacques, Pharmacologie générale - Département de pharmacologie - Université Victor Segalen Bordeaux 2 : http://www.pharmacologie.u-bordeaux2.fr/fr/enseignements/index.htm

- The duration of the trials (which is short): if adverse effects occur often in the early stages of the treatment (allergy, hepatitis, etc.) or remain constant with time, they may sometimes be related to duration and may over time (lymphomas…).

Thus, in more complicated situations, the practitioner uses other standards, which unfortunately are not always easy to apply. Indeed, there are many texts (at least 15 different types of repositories from various sources and with different purposes are identified), which are sometimes contradictory due to the fact that some of them are upgraded faster than the MA[18].

Proper use is a decision process that takes into account not only the clinical needs - covered or not by marketing authorization- but also the requirements of public health and economic constraints. The latter are brought to the fore in the Social Security funding bill of 2013 (PLFSS), which puts a special emphasis on the efficiency of provided care[19] and the 2013 guidance letter from the ministers to the CEPS insisting on its role in the promotion and the proper use of drugs management. We must recall that a better use and appropriate prescription of drugs in order to cut down on costly, unnecessary or non-beneficial drug consumption remain a top priority[20].

1.1.5 Distinguishing the fine line between "off-label-misuse" and "off-label - proper use "

Given what precedes, "off-label" can lead to misuse but may also on the contrary be a therapeutic solution.

Some off-label uses are justified on the basis of evidence (evidence or presumption of a favorable benefit-to-risk ratio). There are several reasons:

- Because of limited RCP:
  - The information –not absolute- does not reflect all possible uses of the drug,
  - The official information is inaccurate;
- In other situations when the MA does not exist, it may be due to:

[18] Bergman et al. (2008). Le bon usage du médicament : définition, référentiels, périmètre et champ d'application, 63(4), 267–273. doi:10.2515/thérapie

[19] Ministère de l'économie et des finances. Projet de Loi de financement de la sécurité sociale 2013: http://www.economie.gouv.fr/projet-de-loi-de-financement-de-la-securite-sociale-pour-2013

[20] Ministère des affaires sociales et de la santé. CEPS. Lettre d'orientation des ministres du 2 avril 2013. http://www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.html

- Administrative delays creating a gap between the MA and the advances of science,
- Economic considerations and strategic choices of development of the firm: some MA are not considered profitable (orphan diseases),
- Ethical and legal choices: clinical trials are almost impossible for children, the elderly, pregnant women ...[21]

However, these uses must be considered with great caution and scientific rigor and for those who have reached a therapeutic " dead end".

They generally involve serious pathological conditions and/or rare diseases. In this case, they cover a public health need, such as some orphan diseases, managed in hospital environment, all situations in which the potential benefits of off-label use may outweigh the risks; they also allow the access to medicines for certain subgroups of patients not covered by the MA; and finally, always in a context of serious illness, economic reasons may justify their use (e.g. the approved anti-cancer Avastin® is also given for the off-label treatment of age-related macular degeneration (AMD) because of a lower cost compared to the standard Lucentis® treatment[22,23]).

In any case, the off-label use from a proper use standpoint, should be based on official recommendations and not from shared isolated experiences.

Also, when 78% of doctors[24] say they prescribe off-label, we can worry about whether these prescriptions fall within the proper use.

In summary, here are the four situations when it comes to prescribing drugs:

1. Prescription complying with the MA (or on-label) and proper use
2. Prescription complying with the MA (or on-label) but not conforming to proper use (or off-proper use or misuse)
3. Off-label prescription but within proper use
4. Off-label prescription and not complying with proper use (or off-proper use, or misuse)

[21] E. Carré-Auger, B. Charpiat, Journal de Pharmacie Clinique. Volume 17, Numéro 4, 187-94, Décembre 1998, Revue générale - Les prescriptions hors AMM : revue de la littérature http://www.jle.com/fr/revues/bio_rech/jpc/e-docs/00/02/71/DC/article.phtml

[22] Le nouvel Obs. Résultats de l'étude française, DMLA : l'Avastin aussi efficace mais pas aussi sûr que le Lucentis. Mai 2013 http://pourquoi-docteur.nouvelobs.com/DMLA----l-Avastin-aussi-efficace-mais-pas-aussi-sur-que-le-Lucentis--2638.html

[23] ANSM. Avastin : données récentes sur l'utilisation hors AMM en ophtalmologie - Point d'information. Septembre 2009. http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Avastin-donnees-recentes-sur-l-utilisation-hors-AMM-en-ophtalmologie-Point-d-information/%28language%29/fre-FR

[24] Survey performed on 5-17 March 2013 with 429 health care professionals: http://www.jim.fr/print/e-docs/00/02/1A/AA/document_actu_pro.phtml

In order to protect the patient in a public health context, situations 1 and 3 must be sought after, situations 2 limited and situations 4 avoided.

Situations and definitions now clearly defined, in the context under consideration, we will try to analyze what in the marketing steps taken by the pharmaceutical companies can lead to situations 2 and 4, and if the restoration of a priori control of advertising may limit these situations.

1.2 Advertising of medicines

The advertising of a drug is part of a set of promotional activities conducted by pharmaceutical companies to boost sales: sales representatives, samples, healthcare professionals meetings and conferences, clinical trials, DTC (Direct-to-consumer) e-promotion, print ads and other marketing channels.

It is through these promotional tools to influence the therapeutic choice that the influence of the industry on the prescription and dispensation of drugs is exercised. This influence can lead to a choice of treatment that is not optimal, a change in prescription habits, and the recommendation of off-label use of drugs, sometimes to the detriment of the patient's health, especially when the informational transparency is not met (e.g. increase of positive effects, the lower bound side effects, the omission of the precautions, promotion of non validated properties...). Thus, despite the high level of training of healthcare professionals, experts from the General Inspectorate of Health and Social Affairs (IGAS) estimated that "it is beyond the reach of any isolated practitioner to exercise a critical look at scientific information presented to him."[25] Healthcare professionals are usually unaware of the effects that the influence techniques used by businesses have produced on them. According to the WHO, we cannot escape the inherent conflict of interest between the legitimate business purposes of the manufacturers and the social, medical and economic needs of care providers and of the public in selecting and using drugs as rationally as possible[26].

It is therefore mainly upstream of the doctors that efforts should be made to control drugs.

[25] Rapport °RM 2007-136P Septembre 2007 : L'information des médecins généralistes sur le médicament

[26] Comprendre la promotion pharmaceutique et y répondre – manuel pratique – OMS et AIS – traduction française 2013 : http://www.has-sante.fr/portail/jcms/r_1506394/fr/connaitre-et-comprendre-la-promotion-et-sa-regulation

1.2.1 Regulatory framework in France[27]

In France, the Public Health Code (CSP) strictly regulates advertising of pharmaceutical products. It is only permitted for drugs having obtained a marketing authorization and that are not subject to a reassessment of the B/R ratio following a pharmacovigilance report.
The advertising of medicinal products for human use is defined by Article L5122 -1 of the CSP:
"*Advertising of medicinal products for human use means any form of information, including door-to-door information, investigation or inducement designed to promote the prescription, supply, sale or consumption of the medicinal products to the exception of the information provided in the context of their functions, by hospital pharmacists.*
Are not included in the scope of this definition:
- Correspondence, possibly accompanied by any non-promotional document, needed to answer a specific question about a particular medication;
- Factual information and reference material relating to, for example, to packaging changes, warnings about adverse effects in the context of pharmacovigilance, as well as sales catalogs and price lists only if they do not include any product description;
- Information relating to human health or human diseases provided there is no reference, even indirect, to a medicinal product. "
It should be noted that this article accurately reflects the provisions of Article 86 of the Community Code relating to medicinal products.

In terms of content and presentation, advertising for medicines must comply with the general principles laid down in Articles L.5122 -2 and L.5122 -3 of the CSP, namely:

- It should not be misleading
- It should not undermine the protection of public health.
- It should promote the proper use of medicines
- It should respect the marketing authorization
- It should observe therapeutic strategies recommended by the High Authority of Health (HAS)

The regulation contains specific provisions on advertising of medicines whether it is for the public (Article L. 5122-6 of the CSP) or healthcare professionals (Article L. 5122-9 of the CSP).

Unlike in most countries, the National Security Agency of Medicines and Health Products (ANSM) exercise the control over drug advertising in France. Advertisements for drugs

[27] See Appendix 4

may be distributed only after obtaining permission from the ANSM called "advertising Visa" Visa PM (for medical advertising) and Visa GP (for the general public).

When advertising does not comply with the general principles laid down in Articles L.5122-2 and L5122-3 an advertising visa can be suspended in case of emergency or withdrawn due to a rational decision of the ANSM;
Withdrawal of a medical advertising visa may result in a penalty of 10% of the "France" turnover made on the designated product in the six months prior and after the date of the withdrawal (Article L. 162-17-4 of the Social Security Code).

1.2.2 The contribution of the Drug Reform on the advertising rules

A) Drug Reform

The Drug reform has emerged under Law No. 2011-2012 of 29 December 2011 on the strengthening of the safety of the drug and health products or commonly called Bertrand Law (See Appendix 2).
Bertrand law is divided into five parts:

- Transparency and Conflicts of Interest
- Governance of Health Products
- Medicinal products for human use
- Medical devices
- Miscellaneous Provisions

A total of 48 items are covering all subject matters.
Those relating to the management of off-label prescriptions are:

- Article 18 manages off-label prescriptions
- Article 21 establishes penalties in case pharmaceutical companies take no action when they are aware of off-label use of the products they sell
- Article 27 concerns the reimbursement of product prescriptions that are used off-label
- Article 28 reinforces the pharmacovigilance system
- Article 29 regulates the advertising of medicinal products for human use
- Article 30 introduces the collective medical hospital visit
- Article 31 requires pharmaceutical companies to ensure the proper use of their medicinal products
- Article 32 concerns the certification of computer software assisting prescription and dispensation

Of the 21 decrees issued to date, **one concerns the advertising of medicinal products for human use**. The other decrees related to the off-label control are:

- Decree No. 2012-1244 on 8 November 2012 related to reinforcement of safety of drugs for human use for which a MA application is required as well as pharmacovigilance;
- Decree No. 2012-1095 on 28 September 2012 related to financial penalties that may apply to firms;
- Decree No. 2012-742 on 9 May 2012 related to temporary recommendations for use (RTU);
- Decree No. 2012-743 on 9 May 2012 related to advertising of medical devices;
- Decree No. 2012-744 on 9 May 2012 related to advertising of in vitro diagnostic medical devices;
- Decree No. 2013-66 on 18 January 2013 related to authorization of temporary use of medicinal products;
- Decree No. 2012-740 on 9 May 2012 related to the social security coverage arrangements for products that benefit from a RTU, or for certain other products and services.

B) Contributions of the reform on drug advertising rules

The most important measure of Article 29 was to **restore[28] a control mechanism for a priori advertisements to healthcare professionals**.

Decree No. 2012-741 of 9 May 2012 clarified the application of the measure and simultaneously updated the regulatory part of the Public Health Code (See appendix 3).

This update actually includes only practical measures the goal of which is to impose a more stringent control apparatus with timetable for filing advertisements to healthcare professionals (windows from one week to 2 months). Silence means acceptance. The visa is granted for two years.

Moreover, another significant measure of the reform concerns the advertising of medicinal products that are under B/R re-assessment following a pharmacovigilance report; such advertising is now prohibited.

[28] In fact, originally, the advertising of medicinal products to the general public was banned in 1941; it is permitted to the medical profession after obtaining an administrative visa from 1963. In 1987, advertising to the general public is allowed again for some drugs (only those not subject to medical prescription and non-refundable by social security) and advertising to health care professionals benefit from a system of control a posteriori.

Comparative table of control mechanism:

	« a posteriori» control (Old)	**« a priori » control (New)**
Authorization principles	*Not applicable*	- Implicit in absence of a decision from ANSM within two months (after the filing period) - Explicit authorization (visa) or refusal within two months
Condition for use	Submission within 8 days after the 1st use	Request for Visa before any use
Period for filing	All along the year	≥ 4 periods / year (visas PM) 13 periods / year (visas GP)
Fees	510€	*Unchanged*
Filing procedures		New modalities including: - A new form - An internal registration number - An electronic copy of the file
Need for approval before use	No	Yes
Validity length	Not specified	2 years (or less if the MA is modified)
Administrative and financial penalties	Letter of formal notice and ban. Up to 10% of turnover 6 months before and after the ban	Suspension and withdrawal Up to 10% of turnover 6 months before and after the sanction

The stated objective of these provisions is of course to ensure that advertising complies with the rules of advertising prior to its release and it is consistent with the requirements of public health; the control is then a component of the action that should be undertaken to promote rationale use of health products. A less overt objective is to limit visas not only with an imposed schedule of filing, but also in the evaluation process because a simple reason for a formal notice under a posteriori control becomes ground for refusal under a priori control.

C) First results and limitations

The basis of the drug reform is to control and limit misuse and off-label prescribing: did the ads previously disseminated by pharmaceutical companies actually convey misleading or off-proper use messages? And if so, do the new rules really have an impact on the quality of these ads?

According to the rapporteurs who carried out the control task of the Parliament on the implementation of the laws, the new provision seems effective[29]. The assessment is made by comparing the numbers of refusals of general public advertisements compared to the number of bans on advertising to healthcare professionals still under a posteriori control in 2012 and just before the introduction of a priori control: 0 ban/999 authorization requests for advertisements to healthcare professionals (a posteriori control) vs 86 refusals of advertising to the general public (a priori control). The rapporteurs suggest these figures show that an a priori control mechanism acts as a filter and guarantees the exclusive broadcast of quality advertising.

The only concern raised by the rapporteurs is about the resources of the ANSM, which are not sufficient to handle all filings, many of which get a tacit approval without being assessed; thus, there is still a risk that some non-compliant messages get disseminated.

The criteria for measuring the effectiveness used by the rapporteurs do not seem relevant: the two types of advertisings (to the general public and to healthcare professionals) are not comparable since the degree of sophistication of the information delivered to healthcare professionals is much higher than that found in campaigns for the general public[30].

Moreover, **the law does not change the definition of advertising**: therefore, the criteria for evaluating an advertisement remain unchanged; if the content and presentation were previously in compliance, there is no reason for the establishment of an a priori control to reveal more or new non-conformities.

On the one hand, advertisements are subject to two levels of control: an internal control by the company before the dissemination of advertisements and an external control by the ANSM, which was previously a posteriori. The law has indeed always required that companies that sell medicinal products have a department in charge of advertising control under the supervision of the responsible pharmacist who ensures compliance with the provisions of Articles L.5122-2 and L.5122 -3 CSP, including the scientific validity of this information.
On the other hand, given the very dissuasive criminal penalties (for the responsible pharmacist in charge) and financial penalties provided in case of non-compliance with

[29] Assemblée nationale. Lemorton C., Robinet A. Rapport d'information sur la mise en œuvre de la loi du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé, juillet 2013.
[30] Sénat. Rapport d'information n° 382 (2005-2006). Les conditions de mise sur le marché et de suivi des médicaments - Médicament : restaurer la confiance. Audition du Dr M.-L. Gourlay. http://www.senat.fr/rap/r05-382/r05-38237.html#toc254

these provisions, companies can say they disseminate advertisements of the expected quality.

