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Les interactions entre l'industrie pharmaceutique et les professionnels de santé : un challenge permanent

Sarah Cohen

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UNIVERSITE JOSEPH FOURIER
FACULTE DE PHARMACIE DE GRENOBLE

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N°

**LES INTERACTIONS ENTRE L'INDUSTRIE
PHARMACEUTIQUE ET LES PROFESSIONNELS DE SANTE :
UN CHALLENGE PERMANENT**

THESE
PRESENTEE POUR L'OBTENTION DU TITRE DE DOCTEUR EN PHARMACIE
DIPLOME D'ETAT

Sarah COHEN

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A Grenoble

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Introduction (French)

Aujourd'hui, de nombreuses interrogations sont soulevées concernant l'indépendance des Professionnels de Santé et des experts, de la transparence et de la qualité des informations donnée par l'industrie aux professionnels de Santé. Par exemple, en mai 2012, les laboratoires Abbott ont plaidé coupables et ont été condamné à payer 1,5 milliards de dollars. Ceci pour avoir fait la promotion de leur médicament Depakote dans le traitement de l'agitation et de l'agressivité dans la démence sénile et dans le traitement de la schizophrénie, indications qui n'avaient pas encore été approuvées par la FDA. Ce cas est un exemple parmi d'autre pour lequel l'industrie doit payer de lourdes amendes pour le non-respect des règles de communication.

Par conséquent, le grand public se demande légitimement si les relations entre l'industrie et les professionnels sont une source d'influence qui pourrait potentiellement modifier le jugement des professionnels et leurs habitudes de prescription.

Ces scandales ont remis en lumière un débat ancien sur les conflits d'intérêt dans le domaine de la Santé. Il existe plusieurs types de conflit d'intérêt impliquant les professionnels de Santé : Industrie-Professionnels ; Professionnels-Autorité de Santé ; Institut de Recherche-Industrie.

L'objectif de ce travail est de déterminer quel est la nature des interactions entre l'industrie pharmaceutique et les Professionnels de Santé dans leur pratique courante et de déterminer ce qui est fait par le législateur et par l'industrie elle-même pour minimiser les risques de conflit d'intérêt.

La communication et les réglementations ne sont pas les même en fonction du type de médicament : OTC et médicaments sur prescription, qui ne sont pas soumis aux mêmes règles. Ce travail se concentrera sur les médicaments soumis à prescription. Ces médicaments ne sont délivrés au patient uniquement il y a prescription d'un professionnel de Santé.

Introduction (English)

Today, many interrogations are raised regarding the independency of the experts, the transparency of the information given by the pharmaceutical industry to physicians. For example, in May 2012, Abbott laboratories pleaded guilty and were condemned to pay \$1.5 billion for promoting to physicians their drug Depakote developed to control agitation and aggression in elderly dementia patients and to treat schizophrenia but not approved yet by FDA. This is one example among many others for which Industry had to pay a heavy toll for the non-respect of the communication rules.

Consequently, the public legitimately wonders if the pharmaceutical industry's relationships with physicians are a source of influence that could potentially modify their judgment and their way of prescribing drugs.

These scandals put under the spotlights the old debate on the conflicts of interest in the health care domain. They are several types of conflict of interest involving Health Care Practitioners: Industry-HCPs, Physicians-Regulatory Authorities, Research institutes-Industry.

The aim of this work is to state what is the nature of the interactions between the Pharmaceutical Industry and Health Care Practitioners in their usual practice and what is done by legislators and the industry itself to ensure that the risk of conflicts of interest is minimized.

The communication and regulations are not the same depending on the type of drug: Over the Counter and prescription-only drugs are not submitted to the same rules. This work will focus on prescription-drug only, meaning that the drug will be delivered to the patient only if it is prescribed by a HCP.

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Disclaimer

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In Bristol-Myers Squibb, European Head Quarter in Paris:

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A la mémoire de mes grands-parents paternels, avec mes plus tendres souvenirs.

Résumé développé en Français

Récemment, d'importants scandales ont souligné la fragilité de la loi face à certaines situations de conflits d'intérêt dans le domaine pharmaceutique. Ces débats ont mis en lumière la méfiance du public vis-à-vis de l'Industrie et particulièrement de son influence potentielle sur les médecins, qui peut-être même pourrait modifier la façon dont les Professionnels de Santé prennent en charge les patients.

1. Les interactions entre l'industrie pharmaceutique et les professionnels de Santé

L'industrie pharmaceutique possède une particularité de taille comparée aux autres domaines industriels : elle n'a pas la possibilité de communiquer avec les utilisateurs finaux que sont les patients. Les industriels passent donc obligatoirement par les experts, à savoir les Professionnels de Santé pour l'évaluation et la prescription de leurs produits. Néanmoins, ces interactions sont indispensables au développement des médicaments et à leur bon usage.

Au cours du cycle de vie d'un médicament, les interactions entre les laboratoires pharmaceutiques et les professionnels de Santé sont nombreuses et de natures diverses. Les différents types d'interactions peuvent être classés en trois catégories : fournir des recommandations scientifiques, participer au développement clinique et partager leur expérience avec leurs pairs lors de réunions scientifiques.

Les Professionnels de Santé peuvent faire profiter l'industrie de leur expertise dans leur domaine de compétence au cours du développement des médicaments. Les experts peuvent en effet mettre leurs connaissances au service de l'industrie pharmaceutique au moment de la conception des essais cliniques et pour déterminer la population qui pourrait bénéficier du traitement.

En outre, les experts participent au développement clinique des médicaments. De par leur position centrale dans les soins des patients, les Professionnels de Santé sont les seuls à pouvoir évaluer le bénéfice d'un nouveau traitement chez les patients. D'autre part les experts ont un rôle clé dans la conception et la coordination des essais.

Les professionnels de Santé font souvent de la recherche clinique, notamment sur les molécules des laboratoires. L'étude sur un certain sous-type de population par exemple. Ils conçoivent l'essai et font alors appel à l'Industrie pour le financement de leurs études. On appelle cela des essais sponsorisés.

Enfin, les experts ont un rôle clé dans la diffusion des informations concernant leurs produits. Il est prouvé que les professionnels de Santé préfèrent recevoir une information de leurs confrères. L'industrie propose donc à certains experts de faire des présentations lors d'évènements d'information, tels que symposiums et présentations d'expert.

Pour toutes ces activités, les experts sont indemnisés pour les services rendus et les frais occasionnés. Ils reçoivent donc de l'argent de la part des laboratoires pharmaceutiques.

Les industries invitent parfois certains professionnels à assister aux congrès en payant leur inscription et leurs frais de déplacement. En outre, beaucoup d'interactions ont lieu à travers la visite médicale. Lors de de leurs visites, les représentants médicaux présentent aux professionnels des informations sur les produits disponibles sur le marché et peuvent leur offrir quelques objets de petite valeur.

2. Deux modes de communication avec les professionnels de Santé : Promotionnelle et non-promotionnelle

La communication entre les industries et les professionnels peut se faire sur deux modèles. Le mode de communication choisie dépendra du contexte, du public visé et de la personne délivrant l'information.

2.1. La communication non-promotionnelle

La communication non-promotionnelle peut être délivrée dans un contexte plus souple et contient des informations différentes par rapport à la communication promotionnelle. Ce type de matériel permet de communiquer avec les professionnels sur des informations hors AMM (autorisation de mise sur le marché).

L'information délivrée ne doit contenir que du matériel d'Education Médicale, en relation avec la maladie traitée en général ou l'implication d'un organe dans une pathologie. Par exemple l'implication du rein dans la régulation de la tension artérielle. Ce matériel peut également contenir des informations issues des essais cliniques de médicaments en cours de développement ou pour l'étude de nouvelles indications, à condition que les résultats aient déjà été publiés.

Ce type d'information peut être délivré lors de la visite de Médecin Régionaux (Medical Science Liaison) à des Leaders d'Opinion. Lors de congrès, les laboratoires ont souvent l'opportunité d'organiser des symposiums en marge du congrès lui-même, lors desquels ils peuvent communiquer de manière non-promotionnelle. C'est souvent à cette occasion que les laboratoires font appel aux experts qui connaissent bien le médicament en tant qu'orateur afin qu'ils puissent délivrer l'information à leurs confrères médecins. Les laboratoires ont également l'opportunité de répondre aux questions éventuelles des Professionnels de Santé lors de ces congrès dans leurs stands d'information.

Les informations hors AMM ne peuvent être communiquées qu'à la demande du Professionnel de Santé.

2.2. La communication promotionnelle

Dans le cas de la communication promotionnelle, les informations qui peuvent être délivrées ne contiennent que les informations contenues dans le Résumé des Caractéristiques du Produit (RCP). Ce qui signifie que seuls les produits qui ont obtenu leur autorisation de mise sur le marché sont concernés. De plus, le produit peut faire l'objet de promotion uniquement au sujet des indications autorisées. La promotion d'un produit ne peut sous aucun prétexte contenir des informations sur des indications qui n'ont pas été autorisées.