Thus, between 2000 and 2011, very few bans were imposed and formal notices (which can lead today to grounds for refusal) were very moderate in number. Advertising practices also improved over the years thanks to greater ownership rules from the industry (advertising working groups within Leem and AFAR) and good educational exchanges between the ANSM and the industry (telephone contacts and seminars of information IFIS for example).

Balance bans and notices for the period 2000-2011[31] :

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number (#) of dossiers	7836	7693	7973	8271	8805	9176	9620	9160	8817	8229	8199	8823
# Notices	461	494	378	371	308	329	430	205	298	180	238	268
% Notices	5,9	6,4	4,7	4,5	3,5	3,6	4,5	2,2	3,4	2,2	2,9	3,0
# Dossiers concerned by each Notice	-	-	905	-	1001	1403	1402	745	1159	709	1085	1645
% Dossiers concerned by Notice	-	-	**11,4**		**11,4**	**15,3**	**14,6**	**8,1**	**13,1**	**8,6**	**13,2**	**18,6**
# Bans	26	13	8	7	19	12	13	15	16	16	7	6
% Bans			0,1	0,1	0,2	0,1	0,1	0,2	0,2	0,2	0,09	0,07
# Dossiers concerned by each Ban	-	-	15	-	55	24	25	53	49	48	12	20
% Dossiers concerned by bans			**0,2**		**0,6**	**0,3**	**0,3**	**0,6**	**0,6**	**0,6**	**0,15**	**0,23**

[31] Source ANSM : http://ansm.sante.fr/Mediatheque/Publications/Bilans-Rapports-d-activite-Bilans-et-rapports-d-activite/%28language%29/fre-FR et archives du Leem

In comparison with the total number of dossiers submitted, there is a negligible rate of bans (0.2-0.6% from 2000 to 2011) and a very low rate of notices (2.2 to 6.4%).
Each case of formal notice or ban may involve several dossiers for the same drug[32] and call the same remarks leading the administration to send letters "bis"; therefore, based on the total number of dossiers concerned, sanction rates are higher (8.6 to 18%).
For comparison, since of the new control mode came into effect, the ANSM[33] has refused 13% of visa applications for advertising to healthcare professionals, which shows a certain consistency in the quality of ads presented.

Moreover, these figures need to be put into perspective given the evaluation system that remains at the discretion of the evaluator. Indeed, the general principles of advertising are subject to interpretation:
- It should not be misleading
- It should not undermine the protection of public health.
- It should promote the proper use of medicines
- It should respect the marketing authorization
- It should observe therapeutic strategies recommended by the High Authority of Health (HAS).

The last two principles seem the easiest to comply with: just present information consistent with or extracted from the SPC and the recommendations of Transparency Committee. However, many comments were made against advertisements presenting the results from studies that although carried out in the conditions of MA - indication, dosage, patient characteristics - contained tolerance results more favorable than the SPC: thus, these advertisements were rejected on the grounds that they did not meet the MA even if the safety data of the SPC are recalled. Thus, it is very difficult to assess what is or is not compliant with the MA.
Regarding the first three principles, the challenge is even greater: to check that the advertising is not misleading, does not affect public health and promotes the proper use, is dependent on subjective criteria in the absence of clear definitions.

For example, when it comes to being misleading, information can be misleading in three main ways:

[32] Each advertising campaign can be broken in several formats such as posters, press ads, for example, or several documents may comprise a common core with the same allegations, figures, arguments such as visual aid, light documents information, prescribing data sheets, brochures, slides kit…
[33] Annual report 2012 of ANSM : http://ansm.sante.fr/content/download/51041/658383/version/3/file/ANSM_Rapport-Activite-2012_v3.pdf

- Inclusion of distorted information (inaccurate, exaggerated, ambiguous or simplistic);
- Omission of relevant information;
- Distraction by irrelevant information.

But very few medical advertisements include such pitfalls, which would show failures or weaknesses in the internal process of the company. Indeed, given a second level of control by the authorities and the risk of sanctions, advertisements comply with a certain standard of information and presentation, and it is difficult to demonstrate the misleading nature of a medical advertisement given that it aimed at healthcare professionals and not lay people. Moreover, the meanings of the terms "likely to mislead" and "misleading" found in grounds for sanctions, assume an intentionality that is difficult to find in drug advertisings. Thus, when the appraiser arrives at these conclusions, the decision may be controversial. Another example, concerning the proper use: the doctrine of the authorities recognizes consensus conferences and recommendations of medical societies as standards of good practice especially when restricting the MA; but they do not accept the case when those guidelines enlarge the MA. We may wonder in this case the objectivity of the authorities that would be inclined to ascribe systematically dishonest intentions to the firms.

Although the ANSM has published some specific guidelines, they are still insufficient to accurately guide the manufacturers in their advertising practices.
Thus, sanctions are subject to very frequent or systematic contradictory procedures in which the firms challenge the observations that are made against them. It would be interesting to know the rate of contradictory procedures and the number of sanctions canceled. The ANSM did not mention them in its report of activities. Only the bans of the former control mode were made public: they were being published in the Official Gazette and the contradictory debates were published on the website of the ANSM.
Admittedly **evaluation of advertising is not a hard science**, and leads most of the time to a consensus among professionals and experts.
That is why we remind the importance of a definition of compliance with the MA and the proper use.

In order to verify the impact of the reform on the ads, we propose to conduct a survey of healthcare professionals and the pharmaceutical industry.

2 SURVEY OF HEALTH STAKEHOLDERS

2.1 Methodology

Our initial plan was more ambitious: we intended to study the various provisions of the drug reform that framed the misuse and off-label prescriptions, and measure their impact. We planned to interview the whole actors of the chain of the drug from the competent authorities (Ministry of Health and its services DGS -Directorate General for Health-, DGOS –Directorate General for Health facilities-, DSS –Directorate for Social Security-, CNAMTS -National Health Insurance Fund for Employees-, ANSM) throughout the pharmaceutical industry, physicians and pharmacists. We have developed questionnaires covering several areas: legal framework, definitions & standards, training, information & advertising, pharmacovigilance, relationships between physicians and pharmacists. The questionnaires were tailored to each actor (See Appendix 5).

However, as we met lots of difficulty in contacting the various actors, we had to resolve the issue **by focusing our research on one provision of the reform: the Article 29, which concerns the Advertising of Medicines**.

This study is limited to describe the results concerning the framework of advertising and discusses the issues identified.

We attempted to interview all medical advertising stakeholders: ANSM, DGS, Regulatory affairs Department in the pharmaceutical industry in charge of control of advertising, physicians, pharmacists;

We attempted to contact the Department in charge of advertising control of the ANSM by phone and email but failed as of today.

The same silence from the Directorate General of Health was given.

Regarding the pharmaceutical industry, we relied on the AFAR Advertising working group and the whole AFAR – Regulatory Affairs French Association- directory to distribute the questionnaire[34].

Concerning the healthcare professionals who are recipients of the ads, doctors and pharmacists, we have also encountered the same difficulties for broadcasting the questionnaires: no body has agreed to distribute our questionnaires[35,36], neither the Colleges of Physicians or of Pharmacists, nor their unions with the exception of the union

[34] Questionnaire for AFAR : https://docs.google.com/forms/d/156AheUXC0WBFMnPHpMdb7FIB4F7ogzOIR9Uwvh3pDhE/viewform

[35] Questionnaire for Doctors: https://docs.google.com/forms/d/1vCNZqGNqzd2GjgBr3SNBXtOZpWVgVG8lcbT8Os0dsDE/viewform

[36] Questionnaire for Pharmacists : https://docs.google.com/forms/d/1MhM7Z1IZ1TvtfrljgFZeEi8Drf0vYf0eiNUF3PuMvjY/viewform

of general practitioners (MG-France) who agreed to post our questionnaire on their website[37]. We met the owners of 20 pharmacies in Levallois-Perret (who have 29) and we proposed them to participate in our survey posted on the Internet; while they agreed to participate at that time, to this day, only one completed the questionnaire. We also sought for the support of the *Prescrire* Journal, but unsuccessfully; after having tried to understand the reason, the latter criticized the questionnaire as being very unattractive as well as the method of dissemination and said not to be interested in results that may emerge.

Thanks to friendly and professional networks, we managed to gather some answers (questionnaires and interviews) of pharmacists and doctors, but the sample remains negligible: 25 pharmacists and 4 doctors. Interviews with three pharmacists (1 from the pharmaceutical industry in regulatory affairs, 1 in town, 1 in hospital) allowed us to refine the questions in our questionnaire.

The questionnaire consisted of multiple choice and open questions.

Despite the limitations of our study, we can still draw some lines of thought.

2.2 Results

2.2.1 Effects of the reform on drug advertisements

Regulatory affairs Department in charge of control of advertising are the direct source of information on advertising by companies: they participate in the marketing strategy, taking an advisory role in relation to the regulation, they validate and submit the advertisements to the ANSM.

Thanks to our special relationship with pharmaceutical companies having been a member of AFAR working group of Advertisement for many years, we raised a significant number of responses to our questionnaire. We were also able to test and discuss the issues in interviews with two members.

We use the questionnaire in response to a deductive approach, to confirm or refute the **hypothesis that the reform did not have the expected positive effects** as we have shown in the first theoretical part. Therefore, questions directly addressed the impact of the reform on their standard practices for the advertising control.

In total, we received 30 responses among a total of 254 pharmaceutical companies registered in France.

Six of them are among the top 10 global pharmaceutical companies (the top 10 companies represent 51% of turnover).

[37] http://www.mgfrance.org/content/view/1839/3999/

Sixteen of them are among the top 50 global companies (the top 50 represent in France 89% of turnover)[38].

The respondents are all from regulatory affairs in charge of advertising control; they are the most relevant people for this survey, as they are the ownership of the process in the firms, and they are also used to understand and apply regulatory texts.

We estimate that we have obtained responses representing 35-40% of the industry. This is a fairly sizable proportion, so our results are broadly reflective of the industry. We present the raw proportions, not the market share weighted proportions, so there may be some bias in the statistics presented here, in addition to the margin of error we would naturally expect given we do not have data for the industry as a whole.

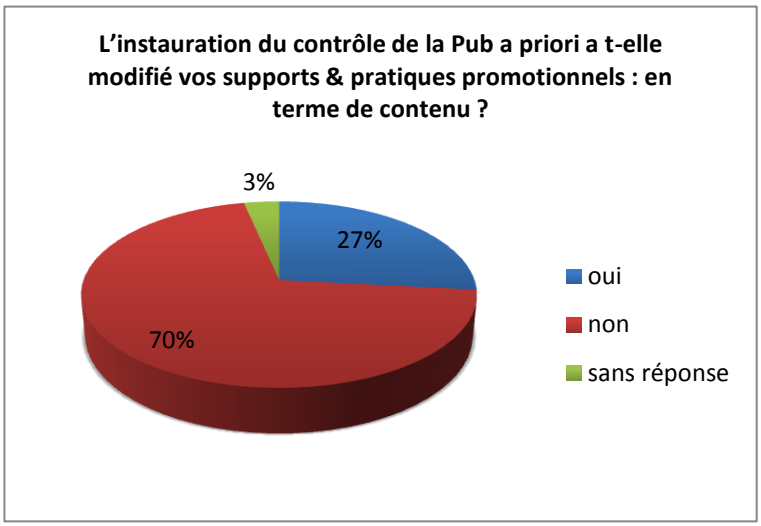
A) Content of advertisements

70 % (21/30) of pharmaceutical firms answered that the reform does not change the content of their advertisements. This confirms the fact that the introduction of a priori control without changing the evaluation criteria of advertising has no impact on its content.

Among those who responded that their content has changed, more than half (5/9) recognized that it is in favor of a more "risk-taking" in the messages presented. Indeed, most firms practiced a kind of self-censorship on certain messages or use of studies: as their foundations had not reached the scientific consensus internally, there was a risk that the authorities raise the same objections than those who identified communication issues internally and therefore it was not certain that the authorities will allow them. In the former control system (a posteriori), if the administration rejected an advertisement, it could apply sanctions to the ban, which resulted in financial penalties sometimes up to 10% of the designated drug turnover 6 months prior and after the sanction. For some firms, the risk of notice should also be avoided because the procedures to change the advertising or procedures for recall and destruction of materials are very expensive. With the new system, even though the law provides the same financial penalties as before in case of ads withdrawal, it should not exist because the advertisements must obtain a visa prior to their release. And it seems unlikely that the ANSM goes back to its decision after having had formally approved an advertisement. Since the firm is no more exposed to the risk of financial penalties applied a posteriori, it can try some messages or studies previously subject to discussion because the regulation is unclear on these issues.

Two firms have recognized, however, to use the grounds for refusal of the ANSM deemed relevant to harmonize their presentations or messages to all of their advertisements (among their all therapeutic areas). This applies mostly to the presentation of safety results.

[38] Source Leem-Gers

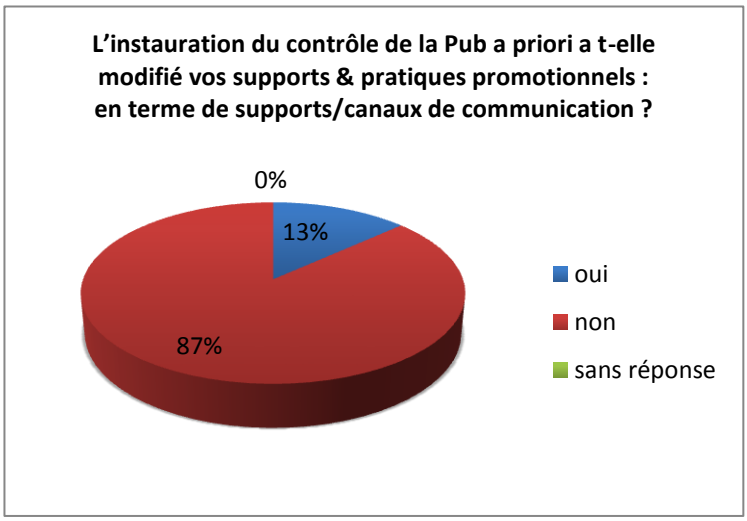


Question: does the introduction of a priori control of the advertising modify your promotional materials and practices: regarding the content?
Responses: yes=oui/no=non/no answer=sans réponse

B) Materials and communication channels

Nearly 87% (26/30) of firms have not changed the materials and communication channels. Excepting promotional goodies and gifts that are slowly disappearing since the "anti-gift law", materials have not changed much[39]. The contribution of new technologies enables new channels of communication (Smartphone applications, social networks, etc. ..), but the regulation makes their deployment difficult[40]. Advertising in the press and on the booths of Congress is also widely used.

We can say that the reform had no impact on the form and content of advertisements.



[39] http://ansm.sante.fr/Activites/Publicite-pour-les-medicaments/Recommandations-pour-la-publicite-aupres-des-professionnels-de-sante/Recommandations-generales/Supports

[40] Charter on communication and promotion of health products (medicinal products and médical devices) on internet and e-media (drafted update)

Question: does the introduction of a priori control of the advertising modify your promotional materials and practices: regarding material/communication channels?

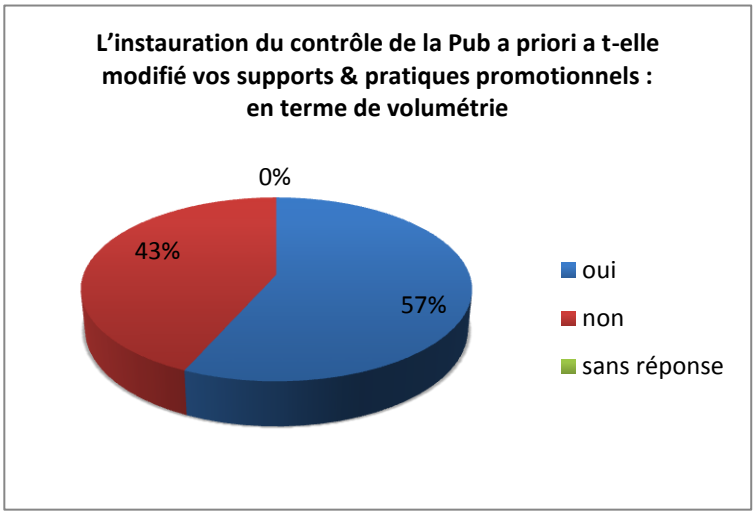
Responses: yes=oui/no=non/no answer=sans réponse

C) Advertising volume

More than half (17/30) of respondents agreed that the reform had an impact on the volume of their promotional materials. 50% of respondents admitted to having reduced the number of promotional materials. Most of the time, the reduction was a consequence of the establishment of a filing timetable, complicating the internal organization with peaks of activity concentrated on four periods in the year while filings was made all along the year in the former system.

A firm says they took no financial risk to duplicate a campaign (same messages, images, studies) in different formats or materials, before the outcomes of the assessment.

Two others mention the contrary: they multiplied materials increasing gradually the level of regulatory risk; in this way, they may find the acceptable level by the administration of message, presentation or studies used.



Question: does the introduction of a priori control of the advertising modify your promotional materials and practices: regarding volume?

Responses: yes=oui/no=non/no answer=sans réponse

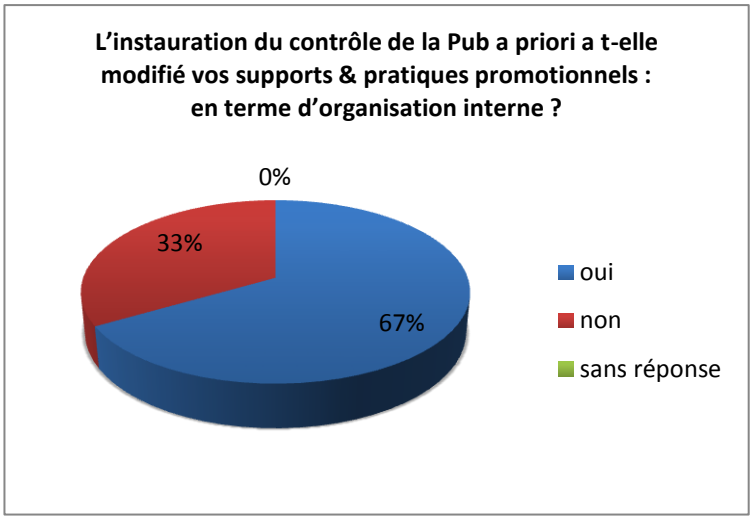
D) Internal organization of firms

Two-thirds (20/30) of firms have had to change their internal organization. The Department in charge of the control of advertising imposed by the law is not the only service that has to adapt its organization; but all cross-functional teams involved

(regulatory, medical, marketing, purchasing, finance, logistics...) have to adapt to new constraints, notably logistics, affecting the internal procedures and approval workflow. The firms have to use increasingly electronic document management systems and must establish systematic retroplannings.

Most regulatory affairs are quite satisfied of the imposed filing timetable, because it implies a better internal organization with greater involvement and mobilization of interdepartmental teams around projects.

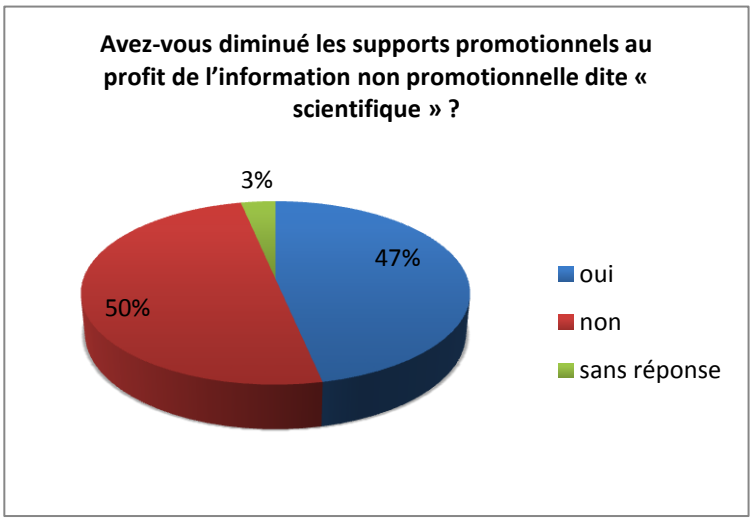
A firm complained of the reduction of its regulatory staff because of the decrease of "advertising" materials. However a dedicated advertising control department does not only review the ads but also ensures that other documents which are intended to provide information on human diseases or on the company can not be re-qualified as advertising (disguised) and thus expose the company to the risk of sanctions. It also provides regulatory and competitive intelligence, and ensures projects upstream regarding regulatory compliance.



Question: does the introduction of a priori control of the advertising modify your promotional materials and practices: regarding internal organization?
Responses: yes=oui/no=non/no answer=sans réponse

E) Other types of communication

Nearly half of respondents (14/30) agreed to have decreased the number of ads in favor of institutional communication or communication for human diseases. They develop more materials on diseases for which the firm has one or more treatments, or they also develop services for healthcare professionals.



Question: did you decrease promotional materials in favor of non-promotional materials so-called "scientific" communication?

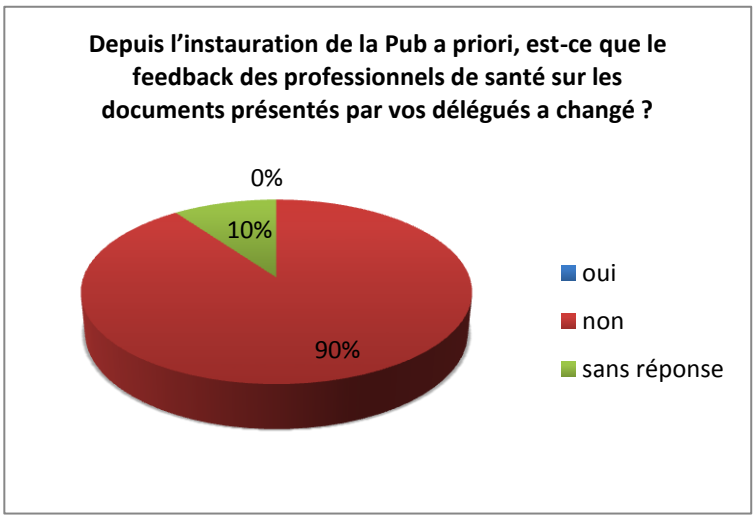
Responses: yes=oui/no=non/no answer=sans réponse

F) Feedback from healthcare professionals on ads

90% of firms (27/30) said they had not noticed change in healthcare professionals perception for their advertisings. This result is not surprising insofar as the form and content of documents have not changed. The measurement is carried out through market research where campaigns are usually tested with a panel of professionals. Sales representatives also bring back information form the field. Moreover, it seems that health professionals have not changed their relationship with the firms: the regulatory teams did not observed such trend.

Three did not answer, as they don't have any information from the field.

A firm evokes the lack of hindsight to be able to measure the impact of the reform with healthcare professionals.



Question: Since the introduction of the a priori control of advertising, do you notice that the perception of healthcare professionals has changed on the ads presented by your sales reps?
Responses: yes=oui/no=non/no answer=sans réponse

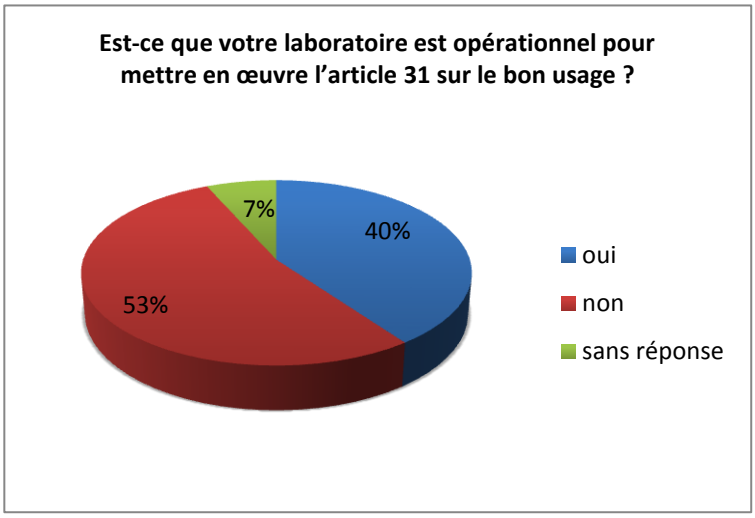
Among pharmacists (1 from hospital and 24 from pharmacy in town) and doctors (1 general practitioner, 1 gynecologist, 2 specialty unknown) who receive directly the questionnaires, the rate of response regarding promotional practices of the pharmaceutical companies is so low that we cannot extract significant figures; however, some have noted no change in either the content or in the forms of advertisements since the implementation of the drug reform, which seems to corroborate the results of the firms and confirms our hypothesis that the reform did not have a particular impact on advertising; others have noted a decrease in visits of sales reps, and finally some have decided not to receive visitors anymore.

2.2.2 Other observations

Regulatory affairs Department in charge of advertising control perfectly master the general principles of advertising including the concepts of compliance with the marketing authorization and proper use. However, as we have risen in the first part, due to a lack of regulation, without a specific definition of "conformity to the marketing authorization" and "proper use", certain measures are difficult to implement. For example, Article 31[41] of the reform requires the pharmaceutical companies to contribute **to the proper use** by notably ensuring that their medicinal products are prescribed **in accordance with their marketing authorization**; they must take appropriate measures to inform healthcare professionals when they find out prescriptions that **are not complying to proper use** of the drug as defined in the first paragraph (e.g. "ensuring notably that their medicinal products are prescribed in accordance to their MA"). There is an amalgam of "proper use" and "in accordance to their MA" to express the same thing, but a blur is introduced with the word "notably", which assumes that the proper use is not limited solely to comply with the MA ... then how to define what is "not conforming to proper use?"
This semantic analysis reveals how complex are these concepts.

[41] Article 31 of the Law on reinforcement of safety of health products: Art. L. 5121-14-3 of CSP. "*The company operates a medicinal product contributes to its proper use, in particular ensuring that the medicinal product is prescribed in accordance to the marketing authorization as referred to in Article L. 5121-8 and, if appropriate, recommendations for temporary use referred to in Article L. 5121-12-1, its temporary use authorization referred to in Article L. 5121-12, registration referred to in Articles L. 5121-13 or L. 5121-14-1, its authorization referred to in Article L. 5121-9-1 or its parallel import authorization referred to in Article L. 5121-17".*
"It takes all the measures it deems appropriate to inform health professionals who are concerned in Part IV of this Code when it finds out prescriptions of the medicinal product not complying to the proper use of this product as defined in the first paragraph requirements and shall promptly notify the national Security Agency of Medicines and health Products. " (Translated from French)

Thus, most of the surveyed firms are not yet operational to implement this article 31, as they don't know how to really define the non-compliance to proper use. In addition, many other practical issues arise that could not find their solutions without a regulatory framework to the "off-label use & off-proper use ": what are the means to detect the off-label uses and/or off-proper uses? What tools and procedures to record, track and manage these uses? By which means to inform the healthcare professionals: personally and one-to-one, by mail, on a website? At what threshold inform all professionals and authorities?



Question: Is your company operational to implement article 31 on Proper use ?

Responses: yes=oui/no=non/no answer=sans réponse

If the pharmaceutical industry proficient in handling regulations is itself in the difficulty of applying some texts, what about health professionals in the field who are faced with an abundance of information from multiple transmitters whose interests are sometimes divergent? How to synthesize all this information to their daily practice? The key question is what level of knowledge do they have on the basic information of the drugs they prescribe or dispense and what standards do they use?

Despite the low rate of responses (25 pharmacists and 4 doctors), we observe the same difficulty to define the terms and concepts of off-label and compliance with the marketing authorization.

Indeed to the questions: "Provide a definition of a prescription in accordance with the MA" and "Provide a definition of a prescription non-compliant to MA", we got a great diversity of responses: from the definition the most complete ("*Prescription complying to MA regarding indications, dosages, interactions and sought for contra-indications*") to the wrong one, which confused the notions of reimbursement with the approved uses ("*Use identical to reimbursable indications and to the leaflet*").

The majority of responses were incorrect (86%): incomplete most of the time, but sometimes completely wrong.
Most incomplete responses are limited to the therapeutic indication as compliance criteria or not.
Moreover, the fact that we get from the same person definitions that are not mirrored to each other (e.g. according to MA = "i*s consistent with surveys and phase I to IV clinical trials supporting the MA*"/ off-label =" *is not prescribed for the reason of its MA but is prescribed for another indication* "), shows that the concept of off-label / conformant to MA is still not well understood or not well-known.
Another study with a more representative sample, would allow better analysis of the responses, especially to check if there is no bias between the state of knowledge and practice.

As for the standards used, very few know the SPC published on the ANSM website. The official recommendations are little used as well. The majority of healthcare professionals refer to Vidal (86*-88**%)[*] and to computer software assisting prescription and dispensation (65*-76**%).
The most widely used standards (ranked in descending order and> 50%):

1. Vidal (French PDR)
2. Computer software assisting Prescription/Dispensation
3. Scientific journals
4. Visual aids and other documents from the pharmaceutical companies
5. Recommendations and alerts of the ANSM (mainly used by pharmacists)

2.2.3 Discussion of Results

A) Limitations of the study

Given our limited resources (budget and time), our research has an exploratory value. This is mostly a reflection and analysis drawn from a review of the literature and our experience.
Difficulty in contacting the various target actors of our research has forced us to redefine the scope of research.
However, this is the first study on the effect of the drug reform one year after its entry into force.
Thus, the only numbers on which we can draw reliable conclusions are those coming from the responses of the pharmaceutical industry on their advertising practices.