Ces informations sont données lors de visites des représentants médicaux aux professionnels de Santé, dans les hôpitaux, les pharmacies, les cabinets de médecine générale ou spécialisée.

Ce type de communication fait l'objet de nombreux contrôles et tout le matériel qui sera présenté ou donné aux Professionnels lors des visites doit être contrôlé et autorisé par les autorités régulatrices en France.

3. Les conflits d'intérêt

Les nombreuses interactions citées ici peuvent parfois mener à des conflits d'intérêt. En effet, l'existence de liens entre les Professionnels et l'industrie crée un terrain propice à l'apparition de conflits d'intérêt.

Il n'existe pas de définition légale des conflits d'intérêt. Cependant les diverses définitions trouvées dans la littérature s'accordent toutes sur un même principe : un conflit d'intérêt apparaît s'il y a une opposition entre les intérêts premiers du professionnel de Santé et ses intérêts secondaires.

Son intérêt premier est la Santé du patient et le choix de la meilleure façon de le traiter dans le respect des règles de Déontologie de sa profession.

Ses intérêts seconds peuvent être multiples. Le premier cité, et considéré comme le plus propice à créer des conflits, est l'argent. Mais peuvent également créer des conflits, l'avancement et la notoriété personnels par exemple.

Comme cela a été expliqué plus haut, les Professionnels consultants pour l'industrie touchent des honoraires. Le fait qu'ils soient rémunérés par un laboratoire pharmaceutique peut faire craindre une influence de leur jugement personnel en faveur du laboratoire, non pas par conviction personnelle mais par gratitude pour l'argent qu'ils ont reçu.

Sur le même principe, les professionnels ayant un rôle d'investigateur dans les essais cliniques d'un laboratoire sont rémunérés pour chaque patient qu'ils suivent. Par conséquent, de l'argent est encore échangé entre les deux parties. De plus, certains investigateurs participent également à la publication des résultats de ces recherches. Il se pourrait donc que les investigateurs ne se sentent pas libre de leur interprétation des résultats étant donné qu'ils ont reçu de l'argent de la part de la compagnie. Et à plus forte raison dans le cas d'essais sponsorisés par les laboratoires. Il a été par ailleurs démontré que ce financement avait effectivement une influence non négligeable sur ces essais.

Les consultants présentant des informations pour le compte des laboratoires et publiant des résultats d'études sponsorisées ou initiées par ces firmes, peuvent également être confrontés à des conflits d'intérêt dans la mesure où ils peuvent bénéficier d'un accroissement de notoriété. En effet leur renom sera nécessairement accru par leur apparition dans de grands congrès et la publication de nombreux articles. Partant de ce principe, les professionnels dans cette situation pourraient ressentir une certaine gratitude vis-à-vis du laboratoire.

La plus ambiguë des interactions reste aussi l'une des plus controversées : l'offre par les laboratoires de cadeaux de plus ou moins grande valeur aux professionnels. Autrefois, il n'était pas rare d'offrir des voyages en famille dans des destinations de rêve à un bon prescripteur. Aujourd'hui, ce type de pratiques est interdit par la loi, seuls des cadeaux sans grande valeur sont autorisés tels que des stylos ou des blocs-notes avec la marque de leurs produits ou de leur compagnie. Mais ces rappels de marques n'en sont pas moins des incitations à prescrire un médicament plutôt qu'un autre. On peut aussi s'interroger sur l'influence que peut avoir ce type d'objet même de faible valeur marchande, sur l'indépendance et le jugement du professionnel.

4. Lutter contre les conflits d'intérêt : une adaptation à tous les niveaux

Pour lutter contre ces situations, une adaptation de la loi et des industries s'est progressivement mise en place. Nous allons nous focaliser sur les Etats-Unis, l'Europe et la France.

4.1. L'encadrement réglementaire

Il n'existe pas de loi internationale régissant les conflits d'intérêts. Par conséquent l'adaptation se fait au niveau régional (Européen) ou national.

Les Etats-Unis possèdent une agence gouvernementale en charge de faire respecter les lois au sein de l'industrie pharmaceutiques et des domaines sanitaire et médicale.

Pour lutter contre les conflits d'intérêts, deux lois font autorité : le Physician Payment Sunshine Act (PPSA) et le Anti-Kickback Act ("AKA").

Le Sunshine Act est un texte imposant aux professionnels de Santé et aux industries de rendre public tout échange financier entre eux. Les conditions des paiements doivent également être décrites et le tout doit être publiquement accessible.

Le Anti-Kickback Act interdit aux professionnels d'accepter tout cadeau de la part des industries et également aux industries de les distribuer.

La législation française rejoint ces deux lois avec la « Loi anti-cadeaux » et la nouvelle loi Bertrand. Les prérogatives de ses lois sont les mêmes que celles des lois américaines mais la loi française est plus stricte dans la mesure où elle inclut également les étudiants.

Dans les deux cas, les conventions conclues dans le cadre du développement d'un médicament (Essais Cliniques, Avis scientifique, Orateur...) sont des exceptions à la « loi anti cadeaux ».

La loi Bertrand attend encore son décret d'application qui devrait contenir le montant minimum de rémunération à déclarer publiquement. C'est l'un des derniers décrets d'application d'une nouvelle loi visant à renforcer le système de sécurité sanitaire en France, la loi n°2011-2012.

En Europe, une directive Européenne regroupe toutes les dispositions en vigueur pour la mise sur le marché, la fabrication, l'étiquetage, la catégorisation, la distribution et la publicité des médicaments à usage humain.

Cette directive recommande notamment que la sponsorship de professionnels aux événements promotionnels ou non-promotionnels soit faite « dans la limite du raisonnable ». Elle interdit aux représentants médicaux d'octroyer des primes ou des avantages significatifs comme technique de promotion des médicaments, limite l'hospitalité offerte lors de manifestations de promotion, restreint la distribution d'échantillons gratuits, dans la mesure où cela pourrait gêner le travail du professionnel¹.

¹ Europa, Synthèse de la législation en UE

http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21230_fr.htm

4.2. Les codes que s'impose l'industrie

Dans une démarche de qualité et d'éthique, les industries s'organisent en associations. Il en existe une européenne (EFPIA), une américaine (PhRMA), une française (LEEM) et nous mentionneront également l'association anglaise (ABPI) car son code sur les interactions entre les industries et les professionnels est très détaillé et décrit particulièrement bien la communication non-promotionnelle.

Ces associations produisent en effet un certain nombre de documents pour aider les entreprises dans leurs démarches de qualité et d'efficacité. C'est dans cette optique que leurs codes de bonne conduite décrivent ce qu'il est bon de faire et de ne pas faire. Ces associations possèdent également des comités éthiques pouvant être saisis par tout membre de la communauté traitant d'éventuels litiges entre deux parties. Parfois, les recommandations données sont plus restrictives que la loi.

Les industries possèdent également des règles internes très strictes qu'elles mettent en place de manière formelle : les procédures normalisées. Ces procédures sont établies en fonction de la loi en vigueur et des pratiques de l'entreprise. Chaque entreprise possède son propre système de procédures et ces propres procédures.

5. Discussion

Il existe diverses formes d'interactions entre les laboratoires pharmaceutiques et les professionnels de santé. Ces interactions sont souvent indispensables et chacune possède des risques de conflit d'intérêts plus ou moins évitables.

Aujourd'hui, la communication non-promotionnelle prend le pas sur la communication promotionnelle, en partie en raison des évolutions réglementaires.

La possibilité d'offrir des avantages, en nature ou financier, aux professionnels évolue et devient de plus en plus restrictive. La loi n'est pas la même dans tous les pays, mais ces pratiques deviennent interdites dans de plus en plus de pays.

La distribution de petits cadeaux de valeur négligeable ne possède pas de réel intérêt pour l'information des professionnels et semble biaiser leur jugement. Leur distribution pourrait donc être stoppée.

La rémunération des services rendus par les experts devient un élément qui sera rendu public. Cette démarche permet au public de prendre conscience du contexte dans lequel l'information est délivrée. Cette transparence des liens d'intérêt est l'un des éléments clés dans les nouvelles législations mises en place. Chaque pays adopte sa propre loi concernant cette divulgation, mais il n'existe aucune harmonisation. Pourtant, l'harmonisation de la lutte contre les conflits d'intérêt serait un élément fort pour simplifier l'application des lois par les entreprises qui sont en général internationales.

L'organisation de Formation Médicale Continue par les laboratoires semble entraîner des biais dans le contenu des formations. Il serait donc intéressant de mutualiser les fonds venant des industries afin de créer un organisme indépendant qui organiserait les formations de manière objective.

De nombreuses mesures ont été prises ces dernières années pour essayer de lutter contre les risques de conflits d'intérêt au sein de la communauté médicale. Cependant, les lois ne suffiront pas à combattre ce risque sans l'éthique individuelle de chaque professionnel de santé.

Acronyms

ABPI: Association of the British Pharmaceutical Industry

AKA: Anti Kick-Back Act

ANSM: Agence National de Sécurité du Médicament et des Produits de Santé (French

CME: Continuing Medical Education

COI: Conflict of Interest

Drug Regulatory Agency)

EFPIA: European Federation of Pharmaceutical Industries and Associations

EMA: European Medicines Agency

FDA: Food and Drug Administration

HCP: Health Care Practitioner or Professionals

INN: International non-proprietary name

ISR: Investigator-Sponsored Research

KOL: Key Opinion Leader

LCM: Life Cycle Management

MSL: Medical Science Liaison

NME: New Molecular Entity

TL: Thought Leader

Methodology

That work was started during an internship in the Pharmaceutical Company Bristol-Myers Squibb. My function there as Project Coordinator in the European Metabolic Team, allowed me to learn several aspects of the Medical Affairs Department activities. It particularly helped me to discover the relationships between the Industry and Health Care Practitioners, focusing on the Thought Leaders. My position gave me the opportunity to attend, organize or analyze closely the different interactions between the two parties.

I also had access to the various codes of behavior and legal codes referring to the interactions between the Industry and HCPs. These documents come from Regulatory Authorities like the European Commission, French Regulatory Agencies as well as Pharmaceutical Companies Unions codes of conduct.

I had a full access to the BMS Standard Operating Procedures. Accessing these documents allowed me to understand the spirit of the company's behavior regarding HCPs.

This analysis was achieved based on personal research, on my personal experience as well as the high level expertise of BMS experts in the European Department of BMS.

This work aims at better understanding the relationship between Industries and Health Care Practitioner and the ethic of these relations. My first experience in the Medical Affairs Department of a Pharmaceutical Industry gave me the opportunity to build my personal opinion on that matter.

1. The interactions between the Pharmaceutical Industry and Health Care Practitioners

1.1. Interactions between Pharmaceutical industry and Health Care Practitioners (HCPs): a necessity²

Generally speaking, industry companies have the opportunity to evaluate their products in association with their consumers. The pharmaceutical industry has the particularity to not have direct relation with its final consumer, the patient. Because the pharmaceutical companies do not have that direct communication with patients, the link between the industry and experts (Healthcare Professionals=HCPs) is very important.

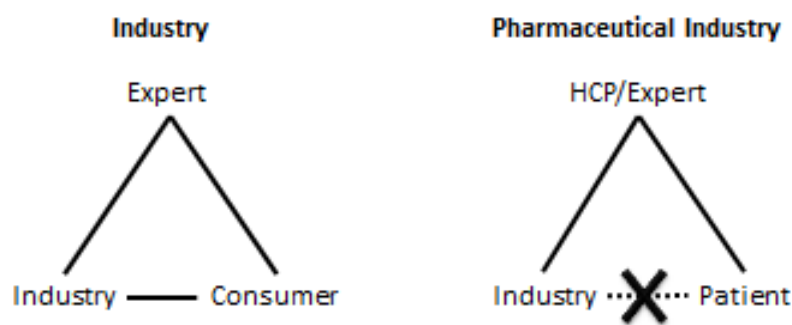


Figure 1: The pharmaceutical industry does not have direct access to the patients

In the medical industry, the products experts are people taking care of patients, they are called Healthcare Professionals or HCPs. They have the responsibility of selecting the treatment given to patients by prescribing or administrating it. They have, in more than this primary role of treating patients, the ability of participating in the development of new drugs. All the actors of the Health care process are HCPs: Physicians, Nurses, Pharmacists, etc.

Furthermore, among HCPs, some are considered by the industry as practitioners of particular interest. Their value resides in their particular expertise in the areas of interest of industries. They are generally called Key Opinion Leaders or Thought Leaders. This notion was first introduced by the sociologists Paul Lazarsfeld and Elihu Katz in their 1955

² Internal Bristol-Myers Squibb experts

book, *Personal Influence*.³ These KOLs are Academic Researchers or Hospital Clinicians having some influence among their peers for their knowledge in Medical Science and contribution to scientific progress. The expertise of HCPs in their domain is also an asset for companies when they need to communicate about their medicines. HCPs have the required knowledge and legitimate status among their peers to make information available within the medical community.

Their selection is at the discretion of each company but the same criteria are generally applied by all companies. It includes their renown in their area of expertise, publications in peer reviewed journals, participation in the activities of their domain of competencies like guidelines committees or society's membership and Clinical Investigation involvement. For all these reasons, having relations with KOLs is a great added value for Pharmaceutical Firms. This selection is usually performed by the field based employees: Medical Science Liaison or Sales Representatives.

1.2. The three kinds of interaction with KOLs⁴

One can classify the interactions between the Pharmaceutical Industry and the HCPs into three different classes of activities: Providing scientific advises, participate to the clinical development and sharing their experience with their peer during scientific meetings.

1.2.1. Providing scientific advises:

The first category of interaction is the advisor role of HCPs. Thanks to his expertise in his domain the KOL provides opinion about Medical Needs in a specific therapeutic area. He advises the company on the most appropriate design of the studies for the Clinical Development Programs. He shares his opinion on the Unmet Medical Needs for a specific disease, like the development of bacterial resistance or viral escape to treatments.

All these discussions between experts and the company take place during meetings called Advisory Boards organized with a limited number of KOLs who are requested to express

³ Cart Elliott, The Secret Lives of Big Pharma's 'Thought Leaders', The Chronicle of Higher Education, Sept 2010 <http://chronicle.com/article/The-Secret-Lives-of-Big/124335/>

⁴ Internal Bristol-Myers Squibb experts

their opinion about specific questions or topics the company would need some input on. These meetings are strictly confidential and everything is open to discussion. Advisory Boards are organized at an international level or a national level depending on the agenda for discussion. For example, a dozen of KOLs from all over Europe will meet during one day and exchange with each other and the laboratory on some precise points requiring solutions.

1.2.2. Participate to the clinical development:

The second kind of interactions of HCPs with laboratories concerns their role of Investigators in the Company's Clinical Trials.

For each drug there is a critical step between the discovery of a New Molecular Entity (NME) and the Marketing Authorization. This part of a drug development, called Clinical Development, includes the Phase I, II, III and IV of the Clinical Trials in Human and will be detailed in 1.3. These tests are essential and mandatory for the development of the drug. They aim at select the final doses given in human and to assessing the Safety and Efficacy profile of the drug. The overall positive benefit/risk ratio needs to be demonstrated in order to get marketing authorization granted. During these clinical trials, the NME will be tested and compared against placebo or standard of care treatment. Clinical Trials are very controlled procedures requesting tight regulations and precise protocols. All the clinical research process are made under the Good Clinical Practices, an International code regulating the clinical investigation in human issued by the International Conference on Harmonization (ICH), an international body providing guidelines transposed by countries into laws. That is why clinical trials require high level professionals with a good knowledge of these rules as well as the opportunity to enroll patients in the trials. Investigators enroll patients after checking that they agree to participate to the study and that they meet the inclusion criteria. Thanks to their direct access to patients, HCPs represent the only opportunity for Pharmaceutical Industries to test the drugs they have in development.

There are two different ways to initiate a clinical trial: the pharmaceutical company will initiate it in order to study its molecule (in development in Phase I, II, III or after

marketing authorization in Phase IV) or a physician will initiate it by himself and search for funding, this is an Investigator-Initiated trial. In the Investigator-Initiated trial, or Investigator Sponsored Research, a physician will have an idea of study about a drug or a treatment and proposes to an industry, logically the industry owning this treatment, to finance the trial. The physician will take care of designing and recruiting patients. The company can also help the physician with the medical writing part if necessary and also provide the drugs for free to patients. ISRs can be of interest for the company, as these trials can bring interesting information about their drugs and opening the way for new uses and indications for their drug.

During clinical investigations, interactions between HCPs and the Industry are unavoidable and interesting for both parties: Physicians are essential for the firms in order to have access to patients and performed medically monitored trials. On the other side, Clinical Trials extend the possibilities of treatments for physicians, particularly in areas where the needs for new treatments are high like in oncology.

1.2.3. Transmitting information:

The third type of interactions is the information of HCPs. The pharmaceutical firms need to inform and educate physicians on new mode of actions and drugs they have. In order to select the appropriate treatment and prescribe and deliver it the right way for each patient, HCPs need to know accurately the treatments, particularly their profile, mode of action and pharmacological particularities. Also, pharmaceutical companies want to promote their drugs among the others and therefore want to reach as many professionals as possible.

Then, companies convey the information, through different channels.

A very well-known one is the Sales Representatives visits. Physicians are visited on a regular basis by professionals trained for advertising products. During regular interviews, the representative will explain the HCP why he should prescribe or deliver the company's product more than the others. The sales rep will visit a very broad public including general practitioners, nurses and community pharmacists. It allows informing a large public that

do not have the opportunity to be informed on every novelty regularly in his or her everyday practice.