[*] results from pooled pharmacists and physicians - ** results from pharmacists only

The correlation between their responses and the effectiveness of the reform to reduce misuse and off-label prescribing is indirect because drawn from the premise that advertising by companies influence the practices and behavior of healthcare professionals.

Our study likely aims to raise questions about the regulations and their applicability, and outline areas for improvement for a "proper use" of the drug.

B) Interest and limits of the drug reform on advertising

The introduction of a priori control of advertising did not reach, according to our analysis, the goal of reducing the misuse and off-label prescriptions insofar as it would have had to demonstrate before that all the ads lead to deviant practices in France. In the contrary, the quality of the information provided in the advertisements of pharmaceutical companies was already very good; and the drug reform, which did not modify either promotional practices or promotional content, has not helped to improve more their quality.

This is corroborated by the findings of the fact-finding mission of the Senate in 2006 after previous Vioxx® and Celebrex® crises that led to their withdrawal[42]. After hearings and analyzes, among the recommendations made by the mission, nothing was needed for the control of advertising, considering the system satisfactory.

The interest of a priori control may be to exclude completely from the circuit the few documents, which contain any objectionable messages that formed previously grounds for formal notice. But it seems that the new organization of the ANSM does not have enough resources to assess all files. Therefore, we expect the same rate of refusals as formal notices under the former control system, which remains low, it should be remembered. Indeed, these formal warnings sometimes reflect internal failure of companies, or are the result of an assessor's viewpoint that is often questionable. At this stage, these ads cannot affect public health.

We regret that the reform did not provide pragmatic solutions such as **specific good practices for content of promotional materials**, rather than keeping the general principles fuzzy and leaving evaluation of advertisements to individual and subjective assessment.

Moreover, the system of formal notice of the former system should have been used as a **means of teaching critical reading of advertisements** for both industrial and for healthcare professionals to whom they are aimed at, **if they had been made public as were bans**. These formal notices that do not comply could also serve as **warning**

[42] Sénat. Rapport d'information n° 382 (2005-2006). Les conditions de mise sur le marché et de suivi des médicaments - Médicament : restaurer la confiance. Audition du Dr M.-L. Gourlay. http://www.senat.fr/rap/r05-382/r05-38237.html#toc254

markers and draw attention to the other promotional activities[43], which have a greater impact on the prescriptions.

C) Lack of knowledge of standards, definitions and responsibilities

Although our sample of healthcare professionals is not representative and is primarily made up of pharmacists, it appears from the questionnaires and interviews that the definitions of "compliance with the marketing authorization" and "off-label" are not well understood and the standards of drugs they are using are not always the official ones (e.g. Vidal, computer software assisting dispensation not certified by the HAS, documents from the firms…).

This lack of knowledge is not really an obstacle in their daily practice to the extent that most of the time, they do not also have access to the doctor's diagnosis. Indeed, the doctor does not have a duty to carry on the prescription the condition for which he prescribed treatment; then the pharmacist can put his/her trust on the doctor or the pharmacist can make a deduction based on his/her experience and the relationship he or she developed with his/her patient. He/she thinks doing well his/her job without risk, which is to verifying the consistency of the prescription however without any specific evidence in hand.

In the rare cases where pharmacists have access to information about their patients' conditions (in town with the specific prescription for chronic diseases -ALD- and in the hospital for special and expensive drugs covered by an “contract of proper use”), they agree that this information clarify their judgment and allow them to fully exercise their responsibilities. This is why a number of them are **in favor of the mention of the indication on the prescription**.

It must be remembered, pharmacists have the duty to provide information and advice. Indeed, the Code of Ethics and Article R.4235-48 of the CSP require the pharmacist to "provide the necessary information and advice on the proper use of medications." They can do so only if they know the condition of their patients and they have mastered the basic information of the drugs they dispense.

Moreover, the Council of State, in a judgment of 11 May 2007 (No. 289518) has estimated that the pharmacist had a duty to refuse to deliver over a long period "atypical combinations of antibiotics, medicines that are contra-indicated for young children and off-label treatments for excessive periods of time" (art. R.4235-61 of CSP).

Thus, knowledge of the standards and of the SPC of medicinal products is essential to the daily practice of healthcare professionals.

[43] R. Chakroun, Gouvernance du contrôle de la publicité des médicaments : étude des modalités de sanction des publicités non conformes - Revue d’Epidémiologie et de Santé Publique 61 (2013) 95–104. http://dx.doi.org/10.1016/j.respe.2012.09.002

The problem, as pointed out by the Giens workshop participants[44], is the abundance of information sometimes conflicting, and from several different legitimate sources that not make easy for professionals who need to make quick decisions.

[44] Bergman et al. (2008). Le bon usage du médicament : définition, référentiels, périmètre et champ d'application, 63(4), 267–273. doi:10.2515/thérapie

3 AREAS FOR RESEARCH AND IMPROVEMENT

3.1 Revise the concept of advertising

Concerning the supervision of the advertising, as we have demonstrated, we do not believe that the measure introduced by the reform of the drug was particularly relevant or sufficient then to control misuse and off-label prescriptions.

On the one hand, because the Advertising as defined by the Public Health Code in France was already highly regulated (unlike in many other countries), not only by a binding legislative and regulatory framework, but also by self-discipline and Code of Ethics implemented in firms; on the other hand, because it represents only a very small percentage of promotional activities, the most important part is devoted to the medical visit (see table).

Breakdown of expenditure on promotion of pharmaceutical companies[45] : Promotional expenditures of firms (% of total budget)	
Sales representatives for specialists: 31% (67% deofs respondents)	Marketing phase IV: 7% (57%)
Sales representatives for general practitioners: 30% (79%)	Medias: 7% (41%)
Congress and training: 17% (83%)	Public Relations: 6% (48%)
Booths and events: 13% (68%)	Patients' association sponsorship: 6% (52%)
POS[46] : 12% (62%)	E-mail marketing: 4% (44%)
Ads Press: 11% (65%)	Marketing on web: 3% (41%)
Samples: 10% (77%)	Lobbying: 2,5% (32%)
Sponsorship: 9% (63%)	Promotions: 2% (32%)
Direct Marketing: 7,5% (59%)	

[45] http://www.strategies.fr/etudes-tendances/dossiers/112484/111690W/les-labos-condamnes-a-innover-en-marketing.html

[46] points of sales

Example of a marketing budget[47] :

This is an example for information; there is no standardized budget, but it gives an idea of the various promotional activities that may differ from a product to another (ethic, generic, biotech, old on the market, newly launched, hospital, primary care, etc…), from a firm to another (depending their culture).

Le budget marketing : exemple

Ventes	3 MF
Investissements (KF)	
Insersions Presse officine	70
Insersions Presses Grand Public	300
Numéro vert	200
Service Minitel	150
"Push and Pull" clientes finales	100
Télé achat	1000
Autres	200
Total publicité	**1920**
Conférence de presse	600
Congrès nationaux	170
Campagne d'Environnement "ménopause"	300
Réunion "comité d'experts"	200
Congrès Internationaux	50
Autres	200
Total Relations extérieures	**1450**
Echantillonnage	200
Remis de visite	50
Présentoirs, PLV	100
Force de vente prestataire	540
Mailing	100
Brochure	150
Autres	200
Total Dépenses terrain	**1340**
Total investissement promotionnel	**4,7 MF**

Among these actions, some are getting out of the control of health authorities because regulation has limitations that allow manufacturers to legally circumvent the principles.

Come back to the definition of advertising:

According to the CSP, article L5122-1: "*Advertising of medicinal products for human use means any form of information, (including door-to-door publicity), investigation, or inducement designed to promote the prescription, supply, sale, or consumption of the medicinal products to the exception of the information provided in the context of their functions, by hospital pharmacists.*

Are not included in the scope of this definition:

- Correspondence, possibly accompanied by any non-promotional document, needed to answer a specific question about a particular medication;

- Factual information and reference material relating to, for example, packaging changes, warnings about adverse effects in the context of pharmacovigilance, as well as sales catalogs and price lists that do not include any product description;

[47] http://fr.slideshare.net/PhilippeBarquet/le-chefdeproduitpharma

- Information relating to human health or human diseases provided there is no reference, even indirect, to a medicinal product. "

It should be noted that this article accurately reflects the provisions of Article 86 of the Community Code relating to medicinal products.

The second part of this definition is very important because **it excludes what falls into the field of advertising**, notably "*information relating to human health or human diseases, provided that there is no reference even indirect, to medicinal product*." Thus, as long as a drug is not mentioned directly or indirectly (International Nonproprietary Name, color and image of the product or brand), all promotional activities to meet these conditions are allowed and **uncontrolled**.

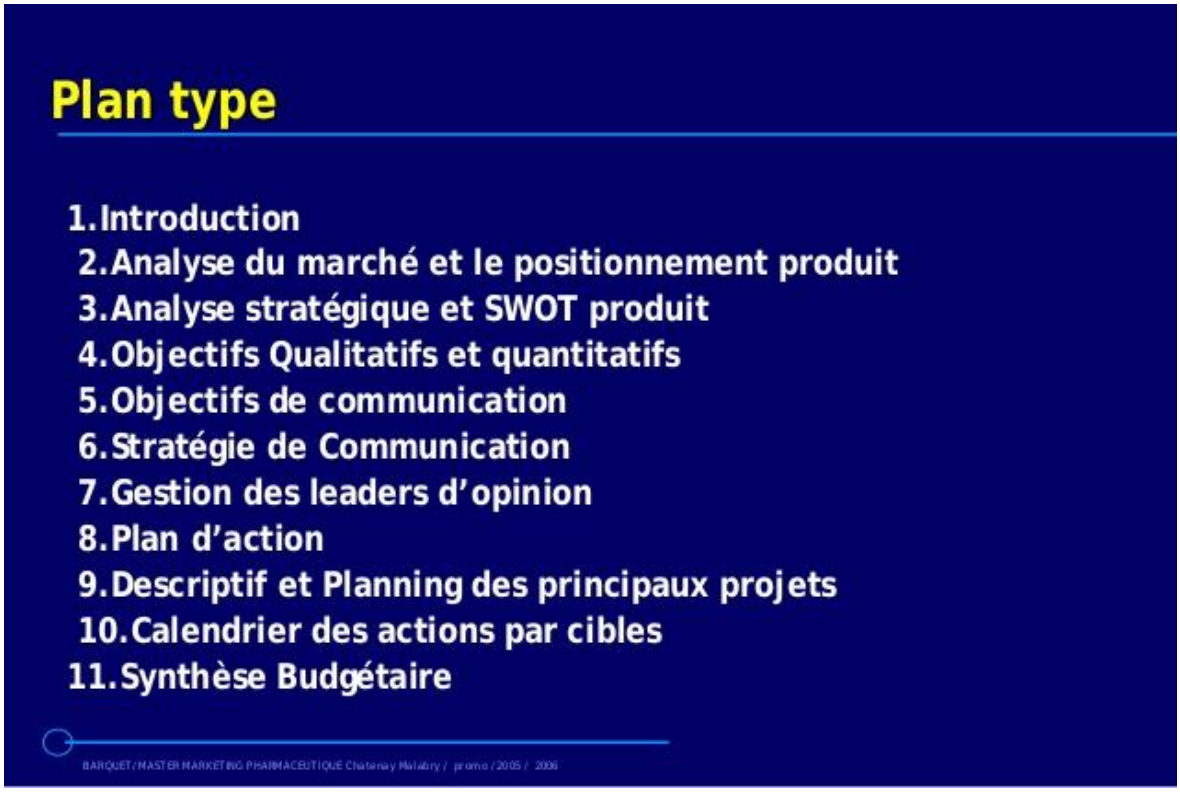
Leem in its professional ethical rules (DDP)[48] provides the following definition that better meets reality: "**Promotion**": "any activity undertaken, conducted, organized or sponsored by a pharmaceutical company or on its behalf, which is directed at healthcare professionals to promote the prescription, recommendation, supply, administration or consumption of its pharmaceutical product(s)".

There is a **distinction between the "Advertising" which covers all the operations of direct advertising of the drug and the "Promotion" which covers in addition, operations of indirect advertising and communications to health professionals, to the general public and to the press**.

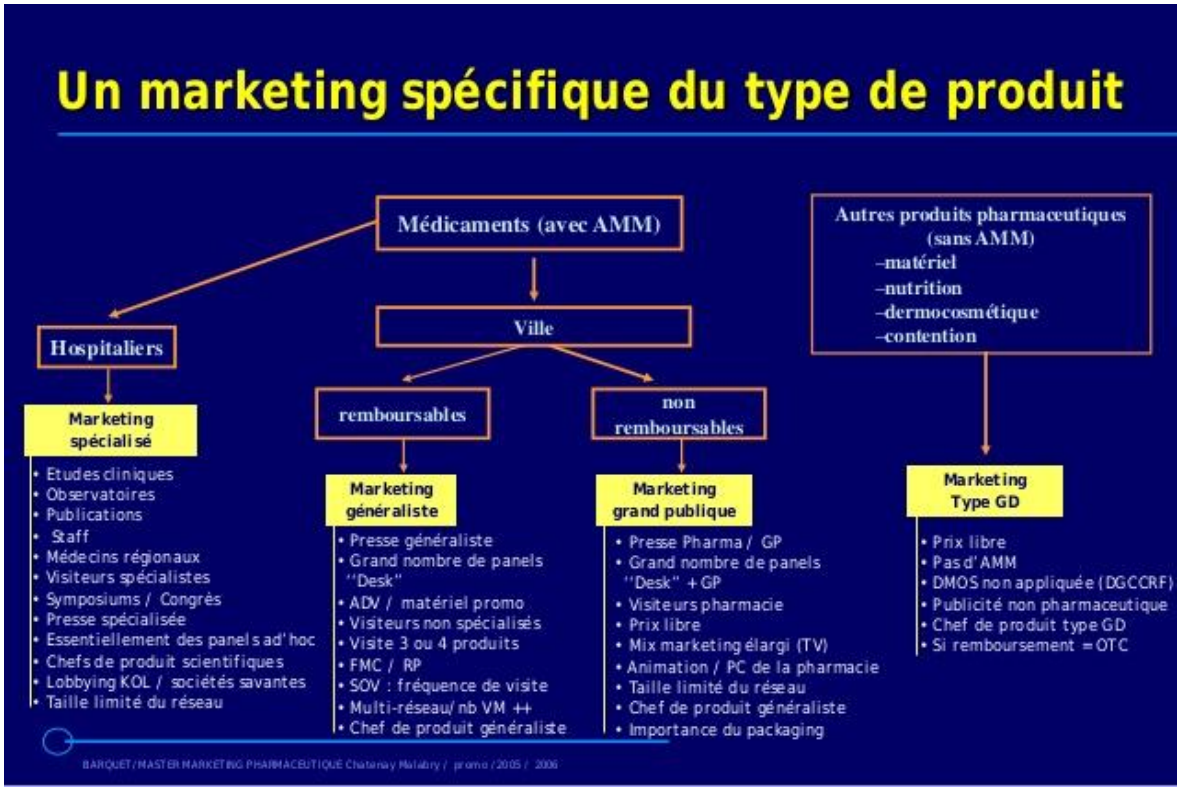
It should not be forgotten that all these actions are part of a marketing plan to promote the drug and increase sales.

[48] http://www.leem.org/article/dispositions-deontologiques-professionnelles

Example of a marketing plan model:



Example of a marketing strategy depending on medicinal product category[49] :



[49] http://fr.slideshare.net/PhilippeBarquet/le-chefdeproduitpharma

Studies demonstrated the great influence of all promotional activities on the practices of health professionals; thus, promotion (as defined by Leem) should have been framed more largely. Despite the existence of the DDP that demonstrate the general willingness of companies to respect the ethics and code of conduct in the operations, they are not mandatory and do not apply to all companies that are not member of Leem.

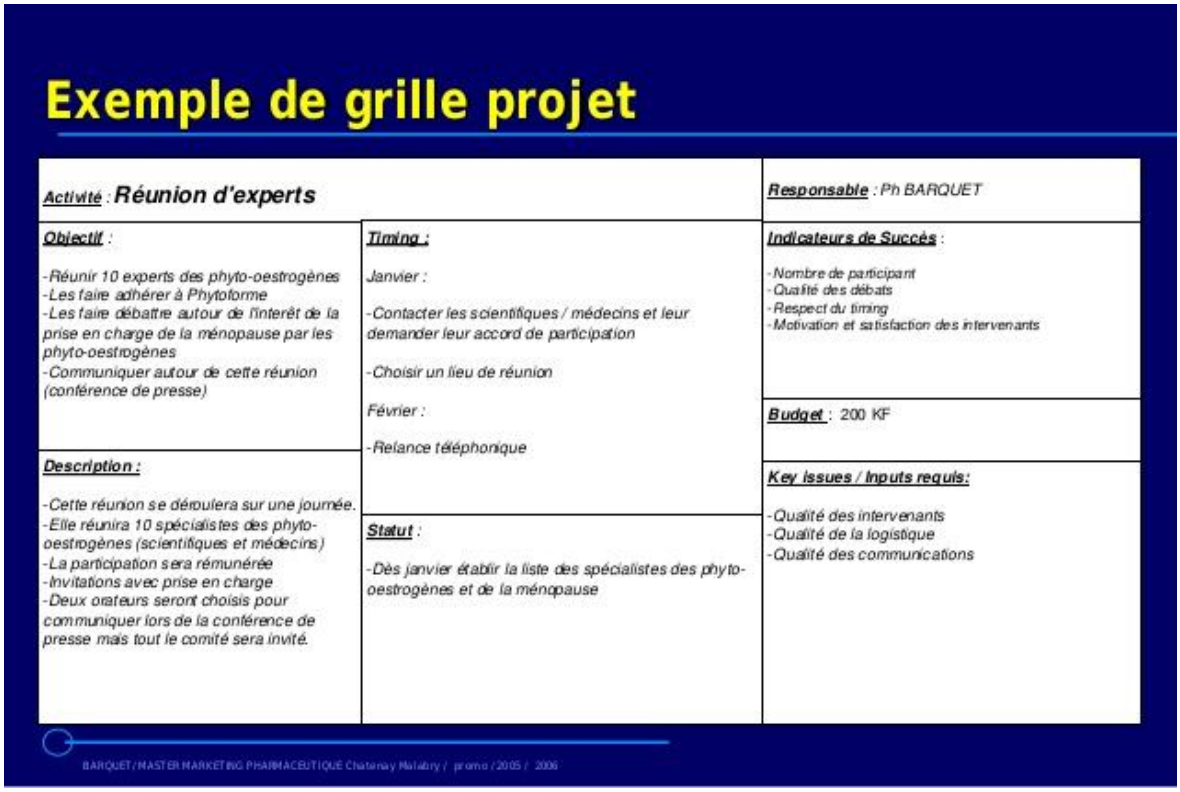
Thus, three activities in particular, which are part of business strategy, need to be better framed:

- Relationships with health professionals considered "opinion leaders," spokesman companies in business meetings, conventions, meetings of advisory committees ("advisory board") ...
- Relations with the press and the 'ghost' writers
- Aimed at the general public "disease oriented" campaigns without brand name

All these actions orchestrated by the product managers of companies that do not use sales representatives but third-party as means of communication are considered outside the scope of "advertising."

Regarding relations with the leaders, most of the time, it falls to the scientists of the company (doctors and pharmacists) to drive these namely "scientific" projects and liaise directly with healthcare professionals.
However, these actions with scientific or informative purposes contribute directly or indirectly to the communication on the drug: it is called "peer to peer" marketing. On these occasions, publications that cannot be used in advertising can be exchanged, and information on product development with preliminary results can circulate ... positively influencing the perception of professionals on the product or at least raising their interest, especially when opinion leaders who communicate. And these leaders are justified in claiming that the work in which they participated reflects their expertise and their own opinions. If most of the time, new information that have not been validated yet by the authorities, are improving knowledge of the drug and in particular are allowing reasonable adjustments in practice, they may unfortunately sometimes go totally against the proper use, because of lack of experience on the drug's safety.

Example of project map of an expert meeting[50]:



Regarding relations with the press, despite the existence of a Code of Ethics governing the relationship between advertisers and the media, the border between information and promotion is not always clear, and the use of the press via press conferences for example, is only a means to communicate legally on the drug that was not possible in the traditional way of advertising.

Of course, scientific integrity and ethics require that press kits are balanced and complete, but we cannot escape a certain bias of information. The journalist uninformed or unskilled can be unconsciously be the spokesperson for the company. Thus, the HAS has recently published a guide to best practices and standards of quality of magazines and newspapers in the French medical press.

Without infringing on the freedom of the press, and from the moment this information is at the initiative of the company, some topics such as the presentation of the results of a new clinical study should fall into the field of advertising; in that case, press releases as well as slideshow on the conference should fall under the control of the ANSM.

Notwithstanding the foregoing, the regulations on advertising to healthcare professionals becoming increasingly stringent, new means of communication have evolved directly to the general public, which is a huge pool of potential patients. As advertising for

[50] http://fr.slideshare.net/PhilippeBarquet/le-chefdeproduitpharma

prescription drugs to general public is prohibited, pharmaceutical companies develop campaigns for diseases for which they have treatments.

With the increasing incidence of chronic diseases, building on patients' associations, some experts and the media, messages and services are increasing: hotline on diseases, information leaflets, brochures presenting biomedical research, program support for compliance to treatment, disease information, e-health tools with practical applications of androids...

These services are part of the means to meet the three main issues of an optimal medical care of patients with chronic disease:

- The issue of screening and diagnosis of chronic disease: Many people are unaware that they are actually affected by a chronic disease,
- The issue of involvement in medical choices, to know to navigate within the health system and to access to the best care possible,
- The issue of compliance and continuing of treatments to successfully control the disease.

By offering these services and information, not only the firms gain a reputation and positive image, but these campaigns identify or create also new recruit patients. In addition, some patients' associations, which are partners and partly funded by the firms do not hesitate to quote the medication at public meetings. If these campaigns and services can help patients to better understand and manage their illness or sometimes to detect and diagnose it earlier; the flip side is that they may raise demand for care by the patient more than necessary and bear by the community the additional costs of unnecessary tests. New diseases are also flourishing, such as disorders of lubrication in women, the social anxiety disorder, premenstrual dysphoric disorder, alopecia... that generate demand for treatment. Finally, some campaigns although without mentioning drugs brand name, are able to generate such interest that the drug can be easily identified (e.g. the campaign of Pfizer for erectile dysfunction). In all cases they are indirect advertisements, which like in the United States that allow advertising to the general public, generate drug overconsumption, which increases the risk of serious misuse and adverse effects, as it was the case for Mediator, causing an overall additional costs for health systems.

Also, it seems that in the context of rationalization of care and costs, in order not to generate unreasonable demands vitiating the prescriber-patient relationship and to preserve our health care system, **only messages and services listed in regularly set priority programs of public health Law should be admitted**.

Finally, there is the question of the performance of the control system: **audits and inspections**.

Indeed, the documentary control of advertising does not address the issue of loyalty that is made by the sales force on the ground. On this last point, in France, the Medical Visit Charter in place since 2004 and the collective visit proposed by the drug reform should reinforce this loyalty. However, self-inspection conducted within companies is not enough in some cases to limit deviant messages, especially when high internal pressures exerted in a context of intense competition. But, just check the in-house training documents as well as the books of campaign intended for sales force use including sales pitches to determine whether the speech is consistent with the approved documents that are presented to healthcare professionals. We never hear from an inspection verifying the consistency of all these documents while it is provided by the regulation (Article R5313-5 CSP). Similarly, "atypical" communications described earlier, which are sponsored by the firms, are not checked. Audits and inspections are limited so far to processes without checking the compliance of documents.

Support of **"sentinel" healthcare professionals networks trained to regulations** may also help to ensure compliance of messages.

3.2 Provide clear definitions

This study has raised the issue of definitions that are not universally shared by the community of health professionals or by the legislator and the administration.

It is essential that everyone have the same definition of compliance with the MA, non-compliance with MA or off-label, proper use and off-proper use to carry out their responsibilities fully and to establish coherent and concrete public health policy.

We suggest completing the Public Health Code of these definitions and integrating these regulatory concepts in the education and training of healthcare professionals.

3.3 Streamline repositories

We also identified through this study the difficulty of the healthcare professional in the field to find the right information, "the glut of information kills information". Some are not even aware of the existence of official information (validated by the authorities). In addition, some basic and complementary information, essential for prescription, can be found on various sites (ANSM, HAS, INCA).

As suggested by the focus group of Giens Workshops, it is desirable that coordination among regulatory authorities and professional societies is in place to prevent the

publication of repositories too redundant or too conflicting or confusing and that these repositories are centralized on one site.

We suggest that the most recent relevant publications are also listed there.

Conclusion

One year after the implementation of the reform, it seems that the crisis caused by the Mediator case is not quite settled: the difficulty we encountered to contact all stakeholders on the subject shows some trauma and distrust regarding people who are trying to work on the topic. Moreover, coming from the industry, we believe we have been a "victim" of this label for explaining this lack of cooperation from institutions for our research. Finally, organizations of healthcare professionals as well as the institutional ones seem to be reluctant to this type of individual research that is not their initiative, probably wanting to avoid exposure to new criticism.

Our contribution is therefore limited and the initial objective to measure the effects of the drug reform on off-label prescriptions has been refocused to studying a single provision of the reform.

Nevertheless, we can draw the conclusion that the measures taken under the fire of a media crisis and arousing public mistrust towards the entire health system are not necessarily the most relevant and most practical ones. The reintroduction of a priori control of advertising is rather an announcement effect, which of course disrupts the internal organization of firms but in terms of efficiency, has been limited to a micro-part of an entire communication strategy of the firms, without really changing the basis.

Meanwhile, the political will to better control the use of drugs is expressed in two texts:

- PLFSS 2013 (Social Security Financing Bill)
- Letter of guidance of the Ministers dated on April 2, 2013

One can note a convergence of objectives not only regarding effective care and to strengthen the security of health products but also to control their costs.

Financial issues related to off-label prescriptions are important; the regulation will be economic with the rise of CEPS as a player in the control of proper use.

However, if the power of sanctions and penalties application given to the CEPS are clearly identified and legitimate (see also Article 21 of the LRSS), it is less clear for the who and how in the detection of off-proper drug use and in the promotion of the proper use among healthcare professionals: it seems that several bodies or agencies are involved without a central organization responsible: CEPS, HAS, ANSM, CNAMTS...?

Also, we think it is important to identify upstream central structure, which is the conductor of the actions that govern the proper use and off-label prescriptions.

Among the areas for improvement that we can then propose:

- Statutorily redefine the concepts of MA and the proper use in mirror of off-label and misuse or off-proper use

- Reform the advertising and adapt the control system to the whole communication of the firm
- Centralize repositories and inform professionals in their education of them

Finally, future research may emerge from some answers to our questionnaires especially regarding the pharmacovigilance system considered time-consuming and complex, but so important in the detection and management of off-label prescriptions.

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Appendices

Appendix 1: The SPC, the cornerstone between assessment and information intended for healthcare professionals use (reminder on clinical pharmacology)

Appendix 2: Law No 2011-2012 on 29 December 2011 related on reinforcement of safety of medicinal and health products

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- ANSM
- DGOS
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- Physicians
- Pharmacists
- Regulatory affairs Department in charge of advertising control in the firms

Appendix 1: The SPC, the cornerstone between assessment and information intended for healthcare professionals use (reminder on clinical pharmacology)

❖ *Section 4.1: Therapeutic indications*

The therapeutic indication of an innovative drug is underpinned by the results of one or more clinical studies[51].

A well-conducted study has a precise objective regarding the efficacy, which should be comparable or greater than the reference strategy of treatment. It is thus conducted on a population whose baseline characteristics are relevant to the disease such as age, sex, comorbidities, etc., and of sufficient size to allow a robust statistical interpretation.

The results of the study will conclude the efficacy of a given treatment and its place in the therapeutic strategy in relation to other available treatments.

The wording of the therapeutic indication should translate these findings. It must unambiguously define its purpose and its target population, by specifying if appropriate, the restrictions; the therapeutic indication should states[52]:

- ✓ Targeted disease or condition treatment:
  - Prevention (primary or secondary)
  - Curative
  - Modifying the evolution or progression of the disease,
  - Symptomatic
  - Diagnostic
- ✓ The population of patients eligible and age groups
- ✓ Where appropriate, the mandatory conditions of use of the drug such as concomitant use of another treatment or specific dietary measures
- ✓ If applicable, the processing line of treatment (first or second or third for example after failure of standard therapy)
- ✓ Finally, if the indication of the product depends on a particular genotype or expression of a gene or a particular phenotype, it must be indicated in the indication.

➔ Failure to comply with an indication may concern each of the points mentioned above.

[51] For generics or well-known active substances, a simplified dossier referring to littérature may be accepted

[52] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000357.jsp&mid=WC0b01ac05806361e1#section1

Any deviation from the wording of the indication may cause an inefficiency or increased toxicity.

❖ ***Section 4.2: Posology and method of administration***

Always based on the conditions of MA studies, this section states:

- ✓ The dosage for each indication claimed:
  - The dose depending on the patient population
  - Frequency of administration
  - Other recommendations:
    - The duration of treatment
    - The maximum recommended dose
    - Dose adjustment
    - Discontinuation
    - In case of missed dose
    - Preventive measures to avoid the side effects
    - Concomitant food and drinks
    - Drug interactions requiring dose adjustments
    - The intervals between courses
- ✓ Special populations[53]:
  - Seniors
  - Patients with renal impairment
  - Patients with hepatic insufficiency
  - The pediatric population
- ✓ The mode and route of administration:
  - Precautions for handling or administering the drug by healthcare professionals and the patient should be referred
  - Specific instructions for administration, route and use
  - The specific recommendations in relation to the pharmaceutical form
  - If necessary, the rate of administration (for example infusions)

➔ The non-compliance with these recommendations may reduce efficacy or increase the risk of adverse effects by altering the bioavailability.