A second way to inform HCPs is the involvement of KOL in Peer to peer exchanges: The information channel using KOL is based on the “Peer Education Model”. According to T. Valente and R. Davis, it was proven that the innovation is better and faster spread when it is carried by KOLs compared to other channels of information.⁵

As the KOL information pathway was described as very efficient, the pharmaceutical industry is keen to use this way of information to reach a large number of health care practitioners. That’s why an information pathway was established as a pyramid (Figure 2: the pyramid-shape information pathway through KOLs).

The information will be cascade through the KOL channel as follows:

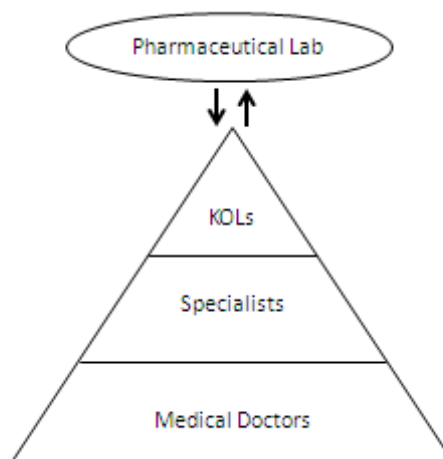


Figure 2: the pyramid-shape information pathway through KOLs

The information is discussed and provided to KOLs, who will then inform the Specialists in special trainings of Diseases Education Meetings. The specialists will finally train the General Practitioners in the same manner.

The pharmaceutical companies ask KOLs to be speakers for their disease education events. They are paid fee for services in exchange of preparation and presentation of

⁵ T. Valente and R. Davis. Accelerating the diffusion of innovations using opinion leaders. The ANNALS of the American Academy of Political and Social Science, 566(1):55 – 67, 1999

disease education information and clinical results. It can take place during events like congress symposiums.

These three types of interaction take place at specific times of the Life Cycle Management of the drug.

1.3. The evolution of interactions through a drug Life Cycle Management

The relationships with HCPs needed by the laboratories evolve in function of the stage of development of the drug. Every drug product, from its discovery to its withdrawal from the market needs various competencies and actors depending on the stage of evolution. The management of this cycle is one of the key success-factor of a medicine product (Figure 3: Interactions of the Industry with HCPs through drug's LCM).

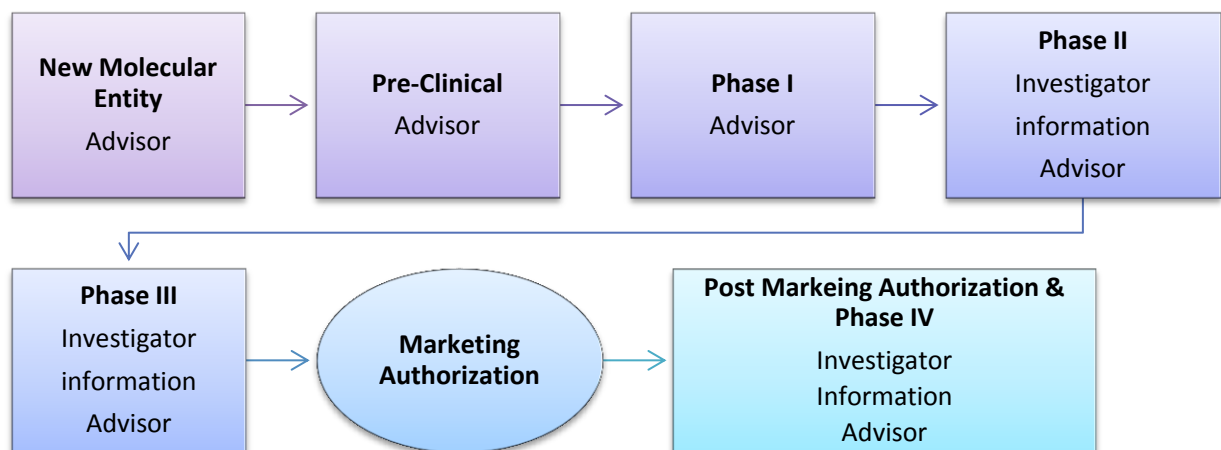


Figure 3: Interactions of the Industry with HCPs through drug's LCM

The development of a product starts with the discovery of a New Molecular Entity (NME). A NME is a new molecule, unknown from the Pharmaceutical Industry. The molecule represents a potential new drug and is studied to determine its mode of action and physiological effects. While it is done, the laboratory has to position its future product in function of the unmet medical needs. These needs are "identified sub-population (e.g., a group of people suffering from a recognized medical condition) for which there is a

shortage or lack of effective therapies and treatments”⁶. Therefore, it is of particular interest for the company, in term of return on investment and patient benefit, if the new molecule could lead to a new treatment and be of potential interest for patients.

At this step, the KOLs give their input regarding the unmet medical need that could eventually reach the new molecule during ad boards, organized by the company. These discussions also help for the positioning of the product on the market.

The product then goes to preclinical trials to study its first main toxicity characteristics: potential for carcinogenicity, genotoxicity and mutagenicity in animals. Once the drug is cleared from major toxicities during these Pre-Clinical Trials, the molecule can start to be tested in Human. These trials in animals are useful to determine roughly the dose at which the Phase I clinical trials should start. This phase does not concern the HCPs.

The Phase I is the first administration of the drug in Human, these studies are made in specialized centers on a few healthy volunteers (10-100) who are constantly monitored. The objective in this first set of trials is to study the pharmacological properties of the drug in human and to test a range of dosages in order to set the minimal efficient dose and the maximal dose that can be given before toxicity.

If primary safety results are good enough, the Phase I is considered as successful. The future therapeutic doses are set and it is time to start clinical trials in sick patients. From that point, the drug under evaluation starts Phase II trials.

During the next steps, Phase II and III, the potential new treatment is compared to a Placebo or the current standard of care for the treated pathology. Therefore, the drug is tested in a group of sick patients and its effect is compared to another group of sick patients, treated with the reference (placebo or standard of care). The study can be blinded or not. The studies are conducted in regular center of care like hospitals or clinic on patients that gave their agreement to participate to the study. The investigator physicians include the patients, following the inclusion criteria of the study.

⁶ Charles M Mather, *Medical innovation, unmet medical need, and the drug pipeline*, Can J Clin Pharmacol Vol 13(1) Winter 2006: e85-e91; Feb 1, 2006

That part of the Clinical Development program is one of the major activities of the companies involving HCPs. At that point HCPs are approached by the pharmaceutical laboratory for various reasons.

First, they give their advice on studies design. This is made during Steering Committees which are groups of 5-6 KOLs, during which they discuss about the design of a clinical study. They set the profile of patients, the inclusion/exclusion criteria for participating to the study, its length, the end points, etc.

HCPs are needed to help design and conduct the Phase II and III trials and are also asked for their Investigator expertise in their practice of medicine. HCPs are personally involved in that phase of development for the enrolment and follow up of patients. Once the starts a clinical trial, he or she will be closely monitored during the whole study by the investigator who will perform various tests described in the clinical trial protocol.

At the end of studies, the results are presented in international congresses and published in peer reviewed journals. Some of the KOLs among HCPs can be speakers to present the results to their peers in non-promotional events and the results can be discussed during non-promotional events with HCPs.

Therefore, the information is spread in the scientific community thanks to events like congress symposia and during events where HCPs are trained like Speaker Trainings.

“Healthcare professionals participate in company-sponsored speaker programs in order to help educate and inform other healthcare professionals about the benefits, risks and appropriate uses of company medicines.”⁷

The clinical research results are leveraging the approval process of the product.

The marketing authorization is a highly regulated process during which, the pharmaceutical company submits his drug to the competent authorities for approval. A Dossier is constituted including all the documents concerning the drug from the discovery to the clinical trials including the manufacturing process. After the analysis of the submission by the legal authorities, they give or not their authorization to put the drug on the market and therefore, to administrate it to patients. After the approval, the medicine

⁷ The Pharmaceutical Research and Manufacturers of America. Code on interactions with healthcare professions. Washington, DC: PhRMA; c2011

can be launch by the company and promoted in the health community through promotional events.

There is no participation of HCPs in the approval process as it is only the business of regulatory agencies. These agencies recruit sometimes experts to advise on these submissions. The independency of these experts is the subject of numerous debates in France these last years. And new recommendations have been issued on that matter.

These different kinds of interactions are not undertaken by the same functions within the company. The promotional and non-promotional activities are usually separated to guarantee an independency of action: Medical and Marketing.

2. Two different ways of communication with HCPs: Medical (Non-promotional) and Marketing (Promotional)

2.1. Non-Promotional communication

2.1.1. Why non-promotional material?

Promotional communication covers a restricted domain of information as it cannot cover for “off-label” information and pre-marketing authorization products. Therefore, the pharmaceutical companies need other tools in order to communicate with HCPs on those areas. This is the scope of the non-promotional activities that mainly covers the pre-approval communication. When the drug is not launched yet, the only communication allowed by authorities is non-promotional.