❖ ***Section 4.3: Contra-indications***

[53] If the drug has no indication in some populations, no dosing recommendations can be made for these specific populations, special precautions should be taken.

These are situations where the drug should not be given for security reasons.

The wording should be concise and unambiguous.

While a lack of data does not necessarily lead to a contra-indication (except in cases of predictable risks), the populations of patients who were excluded from the studies due to a contra-indication for safety reasons must be included in this section.

➔ A prescription in patient populations who are listed in this section may be very harmful.

❖ ***Section 4.4: Special warnings and precautions for use***

These are the risks of treatment that requires precautions for certain categories of patients, or requires special attention from the healthcare professional in monitoring the patient.

➔ To ignore these warnings and precautions exposes the patient to a higher risk of adverse effects.

❖ ***Section 4.5: Interaction with other medicinal products and other forms of interaction***

This section should provide information on the potential for clinically relevant interactions based on the pharmacodynamic properties and in vivo pharmacokinetic studies of the medicinal product, i.e. those resulting in recommendation on the use of this medicine or other medicines.

Regarding the concomitant use of other drugs, there are 3 levels of recommendations:

- ✓ Contraindications of concomitant use
- ✓ Concomitant use not recommended
- ✓ Concomitant use to be taken into account

Interactions can also result in clinical events with effects on plasma levels, on the AUC of parent compound or its active metabolites and/or on laboratory parameters.

Finally, there may also be interactions with herbal medicines, food, alcohol, tobacco, or pharmacologically active substances, which are not used for medical purposes.

These interactions may potentiate the effect of the drug or provide additive harmful effect.

These effects may be increased in certain populations (children, renal failure, elderly ...).

➔ Ignorance of interactions exposes the patient to a risk of adverse effects. Two underlying mechanisms:

- Pharmacodynamic: effects added resulting in a visible or too large effect;
- Pharmacokinetic: changes of fate in the body of a drug by the presence of the other.

❖ ***Section 5.1: Pharmacodynamic properties***

This section provides the pharmacological and clinical data that founded the MA. Only information relevant to the approved therapeutic indication are presented:

- ✓ Mechanisms of action
- ✓ Pharmacodynamic effects
- ✓ Clinical efficacy data: only statistically and clinically relevant results are described
- ✓ Exceptionally relevant subgroup analyzes or post hoc are presented, while moderating the scope of the results given the methodological weaknesses.
- ✓ Relevant clinical data in special populations (eg, children or the elderly).
- ✓ Specific safety data, especially when it is an endpoint of the study.

Appendix 2: Law No 2011-2012 on 29 December 2011 related on reinforcement of safety of medicinal and health products : article 29

CHAPITRE VI

La pharmacovigilance

Article 28

I. – Après le chapitre Ier du titre II du livre Ier de la cinquième partie du code de la santé publique, il est inséré un chapitre Ier *bis* ainsi rédigé :

« *CHAPITRE Ier BIS*

« ***Pharmacovigilance***

« *Art. L. 5121-22.* – La pharmacovigilance a pour objet la surveillance, l'évaluation, la prévention et la gestion du risque d'effet indésirable résultant de l'utilisation des médicaments et produits mentionnés à l'article L. 5121-1.

« *Art. L. 5121-23.* – L'Agence nationale de sécurité du médicament et des produits de santé assure la mise en œuvre du système de pharmacovigilance pour procéder à l'évaluation scientifique de toutes les informations, pour examiner les options permettant de prévenir les risques ou les réduire et, au besoin, pour prendre des mesures appropriées. Elle définit les orientations de la pharmacovigilance, anime et coordonne les actions des différents intervenants, veille au respect des procédures de surveillance et participe aux activités de l'Union européenne dans ce domaine.

« *Art. L. 5121-24.* – Toute entreprise ou organisme exploitant un médicament ou un produit mentionnés à l'article L. 5121-1 est tenu de respecter les obligations qui lui incombent en matière de pharmacovigilance et, en particulier, de mettre en œuvre un système de pharmacovigilance ainsi que d'enregistrer, de déclarer et de suivre tout effet indésirable suspecté d'être dû à un médicament ou produit mentionnés au même article L. 5121-1 dont il a connaissance et de mettre en place des études post-autorisation mentionnées à l'article L. 5121-8-1 dans les délais impartis.

« *Art. L. 5121-25.* – Les médecins, chirurgiens-dentistes, sages-femmes et pharmaciens déclarent tout effet indésirable suspecté d'être dû à un médicament ou produit mentionnés à l'article L. 5121-1 dont ils ont connaissance.

« Les autres professionnels de santé, les patients et les associations agréées de patients peuvent signaler tout effet indésirable suspecté d'être dû à un médicament ou produit mentionnés au même article L. 5121-1 dont ils ont connaissance.

« *Art. L. 5121-26.* – Les règles applicables à la pharmacovigilance exercée sur les médicaments et sur les produits mentionnés à l'article L. 5121-1 sont déterminées par décret en Conseil d'Etat, notamment ses modalités d'organisation ainsi que les procédures de détection, de recueil et d'analyse des signaux et les procédures de suivi et de retour de l'information vers les personnes mentionnées à l'article L. 5121-25. »

II. – Le 13° de l'article L. 5121-20 du même code est abrogé.

III. – L'article L. 5421-6-1 du même code est ainsi rédigé :

« *Art. L. 5421-6-1.* – Est puni de trois ans d'emprisonnement et de 45 000 € d'amende le fait pour toute personne exploitant un médicament ou produit mentionnés à l'article L. 5121-1 ou pour tout titulaire de l'autorisation prévue à l'article L. 4211-6 de méconnaître les obligations de signalement d'un effet indésirable grave suspecté d'être dû à ce médicament ou produit dont il a eu connaissance. »

CHAPITRE VII

Information et publicité sur le médicament à usage humain

Article 29

I. – Le second alinéa de l'article L. 5122-2 du code de la santé publique est complété par les mots : « ainsi que les stratégies thérapeutiques recommandées par la Haute Autorité de santé ».

II. – L'article L. 5122-3 du même code est complété par un alinéa ainsi rédigé :

« La publicité pour un médicament est interdite lorsque ce médicament fait l'objet d'une réévaluation du rapport entre les bénéfices et les risques à la suite d'un signalement de pharmacovigilance. Les professionnels de santé sont informés par l'exploitant du médicament de la réévaluation conduite dans le cadre du présent alinéa. L'information ainsi prodiguée doit être conforme à celle délivrée par l'Agence nationale de sécurité du médicament et des produits de santé. »

III. – Au premier alinéa de l'article L. 5122-5 du même code, après la référence : « L. 5122-8 », est insérée la référence : « , L. 5122-9 » et la référence : « aux articles L. 5122-9 et » est remplacée par les mots : « à l'article ».

IV. – Les troisième à avant-dernier alinéas de l'article L. 5122-6 du même code sont remplacés par quatre alinéas ainsi rédigés :

« Par dérogation au premier alinéa, les campagnes publicitaires pour les médicaments mentionnés à l'article L. 5121-2 ou pour des vaccins soumis à prescription médicale ou remboursables peuvent s'adresser au public.

« Les campagnes publicitaires non institutionnelles auprès du public pour des vaccins mentionnés au troisième alinéa du présent article ne sont autorisées que si les conditions suivantes sont réunies :

« 1° Ils figurent sur une liste de vaccins établie pour des motifs de santé publique par arrêté du ministre chargé de la santé pris après avis du Haut Conseil de la santé publique ;

« 2° Le contenu de ces campagnes publicitaires est conforme à l'avis du Haut Conseil de la santé publique et est assorti, de façon clairement identifiée, des mentions minimales obligatoires déterminées par cette instance. Ces mentions sont reproduites *in extenso,* sont facilement audibles et lisibles, selon le support du message publicitaire concerné, sont sans renvoi et sont en conformité avec des caractéristiques définies par arrêté du ministre chargé de la santé. »

V. – L'article L. 5122-9 du même code est ainsi rédigé :

« *Art. L. 5122-9.* – La publicité pour un médicament auprès des membres des professions de santé habilités à prescrire ou à dispenser des médicaments ou à les utiliser dans l'exercice de leur art est soumise à une autorisation préalable de l'Agence nationale de sécurité du médicament et des produits de santé dénommée "visa de publicité".

« Ce visa est délivré pour une durée qui ne peut excéder la durée de l'autorisation de mise sur le marché pour les médicaments soumis à cette autorisation.

« En cas de méconnaissance des articles L. 5122-2 ou L. 5122-3, le visa peut être suspendu en cas d'urgence ou retiré par décision motivée de l'agence.

« Toute publicité auprès des professionnels de santé pour des vaccins est assortie, de façon clairement identifiée et sans renvoi, des recommandations *in extenso* de l'avis du Haut Conseil de la santé publique. »

VI. – Après le même article L. 5122-9, il est inséré un article L. 5122-9-1 ainsi rédigé :

« *Art. L. 5122-9-1.* – Les demandes de visa prévues à l'article L. 5122-9 sont effectuées selon un calendrier et durant une période déterminés par décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé. »

VII. – Le 5° de l'article L. 5122-16, l'article L. 5422-3 et l'article L. 5422-4 du même code sont abrogés.

VIII. – L'article L. 5422-6 du même code est ainsi modifié :

1° Au premier alinéa, après le mot : « public », sont ajoutés les mots : « ou des professionnels de santé » ;

2° Au 2°, la référence : « à l'article L. 5122-8 » est remplacée par les références : « aux articles L. 5122-8 et L. 5122-9 ».

IX. – Le 3° de l'article L. 5422-11 du même code est ainsi rédigé :

« 3° Qui n'a pas fait l'objet du visa de publicité prévu à l'article L. 5122-9 ou qui est effectuée malgré la décision de suspension ou de retrait de celui-ci prise en application du même article. »

X. – Après le *d* de l'article L. 613-5 du code de la propriété intellectuelle, il est inséré un *d bis* ainsi rédigé :

« *d* bis) Aux actes nécessaires à l'obtention du visa de publicité mentionné à l'article L. 5122-9 du code de la santé publique ; ».

Article 30

I. – A titre expérimental et pour une période ne pouvant excéder deux ans, l'information par démarchage ou la prospection pour les produits de santé mentionnés à l'article L. 5311-1 du code de la santé publique, à l'exception des médicaments réservés à l'usage hospitalier et de ceux à prescription hospitalière initiale ou non ainsi que des produits visés à l'article L. 5211-1 du même code, effectuée dans les établissements de santé ne peut avoir lieu que devant plusieurs professionnels de santé, dans les conditions définies par convention conclue entre chaque établissement de santé et l'employeur de la personne concernée, dont les modalités sont définies par arrêté du ministre chargé de la santé pris après avis de la Haute Autorité de santé.

Avant le 1er janvier 2013, le Gouvernement présente au Parlement un rapport dressant le bilan de l'expérimentation prévue au premier alinéa, réalisé à partir d'une évaluation conduite par la Haute Autorité de santé. Ce rapport peut proposer les évolutions législatives découlant du bilan, notamment en ce qui concerne la pérennisation des dispositions en cause ainsi que leur éventuelle adaptation à la médecine de ville.

II. – L'article L. 162-17-8 du code de la sécurité sociale est ainsi modifié :

1° Le second alinéa est complété par une phrase ainsi rédigée :

« A cet effet, le Comité économique des produits de santé peut fixer des objectifs annuels chiffrés d'évolution de ces pratiques, le cas échéant pour certaines classes pharmaco-thérapeutiques ou pour certains produits. » ;

Appendix 3: Decree N°2012-741 on 9 May 2012 related on advertising for medicinal product for human use

Décrets, arrêtés, circulaires

TEXTES GÉNÉRAUX

MINISTÈRE DU TRAVAIL, DE L'EMPLOI ET DE LA SANTÉ

Décret n° 2012-741 du 9 mai 2012 portant dispositions relatives à la publicité pour les médicaments à usage humain

NOR : ETSP1208477D

Publics concernés : *industries du médicament, professionnels de santé, presse professionnelle, patients.*

Objet : *publicité des médicaments à destination des professionnels de santé et du public.*

Entrée en vigueur : *les dispositions du présent décret sont applicables :*

- *pour la publicité à destination des professionnels, aux demandes déposées dans le cadre de la première période de dépôt prévue à l'article L. 5122-9-1 du code de la santé publique suivant la publication du présent décret ;*
- *pour la publicité à destination du public, aux demandes déposées dans le cadre de la première période de dépôt prévue à l'article R. 5122-5 du code précité suivant la publication du présent décret.*

Notice : *la loi n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé a instauré un mécanisme de contrôle* a priori *pour les publicités à destination des professionnels de santé à l'instar du contrôle en vigueur pour la publicité à destination du public. Le décret précise les modalités d'application de cette mesure en prévoyant, notamment, un régime d'autorisation tacite des demandes de visa. Il procède également à une actualisation de la partie réglementaire du code de la santé publique relative à la publicité des médicaments.*

Références : *les dispositions du code de la santé publique modifiées par le présent décret peuvent être consultées, dans leur rédaction résultant de cette modification, sur le site Légifrance (http://www.legifrance.gouv.fr). Il est pris pour l'application du V de l'article 29 la loi n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé.*

Le Premier ministre,

Sur le rapport du ministre du travail, de l'emploi et de la santé,

Vu le code de la santé publique, notamment ses articles L. 5122-8, L. 5122-9 et L. 5122-16 ;

Vu la loi n° 2000-321 du 12 avril 2000 relative aux droits des citoyens dans leurs relations avec les administrations ;

Vu le décret n° 2012-597 du 27 avril 2012 relatif à l'Agence nationale de sécurité du médicament et des produits de santé ;

Vu l'avis de l'Autorité de la concurrence en date du 26 avril 2012 ;

Le Conseil d'Etat (section sociale) entendu,

Décrète :

Art. 1er. – A l'article R. 5122-1 du code de la santé publique, après les mots : « mentionné à l'article R. 5121-21 », sont insérés les mots : « ainsi qu'aux stratégies thérapeutiques recommandées par la Haute Autorité de santé mentionnées à l'article L. 5122-2 ».

Art. 2. – Après l'article R. 5122-2 du même code, il est inséré un article R. 5122-2-1 ainsi rédigé :

« *Art. R. 5122-2-1.* – Lorsqu'un médicament fait l'objet d'une réévaluation du rapport entre les bénéfices et les risques à la suite d'un signalement de pharmacovigilance, le directeur général de l'Agence nationale de sécurité du médicament et des produits de santé en informe sans délai l'exploitant. Il l'informe également sans délai de l'achèvement et du résultat de la réévaluation.