2.1.2. Non promotional material content⁸

The information delivered in the non-promotional communication has to be Fair, Balanced and Accurate and only Disease Awareness is tolerated. The information delivered cannot be only favorable to the company’s product. The information has to be

⁸ J Barnard, *The Code in Practice*, Third Edition, 2006

fair and therefore encourage the rational use of products without exaggerating their properties or disparaging competitors. In order to be balanced, the information should include other similar studies and their results.

The information delivered will therefore contain general data on the disease related with the molecule, for example Diabetes for a Sulfonylurea or Hypertension for an angiotensin converting enzyme (ACE)-inhibitor. It is also possible to speak about the organ concerned by the mode of action of the drug but not the drug itself. For example for a drug of the Angiotensin Receptor Blocker therapeutic class, the non-promotional information will focus on the role of the kidney in the blood pressure regulation without mentioning the Receptor Blocker effect. According to the 2001/83/EC Art.86, the information should contain statements relating to human health or diseases, with no reference, even indirect, to medicinal products.

However the Clinical Results of the product can be presented using the International non Proprietary name of the product (INN). These results can be presented during non-promotional events once they have been published. But the presentation of the results still has to be Fair, Balanced, Accurate and not branded. The non-promotional events are Advisory Boards, Speaker Training, Satellite Symposia or Medical Information booth on Congresses. However, during these events no brand name or brand colors can be used as they are related to the promotion of the product.

The non-promotional information can also be provided to HCPs on a reactive basis during Medical Science Liaison's visits, but only if the information has been requested by the HCP. Before the Marketing Authorization the Non-promotional information is given on a reactive basis (the information can be delivered to an HCP only if he asked for it) only and the promotional one is forbidden. After the Marketing Authorization, both Promotion and non-promotion can be done on a proactive basis (Figure 4: Communications with HCPs in function of the stage of development).

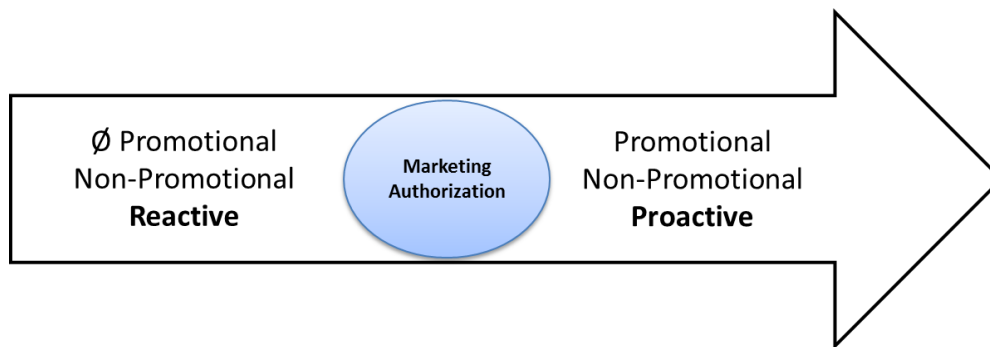


Figure 4: Communications with HCPs in function of the stage of development

The information can be shared proactively in non-promotional communication only after the Marketing Authorization. It means that an MSL can talk to an HCP about non-promotional information on its own initiative without any requests to do so. However the nature of the information remains the same.

The information can be shared by different ways, the most common being discussions based on slide libraries' support during MSL's visits, medical education events and congress symposia. Today, the information using new formats of media are promisingly developing. In particular new media like internet seduce HCPs and laboratories by their interactivity and accessibility. HCP can access the information whenever they want. We therefore assist to the development of platforms on internet containing a large scope of information of disease awareness. It has the double advantage to provide accurate information and documents to HCPs and to create visibility for the laboratory which provides it.

2.1.3. Non-promotional activities

The laboratories have different opportunities to interact with HCPs without promoting their products. They use non-promotional communication for all these different types of interactions. The non-promotional events are of very diverse natures.

First, they are the interactions of the Medical Scientific Liaisons with KOL, as it is described in 2.4.1.3, MSL are medical employees of the pharmaceutical companies that are an interface between the laboratory and HCPs and particularly KOLs. The visits are

taking place regularly and the MSL can discuss non-promotional information, coming events and eventual investigator activity.

Among the largest events organized by the pharmaceutical companies are congresses. Congresses are major events organized by a committee (for example the European Society of Cardiology) which organizes conferences on various subjects of their area of interest about innovations and scientific progresses. These events are of particular interest for the attending HCPs as they stay up to date, learn and discuss on their domain of competencies. During these congresses, pharmaceutical companies have the opportunity to host a booth. It is split in different parts, separating the commercial and medical activities. In the medical part, there is the Medical Information booth, in which delegates have the possibility to ask for precise information and medical specialist from the firm could answer. The booth also hosts a Marketing part in which only the labeled drug can be promoted and discussed.

The companies can also organize symposia based on peer to peer exchange these events are held on the sidelines of national and international congresses. The pharmaceutical industries are allowed to organize their own conferences presented by renowned Opinion Leaders, usually about their new or in development products last clinical results and it is the occasion to create awareness about a novel mode of action and therapeutic class. The information delivered in such events is non-promotional and controlled by the organizing committee of the event. In some major congresses like the ADA (American Diabetes Association) the company pays an independent agency that will organize the scientific content of the congress in order to guarantee a strict neutrality of the content.

As mentioned previously, HCPs and particularly KOLs are participating to Advisory Boards, Steering committees and Educational Events and all these events are exclusively non-promotional ones.

2.2. Promotion and Advertising

The communication toward physicians is necessary for both industry and physicians in order to develop and use a drug the right way. However the difference needs to be made

between the communication aiming to promote the drug and another one which is used as information only, the non-promotional communication described in 2.1.

The Promotional communication's aim is to encourage the sales of a product. The definition of the World Health Organization is "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal products"⁹.

For the European Community: "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products; it shall include in particular:

- the advertising of medicinal products to the general public,
- advertising of medicinal products to persons qualified to prescribe or supply them,
- visits by medical sales representatives to persons qualified to prescribe medicinal products,
- the supply of samples,
- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal,
- sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products,
- sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith."¹⁰

The promotion is the advertisement of the product, its aim is to increase the use of the drug and therefore this type of communication is allowed only after the Marketing Authorization of the product. The promotional material has to be consistent with the Summary Product of Characteristic (SmPC) of the medicinal product which is the official document containing approved data about the Drug. According to 2001/83/EC Art.11, the SmPCs should contain the Pharmaceutical description of the product including

⁹ World Health Organization [Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource \(Generic\) Products: A Manual for Drug Regulatory Authorities - Regulatory Support Series No. 005](#)

¹⁰ European Directive, 2001/83/EC Article 12 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:en:NOT>

pharmaceutical form (e.g. tablets or subcutaneous injection), dosage and composition (active substance and excipients), posology, proper administration of the drug, Contra indications, special warnings and precautions administering them to patients, interactions with products, undesirable effects, pharmacological, pharmacodynamic and pharmacokinetic properties, preclinical safety data.

Moreover, all promotional material has to be reviewed and approved by health authorities. The control of all the material is performed locally by the countries agencies. For example, in France the material is submitted to a commission of the ANSM (The French national drug safety agency), the Commission for Control of Advertizing and Dissemination of recommendations about the Proper Usage of Medicines (« *Commission Chargée du Contrôle de la Publicité et de la Diffusion de Recommandation sur le Bon Usage des Médicaments* »). Before the 1st January 2012, the submission of promotional documents for HCPs was done post-distribution. It implied to withdraw some unauthorized documents after their distribution.

Today, the approval process has to be performed before the distribution of the material. The submission is done on a proactive basis and the material can be distributed only after its approval by national authorities.

2.3. When is the Promotion of medicinal products prohibited?

The promotion of prescription-only drugs is always prohibited for the general public and allowed for HCPs, once the medicine is approved¹¹. In the European Community, the only promotion targeting general public authorized concerns medicine designed to be used without the intervention of a medical practitioner. It is however important to note that the law is different in the United States and New Zeeland. In these two countries only, the advertisement to general public is allowed for all medicinal products including prescription only, psychotropic and narcotic drugs.

According to the European Community all promotional communication of a medicinal product toward HCPs is prohibited before its Marketing Authorization, Art. 87 “Member

¹¹ EMA Directive 2001/83/EC Art. 88

States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law". It implies that the communication before the marketing authorization and the launch of the product can only be non-promotional.

The development of the non-promotional communication requires a dedicated department within the company, separated from the marketing one in order to guarantee the integrity and independency of the information given. That is one of the roles of the Medical Affairs Department.

2.4. Medical Affairs: the main interlocutors of HCPs

The Medical Affairs department is a part of Pharmaceutical Laboratories taking care of actions directly related to Medicine. The role and area of actions of Medical Affairs are not the same in all companies. In some of them, all the activities, including pharmacovigilance, are considered as Medical Affairs, while some other companies prefer to split the functions into different groups.

The Medical affairs department generally frames the Clinical Trials results publication and diffusion, the conduct of clinical trials involving new and novel indications, ensuring the drug information services and takes care of medical conferences management. This is also the department managing the relations with KOLs and HCPs.

The functions of the medical affairs are organized around the relations between the pharmaceutical industry and HCPs.

The separation between Marketing and Medical Affairs should be seen as a fire-wall as it prevents mixing sells objectives and information duty. This could prevent some conflicts of interest and legal and ethical concerns. The separated reporting system will have an influence on the Medical Affairs focus. A Medical Affairs group reporting to clinical development teams is "more scientific focus and is less driven by market forces" compared to a group reporting directly to marketing.

In Bristol-Myers Squibb, for example, the Medical Affairs department is in charge of communicating clinical study results and of generating the disease awareness material.

Management of non-promotional events and investigator-initiated trial Program are also in the scope of its responsibilities. The department has a distinct line management which is independent from the commercial organization.¹²

The medical affairs activities takes care of the non-promotional information, including disease awareness and clinical data management and also organizes the events described in 2.1.3. The medical department managed the Medical Science Liaison field force.

This department is not required by the law but is a logical evolution and is therefore becoming more and independent from the commercial force within companies.¹³

2.4.1. A way to build a high level quality relationship with Opinion Leaders: Medical Science Liaisons (MSL)¹⁴

2.4.1.1. Who are MSLs?

The MSLs are field based employees of Pharmaceutical companies with a high study degree in science (usually Medical Doctors, PhD or Pharmacists PharmD). Usually, MSLs are MDs, but they are more and more PharmD among them, with a strong background in research or clinical practice. They are regular company field employees and clearly state it during their visits and exchanges with HCPs. The MSLs force of the company is divided in therapeutic areas and within an area, each MSL will have its own geographic area to cover. For example, in BMS France they are 5 MSLs positions in the metabolic department. One for each part of France: one for Paris area, and 1 for each quarter of the country. As a result, each MSL will have its “own” physicians and HCPs to see on a regular basis.

¹² Wolin et al., The emerging role of medical affairs within the modern pharmaceutical company 2001, Drug Information Journal Vol 35

¹³ Ed Silverman, Has The Medical Affairs Department Left Marketing?, Pharnalot

<http://www.pharnalot.com/2008/03/has-the-medical-affairs-department-left-marketing/>

¹⁴ Malecha, S. E., Wiejowski, S. A. & Holt, R. J. (2000), The Medical Science Liaison: An A To Z Guide (Albert, E. and Sass, C.). The applied therapeutics team: an innovative model of drug information in the pharmaceutical industry. Drug Inform. J. 34, 1069–1075

2.4.1.2. Where does the concept comes from

This concept started in 1967 in Upjohn Company, an American company today owned by Pfizer. They hired specialists to enhance research collaborations between physicians and the company.¹⁵

At that time, they “utilized face-to-face peer interactions to better understand what their customers needed and to leverage Upjohn products ongoing research activities”. The MSL function was then turned to a marketing one, but based on the peer to peer basis exchanges it evolved to advance the standard of cares and optimizing patient’s outcomes and no product sales anymore. That transition to a medical-based team is credited to E.R. Squibb, one of the two historical Pharmaceutical laboratories that merged to create Bristol-Myers Squibb¹⁶.

Today, in most of the companies, the MSLs depend on the Medical Affairs department and therefore have not to comply with the commercial rules.

2.4.1.3. MSL’s missions

An MSL has several missions attached to his position (Figure 5 from The Medical Science Liaison: An A To Z Guide, Malecha et al.). The KOLs in their specific therapeutic area are their principal stakeholders. One of the most important roles they have is engage with KOL: building a relationship with KOL based on trust and peer to peer exchanges in order to develop activities with them.

¹⁵ Morgan, D. K., Domann, D. E., Collins, G. E., Massey, K. L. and Moss, R. J. (2000), ‘History and evolution of field-based medical programs’, *Drug Inf. J.*, Vol. 34, pp. 1049–1542

¹⁶ Wolin et al., *The emerging role of medical affairs within the modern pharmaceutical company 2001*, *Drug Information Journal* Vol 35

The 5 Basic Elements of the Medical Liaison Role

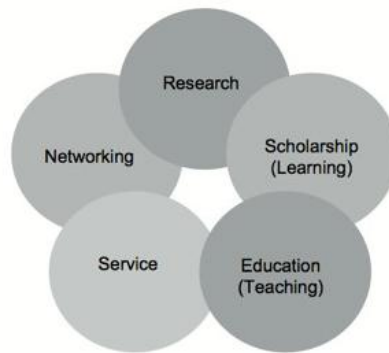


Figure 5 from *The Medical Science Liaison: An A To Z Guide*, Malecha et al.¹⁷

An MSL visits HCPs and particularly KOLs on a regular basis to discuss the various interactions they are between the two parties. MSLs have also the possibility to visit the HCP on their request, if one of them needs more medical information about the company's products and disease education.

The four main activities of MSLs according to Logan and Lewes study are based on one to one exchanges with HCPs and always concern scientific knowledge. After interviewing, MSLs declared that they consider their principals actions as: "Scientific exchange on company products/development compounds with HCPs in 1:1 meetings" "Responding to unsolicited requests for off label information", "Performing group medical presentations to HCPs on company medicines", "Scientific Exchange on disease area with HCPs in 1:1 meetings". At least 84% of MSLs in UK up to 98% consider they are performing these actions.¹⁸

MSLs are also implied in the process of exchanges between HCPs and companies for Investigator-Sponsored Research (ISR) submissions. The ISR activity is in first place mediated by MSLs as they facilitate the communication between both parties and explaining their company's specificities and process of submission to physicians. But the

¹⁷ Malecha, S. E., Wiejowski, S. A. & Holt, R. J. (2000), *The Medical Science Liaison: An A To Z Guide* (Albert, E. and Sass, C.). *The applied therapeutics team: an innovative model of drug information in the pharmaceutical industry*. *Drug Inform. J.* 34, 1069–1075

¹⁸ Gilian Logan and Mo Lewes, *Results of a survey of the Medical Scientific Liaison (MSL) function in the UK*, *Pharmaceutical Physician*, July 2012, No 1, vol. 23

Medical Affairs department is responsible for the selection of the research funded by their firm.

MSLs have the very important role of identifying and profiling potential KOLs, identifying their potential capacities and wishes to interact with the company in further activities like advising, speaker services or investigator activities. Once the MSL has identified the needs and wishes and competencies of KOLs they can build activities with them at a local level and also identify the ones they can recommend for international activities as well.

An MSL has also an internal role of Medical Expert within his company on his area of expertise, he is solicited by the other functions of the company for training and support. 82.5% of the UK MSLs are training sales force and other internal functions about disease awareness and medical knowledge and 77.3% of them provide medical support to marketing-led activities. MSLs have a transversal role in the company as they are interacting with various other departments: Sales, Marketing, Clinical Development, Research and Development, Medical Affairs and Medical Information, Managed Markets.

2.4.1.4. Areas of discussion with HCPs

MSLs are only allowed to discuss non-promotional information with HCPs. It implies disease awareness and medical education and concerning the products, only development data can be discussed regarding the product itself. The main area of discussion between MSLs and HCPs is treatment issues, side-effect management strategies and current or future research. These discussions are conducted on a peer to peer basis and this represents one of the major differences with the Sales Rep.

No promotional discussions are allowed for MSLs during their face to face with HCPs.

2.4.1.5. Place of MSLs within the company

All the companies do not have a MSLs force in place. Even if this concept is not a recent one, its development in the companies started to be significant in the early 2000's.

According to K. Werling et al. the number of MSLs rose up to 48% between 2003 and 2008. But the development of this type of employee depends on the firm, as there is no law directly regulating the MSL position.

Therefore, depending on the company, the MSL force is not developed and organized the same way. MSLs constitute a group of experts about a therapeutic area. Usually, they are placed under the country medical affairs management and the teams are organized by therapeutic area. Medical Affairs are more and more independent as a survey showed that Medicals were 43% under the marketing department in 2003 while they were 7% in 2008. This tendency confirms the wish of companies to make a clear distinction between promotion and non-promotional information of products.

2.4.1.6. Difference with Sales representatives

Sales Representatives, or Sales Rep, are Field based employees referring to the Marketing department of the company. They are trained for promoting products. Their communication is carefully controlled and highly restricted as Sales Rep are able to talk only about the label of a product. Only the SmPCs can be addressed during their meetings with HCPs. It implies that the product should be marketed (obtained its marketing authorization) to be presented. Therefore, every discussion about off-label indications for marketed product or in development drugs are prohibited.

Also, in function of the type of field employees, the HCPs targeted are not the same. For Sales Reps, the objective is to reach as much as direct prescriber HCPs as possible to sensitize them to his company's products. They are General Practitioners, nurses or community pharmacists that need a practical and accurate knowledge of what is currently possible or not with the drug. On the contrary, it is difficult for them to reach KOLs for their communication.