« Si la réévaluation donne lieu à une modification de l'autorisation de mise sur le marché ou de l'enregistrement imposant une modification des mentions figurant dans une publicité qui bénéficiait, avant la réévaluation, du visa mentionné aux articles L. 5122-8 ou L. 5122-9, l'exploitant doit, pour reprendre la

publicité, obtenir un nouveau visa. Dans ce cas, par dérogation aux dispositions des articles R. 5122-5 et R. 5122-13, la demande de visa peut être déposée en dehors des périodes déterminées par décision du directeur général de l'agence et est réputée acceptée en l'absence de décision du directeur général dans un délai de deux mois à compter de la date de réception de la demande. »

Art. 3. – L'article R. 5122-3 du même code est ainsi modifié :

1° Au premier alinéa du 2°, les mots : « , outre les mentions obligatoires prévues au dernier alinéa de l'article L. 5122-6 » sont supprimés ;

2° Au *a* du 2°, les mots : « lorsque le médicament ne contient qu'un seul principe actif » sont supprimés ;

3° Sont ajoutés deux alinéas ainsi rédigés :

« *e)* Pour une spécialité générique, la mention de cette qualité et, si le groupe générique auquel appartient la spécialité comporte une ou plusieurs spécialités de référence, la mention : "Cette spécialité est un générique de", suivie du nom de la ou des spécialités de référence, de leur dosage et de leur forme pharmaceutique. En ce cas, la publicité comporte également la mention : "Médicament inscrit au répertoire des génériques. Lors de la substitution, consultez la liste des excipients à effet notoire figurant sur l'emballage ainsi que le répertoire des génériques pour prendre connaissance des mises en garde éventuelles y figurant."

« Pour une publicité sur un support de diffusion radiophonique, la mention de la dénomination commune prévue au *a* n'est requise que lorsque le médicament ne contient pas plus de deux principes actifs. En outre, pour l'application du *e*, seule est requise la mention que la spécialité est générique. »

Art. 4. – Au 4° de l'article R. 5122-4 du même code, le mot : « deuxième » est remplacé par le mot : « troisième ».

Art. 5. – Les articles R. 5122-5 à R. 5122-7 du même code sont remplacés par les dispositions suivantes :

« *Art. R. 5122-5.* – Un calendrier des périodes de dépôt des demandes de visa mentionnées à l'article L. 5122-8 est fixé pour chaque année, par décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé, avant le 1er novembre de l'année précédente. Ce calendrier détermine au minimum quatre périodes par an, d'une durée comprise entre une semaine et deux mois chacune, au cours desquelles les demandes doivent être déposées.

« Les demandes de visa sont réputées acceptées en l'absence de décision du directeur général de l'agence dans un délai de deux mois à compter du jour suivant la fin de la période au cours de laquelle elles ont été déposées.

« La durée de validité du visa est de deux ans.

« *Art. R. 5122-6.* – Lors du dépôt de la demande de visa, le demandeur attribue, à chacun des supports prévus pour la publicité, un numéro interne de référencement, selon des règles définies par une décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé.

« La publicité diffusée auprès du public fait mention de ce numéro, sauf pour une publicité sur un support de diffusion radiophonique.

« *Art. R. 5122-7.* – Le retrait de visa prévu au troisième alinéa de l'article L. 5122-8 est prononcé par le directeur général de l'Agence nationale de sécurité du médicament et des produits de santé après que le bénéficiaire du visa a été invité, par tout moyen permettant de rapporter la preuve de la date de réception de cet avis, à présenter ses observations écrites ou orales dans un délai fixé par le directeur général, qui ne peut être inférieur à un mois.

« En cas d'urgence, le directeur général de l'agence peut suspendre le visa, pour une durée de trois mois au plus. »

Art. 6. – L'article R. 5122-8 du même code est complété par un 16° ainsi rédigé :

« 16° Pour une spécialité générique, la mention de cette qualité et, si le groupe générique auquel appartient la spécialité comporte une ou plusieurs spécialités de référence, la mention : "Cette spécialité est un générique de", suivie du nom de la ou des spécialités de référence, de leur dosage et de leur forme pharmaceutique. En ce cas, la publicité comporte également la mention : "Médicament inscrit au répertoire des génériques. Lors de la substitution, consultez la liste des excipients à effet notoire figurant sur l'emballage ainsi que le répertoire des génériques pour prendre connaissance des mises en garde éventuelles y figurant." Toutefois, pour une publicité sur un support de diffusion radiophonique, seule est requise la mention que la spécialité est générique. »

Art. 7. – Au premier alinéa de l'article R. 5122-12 du même code, les mots : « le dépôt de publicité pour un médicament, prévu à l'article L. 5122-9, a lieu » sont remplacés par les mots : « la demande de visa de publicité pour un médicament, prévu à l'article L. 5122-9, est formée ».

Art. 8. – Les articles R. 5122-13 à R. 5122-15 du même code sont remplacés par les dispositions suivantes :

« *Art. R. 5122-13.* – Un calendrier des périodes de dépôt des demandes de visa mentionnées à l'article L. 5122-9 est fixé pour chaque année, par décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé, avant le 1er novembre de l'année précédente. Ce calendrier détermine au minimum quatre périodes par an, d'une durée comprise entre une semaine et deux mois chacune, au cours desquelles les demandes doivent être déposées.

« Les demandes de visa sont réputées acceptées en l'absence de décision du directeur général de l'agence dans un délai de deux mois à compter du jour suivant la fin de la période au cours de laquelle elles ont été déposées.

« La durée de validité du visa est de deux ans.

« *Art. R. 5122-14.* – Lors du dépôt de la demande de visa, le demandeur attribue, à chacun des supports prévus pour la publicité, un numéro interne de référencement, selon des règles définies par une décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé.

« La publicité diffusée auprès des professionnels de santé fait mention de ce numéro, sauf pour une publicité sur un support de diffusion radiophonique.

« *Art. R. 5122-15.* – Le retrait de visa prévu au troisième alinéa de l'article L. 5122-9 est prononcé par le directeur général de l'Agence nationale de sécurité du médicament et des produits de santé après que le bénéficiaire du visa a été invité, par tout moyen permettant de rapporter la preuve de la date de réception de cet avis, à présenter ses observations écrites ou orales dans un délai fixé par le directeur général, qui ne peut être inférieur à un mois.

« En cas d'urgence, le directeur général de l'agence peut suspendre le visa, pour une durée de trois mois au plus. »

Art. 9. – L'article R. 5122-16 du même code est ainsi modifié :

1° Les mots : « prévues aux articles R. 5122-13 à R. 5122-15 » sont remplacés par les mots : « prévues à l'article R. 5122-15 » ;

2° La référence à l'article R. 5132-92 du même code est remplacée par la référence à son article R. 5132-97.

Art. 10. – L'article R. 5122-17 du même code est ainsi modifié :

1° Le premier alinéa est remplacé par les dispositions suivantes :

« I. – La remise d'échantillons gratuits mentionnée à l'article L. 5122-10 n'est admise que pendant les deux années suivant la première commercialisation effective en France :

« 1° D'une spécialité bénéficiant d'un premier enregistrement ou d'une première autorisation de mise sur le marché ; ou

« 2° D'une spécialité déjà enregistrée ou autorisée ayant obtenu un enregistrement ou une autorisation de mise sur le marché pour un nouveau dosage ou une nouvelle forme pharmaceutique, si l'enregistrement ou l'autorisation est assorti d'une extension d'indication.

« Elle est également admise pendant les deux années suivant une modification du classement du médicament mentionné au 1° de l'article R. 5121-36.

« II. – La remise d'échantillons gratuits respecte en outre les conditions suivantes : » ;

2° Au 2°, les mots : « dix par an et par destinataire » sont remplacés par les mots : « quatre par an et par destinataire ».

Art. 11. – Les deux premiers alinéas de l'article R. 5122-22 du même code sont remplacés par les dispositions suivantes :

« Pour un produit mentionné à l'article L. 5122-14, le visa de publicité à destination des professionnels mentionné à l'article L. 5122-9 est délivré et peut être suspendu ou retiré dans les conditions prévues aux articles R. 5122-13 à R. 5122-16.

« Les dispositions de l'article R. 5122-20 sont applicables à la demande de visa de publicité. La publicité mentionne, en outre, la date à laquelle elle a été établie ou révisée en dernier lieu. »

Art. 12. – La section 3 du chapitre IV du titre III du livre Ier de la cinquième partie du même code est ainsi modifiée :

1° A l'article R. 5134-11, avant la référence à l'article R. 5122-5, est insérée la référence à l'article R. 5122-2-1 ;

2° L'article R. 5134-12 est ainsi modifié :

a) Au *a* du 2°, les mots : « lorsque le produit ne contient qu'un seul principe actif » sont supprimés ;

b) Il est ajouté un alinéa ainsi rédigé :

« Pour une publicité sur un support de diffusion radiophonique, la mention de la dénomination commune prévue au *a* n'est requise que lorsque le produit ne contient pas plus de deux principes actifs. » ;

3° Au second alinéa de l'article R. 5134-15, les mots : « et les dépôts de publicité sont accompagnés » sont remplacés par les mots : « sont accompagnées ».

Art. 13. – I. – Le II de l'article R. 1161-17 du même code est ainsi modifié :

1° Le troisième alinéa est supprimé ;

2° La première phrase du dernier alinéa est remplacée par les dispositions suivantes : « A compter de la réception de l'avis de l'association consultée ou de l'expiration du délai qui est imparti, le directeur général se prononce sur la demande dans le délai de deux mois. »

II. – Les 2° et 3° de l'article R. 1521-3 du même code sont supprimés.

Art. 14. – I. – Par dérogation aux dispositions des articles R. 5122-5 et R. 5122-13 du code de la santé publique, les calendriers des périodes de dépôt des demandes de visa de publicité pour l'année 2012 sont fixés par une décision du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé prise dans le délai de quinze jours après la publication du présent décret et prévoient au minimum deux périodes de dépôt.

II. – Les dispositions des articles R. 5122-5, R. 5122-6, R. 5122-13 et R. 5122-14 du même code, dans leur rédaction résultant du présent décret, s'appliquent aux demandes de visa déposées à compter du premier jour de la première période des calendriers fixés en application du I.

III. – A compter de la même date, les dispositions du premier alinéa du II de l'article 6 du décret n° 2012-597 du 27 avril 2012 relatif à l'Agence nationale de sécurité du médicament et des produits de santé cessent d'être applicables aux décisions prises en application du chapitre II du titre II du livre Ier de la cinquième partie du code de la santé publique.

IV. – Les personnes ayant procédé à des dépôts de publicité avant la date d'entrée en vigueur du présent décret en conservent le bénéfice, sous réserve des mises en demeure et des décisions d'interdiction éventuellement prononcées à leur encontre, à condition de présenter une demande de visa de publicité au cours de l'une des deux premières périodes du calendrier fixé en application du I et jusqu'à l'intervention d'une décision explicite ou implicite sur cette demande.

Art. 15. – Le ministre du travail, de l'emploi et de la santé et la secrétaire d'Etat auprès du ministre du travail, de l'emploi et de la santé, chargée de la santé, sont chargés, chacun en ce qui le concerne, de l'exécution du présent décret, qui sera publié au *Journal officiel* de la République française.

Fait le 9 mai 2012.

FRANÇOIS FILLON

Par le Premier ministre :

Le ministre du travail,
de l'emploi et de la santé,
XAVIER BERTRAND

La secrétaire d'Etat
auprès du ministre du travail,
de l'emploi et de la santé,
chargée de la santé,
NORA BERRA

Appendix 4: Reminder of regulatory texts on advertising in France

The legislative provisions on advertising for medicinal products for human use are found in the Code of Public Health Articles L5122-1 to L5122-13 and L5122-16.

Regulatory measures taken in application of Law are distributed as follows:

- General provisions (section 1): Articles R5122-1 / R5122-2
- Advertising to the general public (section 2): Articles R5122-3 R5122-7
- Advertising to healthcare professions (Section 3): Articles R5122 R5122-8-17

Criminal sanctions apply in case of failure to the above provisions: Articles L5422-1 to L5422-17.

Moreover, the ANSM publish recommendations that specify the general principles of law in particular contexts or presentations, which should be taken into account in the development of advertising.

Appendix 5: Questionnaires

ANSM – Direction de la Surveillance - Département en charge du contrôle de la publicité

Questionnaire ANSM **Date :**

1. **Question 1 :** Quels changements notables avez-vous observé depuis la réforme du médicament ?
   - au niveau de l'évaluation ?
   - en terme d'organisation interne ?
   - autres ?

2. **Question 2 :** Qu'est que l'instauration du contrôle de la Publicité a priori a modifié ?
   - en terme de contenu ?
   - en terme de mode de communication ?
   - en terme de volumétrie ?
   - autres ?

3. **Question 3 :** En dehors des documents que vous soumettent les laboratoires, avez-vous connaissance de la communication/information diffusée par les laboratoires et qui n'est pas déposée ?

4. **Question 4 :** Quels sont les moyens dont vous disposez pour vérifier la conformité de la communication des laboratoires en dehors des supports déposés ?

5. **Question 5 :** Avez-vous des groupes de travail ou réunions transverses régulières avec les équipes internes pour discuter des cas émergents de mésusage/hors AMM :
   Si oui, cocher :
   - ☐ Inspection ?
   - ☐ Pharmacovigilance ?
   - ☐ Essais cliniques ?
   - ☐ Affaires réglementaires ?
   - ☐ Direction produits ?
   - ☐ Autres ?

6. **Question 6 :** Quelle est l'organisation mise en place au niveau de l'ANSM pour veiller à la mise en œuvre de l'article 31 de la Loi relative au renforcement de la sécurité sanitaire du médicament et des produits de santé (LRSS) au sein des laboratoires ?

7. **Question 7 :** Concernant l'article 31 de la LRSS, comment articulez-vous le hors AMM et le hors Bon Usage ?

8. **Question 8 :** Définitions :
   - Quelle définition donnez-vous à une prescription conforme à l'AMM ?
   - Quelle définition donnez-vous au bon usage ?
   - Quelle définition donnez-vous au hors AMM ?
   - Quelle définition donnez-vous au hors bon usage ?

A renvoyer à Tô Quynh Gandolphe : lou-mc@noos.fr

Direction générale de la santé

Questionnaire DGS **Date :**

1. **Question 1 :** quelle définition donnez-vous à :
   a. une prescription conforme à l'AMM ?
   b. une prescription hors AMM ?
   c. bon usage des médicaments ?

2. **Question 2 :** quel est le champ d'intervention de la DGS concernant l'encadrement des prescriptions hors AMM ?

3. **Question 3 :** quel est le champ d'intervention de la DGS concernant la mise en œuvre de l'article 31 de la loi sur le renforcement de la sécurité sanitaire, relative au bon usage du médicament[1] ?

4. **Question 4** : comment assurer et vérifier une prescription conforme aux référentiels en vigueur ?

5. **Question 5** : avez-vous un retour qualitatif du contrôle a priori de la publicité ?

6. **Question 6 :** est-il prévu un reformatage de la formation initiale (1er et 2ème cycles) des prescripteurs et des pharmaciens, notamment les connaissances fondamentales ? si oui, quels seraient les changements les plus notables ? A quelle échéance ?

7. **Question 7 :** comment serait concrètement organisée la formation continue des prescripteurs et pharmaciens ? à quelle échéance le développement personnel continu (DPC) des médecins et pharmaciens sera-t-il opérationnel ?