MSLs have access to renowned physicians to which sales rep cannot easily have access. "KOLs demand information from individuals who are not incentivized on the sale of a

product” according to Sam Dyer, an MSL expert.¹⁹ The discussion between both parties is not focused on the same subjects and do not rest on the same material as stated before. MSLs and Sales Representatives do not have the same educational backgrounds. The degree required to be Sales Representative is a two or three years degree aiming to promote products while MSLs usually have a science driven Doctorate in Medicine, Pharmacy or Science.

In a near future, MSLs will probably replace Sales Rep force according to the hiring trends in the pharmaceutical industry: The total amount of Sales Rep worldwide drops while the number of MSLs increases.

	Sales Representatives	Medical Science Liaisons
Education	Two years degree	Doctorate (MD, PharmD, PhD)
Area of Discussion	SmPC only	Non-promotional Information
Meeting orientation	Sales Promotion	Scientific Discussion

MSLs are the interface between the pharmaceutical company and the nationally and internationally renowned KOLs. Therefore, their interactions like the interactions with Sales Rep could be of potential risk of conflicts of interest.

¹⁹ *Pharma and the evolving role of MSLs*, Eye for Pharma, Feb 2012
<http://social.eyeforpharma.com/sales/pharma-and-evolving-role-msls>

3. Conflicts of Interest (COI)

As explained above, HCPs are critical stakeholders for the industry for accessing markets. Thanks to their different roles HCPs have some specific powers: being prescribers they have the power of influencing the sales of a drug by prescribing one instead of another, being speakers, they have the power about the content they communicate about drugs and being investigators, they have the one of evaluating medicines. The risk that both parties use this situation to their own profit is particularly tangible in the pharmaceutical industry and could lead to the apparition of conflicts of interest.

An influence of HCPs by the pharmaceutical industry could therefore be a major issue in the ethic of the medical domain. First concerns about it were raised in the 80's in medical journals, starting to point out the potential conflicts of interest between the Pharmaceutical Industry and physicians. Today the bets of this debate remain the same.²⁰

3.1. What do we mean by conflict of interest?

We will study what is considered as conflict of interest in the scientific community and in the law. As stated by Robert D. Greenberg in *Conflicts of Interest: can a physician serve two masters?* "It is recognized that various definitions of COI exist, which can lead to misunderstanding and confusion as to what is actually meant by a COI".²¹ Therefore the first problem identified is the definition itself of the notion of conflicts of interest. There are several ways to describe this notion.

A broad definition of conflicts of interest refers to interests of various natures. For Dennis Thompson from the Harvard University, in the *New England Journal of Medicine*,²²

"A conflict of interest is a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain). Conflict-of-interest

²⁰ Dennis F. Thompson, Ph.D. *Understanding Financial Conflicts of Interest* N Engl J Med 1993; 329:573-576 August 19, 1993 <http://www.nejm.org/doi/pdf/10.1056/NEJM199308193290812>

²¹ Robert D. Greenberg, *Conflicts of Interest: can a physician serve two masters?*, *Clinics in Dermatology* (2012) 30, 160–173

²² Dennis F. Thompson, Ph.D. *Understanding Financial Conflicts of Interest* N Engl J Med 1993; 329:573-576 August 19, 1993 <http://www.nejm.org/doi/pdf/10.1056/NEJM199308193290812>

rules, informal and formal, regulate the disclosure and avoidance of these conditions.”

In the case of HCPs, the primary interest represents the professional duty of the HCP. It generally includes the health of patients, the integrity of his research and the education of students. His actions and ideas during these activities are motivated by his professional ethic: the patient health for the health care practitioner and scientific progress in research.

The secondary interests, the ones that lead to a COI, are not limited to financial nature as they can also concern HCP’s personal renown for example as “an interest in obtaining provocative results” or pressure to favor “previously published findings of colleagues, friends, or researchers in collaborating groups”.

The Lancet considers also in its conflicts of interests statutes that the interests can be of different nature: “Financial relationships are easily identifiable, but conflicts can also occur because of personal relationships, academic competition, or intellectual passion.”²³

Dennis Thompson and The Lancet introduce the interesting subject of the personal and professional advantages as factors influencing HCPs and leading them to COI.

Both of them also highlight the fact that financial advantages appear to be the main reason for one to be influenced in his actions and point of view.

Financial gains are the interests that are the most considered by the authorities because they are more objective and more tangible than other secondary interests and therefore easier to legislate. That is why most of the definitions take into account only the financial interests. The FDA definition, for example, explicitly states that a conflict of interest concerns only financial nature interests:²⁴

“A conflict of interest is of a financial nature. FDA reviews all financial interests related to the particular topic of a meeting to determine if a conflict exists. If the financial interest is not related to the meeting topic, a conflict of interest may not exist. In order to be considered a financial conflict of interest, FDA determines

²³ Alain Wasniewski, *Conflits d'intérêts : les mots ont-ils un sens ?*, Voix Médicale, April 2012

²⁴ FDA Website: <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm222231.htm>

whether the discussion at the meeting or outcomes of the meeting will have a direct and predictable effect on the individual's interest.”

However the other kinds of secondary interests (professional and personal advantages) should not be neglected and will be described later in 3.3.

For the rest of this work we will use the broader definition of Dennis Thompson that considers that interests could be of various natures.

The danger of conflicts of interest is therefore the risk of modification of the actions and judgment of HCPs because of other considerations. We can now examine the consequences of COI.

A COI can modify one's judgment and particularly his prescriptions habits in the case of HCPs. The choice of a treatment for a patient is made in the best interest of the patient for his health and safety. But for two equivalent drugs which one to choose? For example, two drugs A and B treat the same condition and are from the same pharmaceutical family they are considered as equivalent. If the recent sales rep visit is the trigger for the prescription of A, is there a conflict of interest?

It can also modify the discourse of HCPs towards their peers and therefore give information in favor of a product or a company, not because he believes in it, but because he has an interest in doing so.

This influence of HCPs can be voluntary or not. Therefore the HCPs do not realize that he is having conflicts of interest.

3.2. The difference between links of interest and conflicts of interest

The difference has to be made between conflicts of interest and links of interest. Having relations with the industry does not necessarily imply that there is a modification of the HCP judgment or actions.

A link of interest represents an interaction between two parties. After this interaction, something exists between them. This link can be of various natures like financial or informational but it does not necessarily introduce a bias of the HCPs professional duty. A

link is indeed established but it did not influenced the HCP's judgment or actions and therefore do not generate a conflict of interest.

The conflict appears as soon as this link impedes his professional work and that his professional duty and his secondary interests are in conflict.

3.3. Opportunities for COI in the relations between HCPs and the Pharmaceutical Industry

For all the interactions described in the previous parts, there are potential risks of conflicts of interest. As soon as something is given to a HCP, there is a risk of modification of his judgment toward the company, the company's products and everything related to them. The following review will describe the opportunities for COI in function of the secondary interest that is in potential competition with the duty of the HCP: Financial advantages, Professional advantages or Personal advantages.

3.3.1. The financial advantages: compensations and fees for service

In this case the amount of money given to the HCP could be a reason for him to modify his behavior in favor of the company or its products.

Speaker services and advisor services:

In regard to speaker services and advisor activities they are potential risks for COI if the amount of the fees for services is inappropriately high. It could be tempting for the firms to pay more a speaker in order to influence his speech in favor of the company or its medicines. With the same idea, it could be tempting for the HCP to ask more for his speech.

For this reason, the concept of benchmark was introduced through years giving an order of magnitude for the hourly rate of HCPs' fees and pharmaceutical industries are paying about the same fees for each speaker. The payment of an HCP will vary in function of his national and international renown and the duration of his activities during the event.

Companies' Clinical studies:

Pharmaceutical firms need to perform clinical trials in order to evaluate their drugs. As they do not have access to patients, they need HCPs as investigators for enrolling patients in trials and make their follow up for all the trials duration. Physicians are paid for their work in that matter and companies apply a large price range from 1000€/patient to many thousands for a patient.

The potential conflict of interest here would be to pay too much physicians to influence them toward the company or about the conduct of the study.

That's why there are a limited number of enrolled patients for each investigator and payments are indexed on consultations prices.

3.3.2. The Professional advantages: personal relationships, academic competition

Speaker services:

Being speaker in well-known congresses could represent an opportunity for HCPs to increase their renown among their peers. Therefore, their personal desire to recognize could be in conflict with the utility of being speaker for an Industry.

Sponsored studies:

In ISRs, physicians ask for funds in order to performed clinical trials, often related to the company's medicines. Therefore, the risk associated is that studies sponsored by companies are more likely to favor the products of the company that funds the research.²⁵

Conflicts of interest could occur voluntarily or not in the scope of sponsored studies.

Clinical Trials Results:

²⁵ Lexchin J, Bero LA, Djulbegovic B, et al. *Pharmaceutical industry sponsorship and research outcome and quality: a systemic review*. BMJ 2003;326:1167-70

Liss H. *Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship*. Isr Med Assoc J 2006;8:451-4.

Investigators are directly confronted to the results of trials. Even if a trial is blinded, they can have a hint of what is going on. This situation could be an opportunity for conflicts of interest.