8. **Question 8 :** comment est assurée la passerelle ville-hôpital et le retour en ville en ce qui concerne les prescriptions ? le dossier médical personnel (DMP) répond-il à cette problématique ? à quel terme sera-t-il opérationnel sur le territoire national ?

9. **Question 9** : pourquoi le DMP et le DP (dossier pharmaceutique) sont-ils gérés séparément ?

10. **Question 10** : lorsque le DMP sera mis en place, pourrait-on envisager de transférer l'acte de prescription (médicament, dosage, forme, durée) au pharmacien, qui s'appuierait sur la recommandation du médecin sur une classe thérapeutique ou DCI ?

[1] « Art. L. 5121-14-3 du CSP: L'entreprise qui exploite une spécialité pharmaceutique contribue au bon usage de cette dernière en veillant notamment à ce que la spécialité soit prescrite dans le respect de son autorisation de mise sur le marché mentionnée à l'article L. 5121-8 et, le cas échéant, des recommandations temporaires d'utilisation mentionnées à l'article L. 5121-12-1, de son autorisation temporaire d'utilisation mentionnée à l'article L. 5121-12, de son enregistrement mentionné aux articles L. 5121-13 ou L. 5121-14-1, de son autorisation mentionnée à l'article L. 5121-9-1 ou de son autorisation d'importation parallèle mentionnée à l'article L. 5121-17.
« Elle prend toutes les mesures d'information qu'elle juge appropriées à l'attention des professionnels de santé relevant de la quatrième partie du présent code lorsqu'elle constate des prescriptions non conformes au bon usage de cette spécialité tel que défini au premier alinéa et en avise sans délai l'Agence nationale de sécurité du médicament et des produits de santé. »

A renvoyer à Tô Quynh Gandolphe : lou-mc@noos.fr

Direction générale de l'offre de soins

Questionnaire DGOS **Date :**

1. **Question 1 : quelle définition donnez-vous à :**
   - une prescription conforme à l'AMM ?
   - une prescription hors AMM ?
   - bon usage des médicaments ?
2. **Question 1 :** quel est le champ d'intervention de la DGOS concernant l'encadrement des prescriptions hors AMM ?
3. **Question 2 :** quel est le champ d'intervention de la DGOS concernant la mise en œuvre de l'article 31 de la loi sur le renforcement de la sécurité sanitaire, relative au bon usage du médicament[1] ?
4. **Question 3** : comment assurer et vérifier une prescription conforme aux référentiels en vigueur ?
5. **Question 4 :** est-il prévu un reformatage de la formation initiale (1er et 2ème cycles) des prescripteurs et des pharmaciens, notamment les connaissances fondamentales ? si oui, quels seraient les changements les plus notables ? A quelle échéance ?
6. **Question 5 :** comment serait concrètement organisée la formation continue des prescripteurs et pharmaciens ? à quelle échéance le développement personnel continu (DPC) des médecins et pharmaciens sera-t-il opérationnel ?
7. **Question 6 :** comment est assurée la passerelle ville-hôpital et le retour en ville en ce qui concerne les prescriptions ? le dossier médical personnel (DMP) répond-il à cette problématique ? à quel terme sera-t-il opérationnel sur le territoire national ?
8. **Question 7** : pourquoi le DMP et le DP (dossier pharmaceutique) sont-ils gérés séparément?
9. **Question 8** : lorsque le DMP sera mis en place, pourrait-on envisager de transférer l'acte de prescription (médicament, dosage, forme, durée) au pharmacien, qui s'appuierait sur la recommandation du médecin sur une classe thérapeutique ou DCI ?

[1] « Art. L. 5121-14-3 du CSP: L'entreprise qui exploite une spécialité pharmaceutique contribue au bon usage de cette dernière en veillant notamment à ce que la spécialité soit prescrite dans le respect de son autorisation de mise sur le marché mentionnée à l'article L. 5121-8 et, le cas échéant, des recommandations temporaires d'utilisation mentionnées à l'article L. 5121-12-1, de son autorisation temporaire d'utilisation mentionnée à l'article L. 5121-12, de son enregistrement mentionné aux articles L. 5121-13 ou L. 5121-14-1, de son autorisation mentionnée à l'article L. 5121-9-1 ou de son autorisation d'importation parallèle mentionnée à l'article L. 5121-17.
« Elle prend toutes les mesures d'information qu'elle juge appropriées à l'attention des professionnels de santé relevant de la quatrième partie du présent code lorsqu'elle constate des prescriptions non conformes au bon usage de cette spécialité tel que défini au premier alinéa et en avise sans délai l'Agence nationale de sécurité du médicament et des produits de santé. »

A renvoyer à Tô Quynh Gandolphe : lou-mc@noos.fr

Physicians:
https://docs.google.com/forms/d/1vCNZqGNqzd2GjgBr3SNBXtOZpWVgVG8lcbT8Os0dsDE/viewform

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Réforme Bertrand - Questionnaire Médecins

*Obligatoire

Connaissance du cadre juridique et des responsabilités légales

Quels sont vos référentiels de médicaments ? (plusieurs réponses possibles) *

- [ ] Résumé des caractéristiques du produit (RCP) (ANSM)
- [ ] Vidal
- [ ] Avis de la commission de Transparence
- [ ] Recommandations HAS, INCA
- [ ] Recommandations / Alertes ANSM
- [ ] Conférence de consensus, sociétés savantes
- [ ] Revues/littérature
- [ ] Logiciel d'aide à la prescription (LAP)
- [ ] Aides de visite et autres documents des Laboratoires
- [ ] Autre :

Donner une définition d'une prescription "conforme à l'AMM"

Donner une définition d'une prescription "hors AMM"

Quel degré de connaissance avez-vous de la mention NR portée sur une ordonnance ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous de la mention "hors AMM" portée sur une ordonnance ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous du dispositif dérogatoire de prise en charge (Article 56 de la LFSS) ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous des protocoles thérapeutiques temporaires (PTT) et les recommandations temporaires d'utilisation (RTU) ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous de la responsabilité légale & du code de déontologie ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Vos liens avec les pharmaciens

Fonction du pharmacien

- [ ] hôpital
- [ ] officine

Types de contacts

- [ ] téléphoniques
- [ ] réunions
- [ ] Autre :

Fréquence des contacts

- ○ fréquents
- ○ rares

Motifs de vos contacts

- ☐ contenu de l'ordonnance
- ☐ considération économique
- ☐ Autre :

Le système de Pharmacovigilance

Quel degré de connaissance avez-vous du système de pharmacovigilance ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

○ ○ ○ ○ ○ ○

Que pensez-vous du système de signalement ?

A qui adressez-vous vos cas PV ? (plusieurs choix possibles)

- ☐ ANSM
- ☐ CRPV
- ☐ Laboratoire

A quelle fréquence remontez-vous les cas de PV ?

Quelles difficultés rencontrez-vous dans votre pratique quotidienne dans l'acte de prescription (et/ou renouvellement) et du suivi de vos patients ?

- [ ] non
- [ ] oui

si oui, préciser:

Concernant les publicités et les informations délivrées par les laboratoires (via la Visite Médicale et autres canaux de communication), avez-vous observé des changements depuis la mise en place de la réforme du médicament -juin 2012- : en terme de volumétrie ?

- [ ] non
- [ ] oui

si oui, préciser:

Pistes d'amélioration

Utilisez-vous le Dossier Médical Personnel ?

- [ ] non
- [ ] oui

Etes-vous prêt à mentionner sur l'ordonnance l'indication pour laquelle le médicament est prescrit ?

Que pensez-vous des logiciels d'aide à la prescription ?

Commentaires libres

Identification

les données sont recueillies pour le suivi mais seront anonymisées

Ville / Département *

Médecin *
cocher toutes les cases qui vous correspondent

- ☐ hospitalier
- ☐ ville
- ☐ primo-prescripteur
- ☐ renouveleur
- ☐ spécialiste
- ☐ MG

précisez votre spécialité:

Année Diplôme

adresse e-mail

Envoyer

N'envoyez jamais de mots de passe via l'outil Formulaires Google.

Pharmacists:
https://docs.google.com/forms/d/1MhM7Z1IZ1TvtfrljgFZeEi8Drf0vYf0eiNUF3PuMvjY/viewform

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Réforme Bertrand - Questionnaire Pharmaciens Hôpital & Officine

*Obligatoire

Connaissance du cadre juridique et des responsabilités légales

Quels sont vos référentiels de médicaments ? (plusieurs réponses possibles) *

- [ ] Résumé des caractéristiques du produit (RCP) (ANSM)
- [ ] Vidal
- [ ] Avis de la commission de Transparence
- [ ] Recommandations HAS, INCA
- [ ] Recommandations / Alertes ANSM
- [ ] Conférence de consensus, sociétés savantes
- [ ] Revues/littérature
- [ ] Logiciel d'aide à la dispensation (LAD)
- [ ] Aides de visite et autres documents des Laboratoires
- [ ] Autre :

Donner une définition d'une prescription "conforme à l'AMM"

Donner une définition d'une prescription "hors AMM"

Quel degré de connaissance avez-vous de la mention NR portée sur une ordonnance ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous du dispositif dérogatoire de prise en charge (Article 56 de la LFSS) ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous des protocoles thérapeutiques temporaires (PTT) et les recommandations temporaires d'utilisation (RTU) ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Quel degré de connaissance avez-vous de la responsabilité légale & du code de déontologie (Art. R.4235-61 du CSP) ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Vos liens avec les prescripteurs

Types de contacts

- [ ] téléphoniques
- [ ] réunions
- [ ] Autre :

Fréquence des contacts

- ○ fréquents
- ○ rares

Motifs de vos contacts

- [ ] contenu de l'ordonnance
- [ ] considération économique
- [ ] Autre :

Le système de Pharmacovigilance

Quel degré de connaissance avez-vous du système de pharmacovigilance ?
échelle de 0 à 5 (5 étant une parfaite connaissance)

0 1 2 3 4 5

Que pensez-vous du système de signalement ?

A qui adressez-vous vos cas PV ? (plusieurs choix possibles)

- ☐ ANSM
- ☐ CRPV
- ☐ Laboratoire

A quelle fréquence remontez-vous les cas de PV ?

Quelles difficultés rencontrez-vous dans votre pratique quotidienne dans l'acte de délivrance et du suivi de vos patients ?

Formation, Information, Publicité

Quel avis avez-vous sur la formation pharmaceutique initiale et continue ?

Quel type de formation continue suivez-vous ? (plusieurs choix possibles)

- [ ] FPC
- [ ] Congrès
- [ ] Visite pharmaceutique laboratoire
- [ ] Autre :

Concernant les publicités et les informations délivrées par les laboratoires (via la Visite Pharmaceutique et autres canaux de communication), avez-vous observé des changements depuis la mise en place de la réforme du médicament : en terme de contenu ?

- [ ] non
- [ ] oui

si oui, préciser:

Concernant les publicités et les informations délivrées par les laboratoires (via la Visite Pharmaceutique et autres canaux de communication), avez-vous observé des changements depuis la mise en place de la réforme du médicament : en terme de supports/canaux de communication ?

- [ ] non
- [ ] oui

si oui, préciser:

Concernant les publicités et les informations délivrées par les laboratoires (via la Visite

Pharmaceutique et autres canaux de communication), avez-vous observé des changements depuis la mise en place de la réforme du médicament : en terme de volumétrie ?

- ☐ non
- ☐ oui

si oui, préciser:

Pistes d'amélioration

Utilisez-vous le Dossier Pharmaceutique ?

- ☐ non
- ☐ oui

Utilisez-vous le Dossier Médical Personnel ?

- ☐ non
- ☐ oui

Que pensez-vous de la mention de l'indication sur l'ordonnance ?

Que pensez-vous des logiciels d'aide à la dispensation?

Commentaires libres

Identification

les données sont recueillies pour le suivi mais seront anonymisées

Ville / Département *

Pharmacien *

- [ ] hospitalier
- [ ] officine

Année Diplôme

adresse e-mail

Envoyer

N'envoyez jamais de mots de passe via l'outil Formulaires Google.

Regulatory affairs department in charge of advertising control in the firms (AFAR)
https://docs.google.com/forms/d/156AheUXC0WBFMnPHpMdb7FIB4F7ogzOIR9Uwvh3pDhE/viewform

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Réforme Bertrand - Questionnaire AFAR PUB

L'instauration du contrôle de la Pub a priori a t-elle modifié vos supports & pratiques promotionnels ?

En terme de contenu

- [ ] non
- [ ] oui (précisez dans "autre")
- [ ] Autre :

En terme de supports/canaux de communication ?

- [ ] non
- [ ] oui (précisez dans "autre")
- [ ] Autre :

En terme de volumétrie

- [ ] non
- [ ] oui (précisez dans "autre")
- [ ] Autre :

En terme d'organisation interne ?

- [ ] non
- [ ] oui (précisez dans "autre")
- [ ] Autre :

Avez-vous diminué les supports promotionnels au profit de l'information non promotionnelle dite « scientifique » ?

- [ ] non
- [ ] oui (précisez dans "autre")
- [ ] Autre :

Depuis l'instauration de la Pub a priori, est-ce que le feedback des professionnels de santé sur les documents présentés par vos délégués a changé ?

- [ ] non
- [ ] oui (précisez dans "autre")

Autre :

Continuer »

GANDOLPHE	Tô Quynh	September 2013

EHMBA

Class of: 2012 - 2013

Is the introduction of a priori control of advertising of medicinal products for healthcare professionals effective in reducing the risk of misuse and off-label prescriptions?

University partnership : ESCP Europe, LSE, Mailman School of Public Health

***Abstract*:**

Given that spending on marketing activities and promotion represents approximately 23% of sales of pharmaceutical companies, it has been established that their promotional efforts (advertising, sales force, conferences, medical journals ..) could have a negative influence on medical prescriptions going against health requirements as was the case in the Mediator affair; thus Law No. 2011-2012 of 29 December 2011 (Bertrand Act) restored a priori control of the advertising of drugs, measure that is intended to limit misuse and off-label prescriptions.
The purpose of the study is to investigate the validity of this measure on the off-label prescribing and off-proper use.
Methodology: Survey of pharmaceutical companies (departments in charge of control of advertising) and professionals (doctors and pharmacists).
Results: We received 30 responses from firms, 25 pharmacists, four doctors. The majority of firms responded that the reform of the drug did not change either the content of their advertisements (70%) nor materials and channels of communication (87 %), however they have reduced the volume of their ads in favor of corporate communications and information on human disease and adapted their organization. Health professionals surveyed did not also noted changes in the content of advertising.
Conclusion: It seems that the restoration of a priori control of advertisements for drugs is not a particularly relevant measure to limit misuse and off-label prescriptions. On the one hand, because advertising is only a small part of the promotional activities, some of which are not or poorly framed; on the other hand, the advertising in France was already good. Furthermore, this study has raised an issue regarding definitions and standards, which make it difficult to implement the regulations.

***Key words*:**

Prescription, comply with marketing authorization, proper use, not conformant to MA, off-label, misuse, off-proper use, advertising, promotion, standards, repositories