For example it happened that an investigator in one of the pivotal trials for an in development medicine, an investigator had access to the results of the study as first investigator. Facing bad results, he advised members of the company to sell their stocks options before the publication of the results and before the drop of the action value.

The FDA created a “Black List” of investigators, it includes investigators that messed up with studies. The black listed physicians are not allowed to perform clinical trials or the agency will not consider any results coming from a study they were involved in.²⁶

Publications:

Being investigator is interesting for physicians from a personal point of view because as investigators, some are implied in the publication and communication of the study results and authors of the publication article and they have the opportunity to present the results in medical events. It is rewarding and gives HCPs recognition and renown among their peers. The danger here of conflicts of interest resides in the eventual felling of liability toward the company.

3.3.3. The Personal advantages: gifts and hospitality

Gifts:

As part of the sales representative’s visits, they were allowed to offer gifts to HCPs. The offer of gifts is perceived as a source of bias in HCP’s choice in a therapeutic prescription.²⁷ Today, the law is not the same in every country and is evolving very fast. But the American Anti-Kickback Act and the French Anti-Gift Law are regulating this practice.

Participation to events:

²⁶ FDA Website: <http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm>

²⁷ J Dana G Loewenstein, *A Social Science Perspective on gifts to Physicians from Industry*, American Medical Association, July 9, 2003, Vol 290 – No 2

When an HCP attends internal meetings, such as advisory boards, speaker training or external events such as congresses, pharmaceutical companies often pay travels, expenses and accommodations for the HCPs and KOLs. The company will also organize some events around the congress involving the HCP like dinners.

The risk is that laboratories pays or provides more than the strictly necessary and therefore imply an explicit or implicit situation where the HCPs become indebted to the laboratory. The HCP's judgment toward the firm and its products could be distorted and influenced by the personal advantages that the HCP get from the company.

For example, the firms used to pay business class plane tickets, organized three stars dinners and sightseeing tours for their delegates at congresses. These activities were not justified from a pharmaceutical communication point of view and therefore are now illegal. Today, the rules toward HCPs sponsorship in congresses are stricter and reduced to the minimum. More and more companies such as AstraZeneca made the decision to not invite HCPs to attend congresses.

Seeing all these potential opportunities for conflicts of interest in the relations between HCPs and the pharmaceutical companies, there is strong need for clear rules about these interactions.

4. Fighting Conflicts of Interest: Regulations and Industrial adjustments

While some experts think that “the symbiotic relationship between the medical and drug industries is a uniquely complex one, not governed by a clear code of ethics” they are already some existing watchdogs that limit the risks of conflicts of interest in the relations between HCPs and Pharmaceutical Industry. The current framework is set by regulatory authorities and Industry associations all over the world. United States and Europe are the key markets for the European Companies and that is why we will focus on it in this work.

Country/Region	Regulatory Agencies	Industry Associations
United States	FDA	PhRMA
Europe	EMA	EFPIA
France	ANSM	LEEM

4.1. The existing legal framework, focus on United States, Europe and France

In this section we will study the legal rules that have already been set by regulatory authorities. The regulatory authorities are organized in agencies, which are a government department, or an organization connected with a government, that deals with a particular subject²⁸. These agencies exist all over the world, in countries and in regional unions like the European Union. These agencies have in the scope of their activities the power to impose the application of the law by companies and help them to do so. They also have a power of control and repression in case of disrespect of it. Companies have to comply with these laws and if they do not, every infraction is punished by justice.

The authorities are not the same all over the world. In Europe, there are two levels of authorities: one at the European level EMA (European Medicines Agency) and one at the country level. The EMA missions are Marketing authorizations, Safety-monitoring of medicines and Stimulating innovation. EMA is the agency which decides if the drug will be

²⁸ MacMillan Dictionary ed.2012

marketed or not in the European Community. Then the Agencies at the country level adapt the product SmPC (Summary of the Product Characteristics) once it is approved and negotiate the price and reimbursement level ratio.

4.1.1. Worldwide

There are no international laws regulating the interactions between the Industry and HCPs. Therefore, the countries all over the world are not submitted to the same rules. There are only codes enacted by Pharmaceutical Companies federations or associations as it is explained in 4.2. The laws and regulations are only regional (in the case of the European Union) or national.

4.1.2. United States²⁹

In the United States, the FDA (Food and Drug Administration) is the regulatory authorities. One of its missions is to make the Federal Laws applied regarding health care in the United States (by the industry, HCPs...).

4.1.2.1. The Physician Payment Sunshine Act (PPSA)

The Physician Payment Sunshine Act (PPSA) was voted in the United States by the Centers for Medicare & Medicaid Services (CMS), an US Federal Agency in March 2010. The objective of this act is the transparency in the financial exchanges between physicians and Pharmaceutical firms in the US.

The sunshine act aims are:

- clarifying the direct financial relationships between physicians and industry for purposes of reporting
- requiring companies to describe the context of relationships so that consumers understand them

²⁹ *Regulations on Physician/Industry Interaction Must Include Clarification, Context, Consistency*, American Academy of Family Physicians <http://www.aafp.org/online/en/home/publications/news/news-now/government-medicine/20110413sunshineprovisions.html>

- requiring companies to consistently collect and report data in a standardized and uniform fashion

However the complexity of the application of this act postpones its official application's deadline. Today, the industry and physicians are supposed to apply the Sunshine Act from beginning of 2013.

4.1.2.2. The Anti-Kickback Act ("AKA")³⁰

The Anti-Kickback Act ("AKA") is an US law issued in 1986 and prohibits those involved in government contracting from offering, accepting, or attempting to accept inducements for favorable treatment in awarding contracts for materials, equipment, or services of any kind. This represents money, fees, commissions, credits, gifts and gratuities.

For any non-compliance to that law an HCP may incur fines and up to 10 years of prison.

4.1.3. Europe

In Europe they are: a unique European Agency and a national agency for each country. The regional agency is the European Medicine Agency (EMA).

In the European Union, the community agency, the EMA, legislates for all the member states. The European Parliament issued the European Directive, 2001/83/EC, regarding Medicinal Products for Human use. The first version of the code was published in November 2001, followed by numerous amendments. Today it is the legal text regulating the matter all over the European Community.

The 2001/83/EC directive covers all the area of development and commercialization of a drug including Manufacturing, labeling, distribution, advertising, pharmacovigilance, supervision and sanction.³¹

For example, regarding the hospitality of HCPs the text states that it should be strictly limited to the main purpose of the event and must not be extended to persons other than HCPs.

³⁰ American Law: 41 U.S.C. § 52 : US Code on <http://codes.lp.findlaw.com/uscode/41/1/52>

³¹ Directive 2001/83/CE : http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf

However, each country also has its own regulations in addition to the European Directive and there is a national regulatory agency in each country of the community. Among the various countries of Europe, we will focus on the French example.

4.1.4. France

4.1.4.1. “Loi Bertrand” or French Sunshine Act³²

In France, a recent crisis raised serious questions about transparency in the health care system. The case, called “l’affaire Mediator”, was raised by the scandal of potentially hidden information by a pharmaceutical company leading to an abusive use of the drug and patient deaths.

Following this crisis, a law was voted on the 29th December 2011 after many discussions and modifications in Parliament and Senate. That text has a very large field of action, aiming to change deeply the organization of the national agencies, medicines approval processes and transparency rules for all the actors of the drug approval process. Some application decrees were released in 2012.

The national Agency for Drug changed from the AFSSAPS to the ANSM. This new Agency was created by decree (No. 2012-597 published April 29, 2012) which concerns the agencies organization. The organization of this new agency changed and the areas of competencies widened. The condition to be part of the agency became more restrictive than before.

Regarding the transparency of the relations: The French Sunshine act, or « Loi Bertrand », was voted in the 29th December 2011 text and is based on the same principles of transparency than the Physician Payment Sunshine Act (PPSA) voted in the United States. This French law applies to more categories of people than the US one. Now, companies have to report concluded agreements and afforded benefits to the following persons and organizations:

- Health professionals and their associations;
- Students intending to these professions and their associations and groups;

³² French Sunshine Act: <http://www.loibertrand.info/> and <http://www.legifrance.gouv.fr/>

- Associations of users of the health system;
- Health facilities;
- Foundations, societies, companies or organizations involved in the sector;
- Software supports for prescribing and dispensing;
- Legal persons providing the initial training of staff health (faculties and schools).

However, it does not apply to research activities during the preparation of a diploma and hospitality offered in scientific events for students' participations.

Today, several decrees of application on the 29th December 2012 law were published in May 2012, but none of them concerned the Chapter III regarding transparency in the relations between the Industry and Health Care Professional.

The planned decree of application of that law will set the precise conditions of application of the law particularly regarding the balance between conflict of interest disclosure and protection of HCP's privacy. It will also have to take into consideration the protection of trade secrets.

The project of decree³³ is waited for January 2013 and plans the details of the disclosure rules mentioned in the law *n°2011-2012*. It will include the agreements concluded with HCPs between the 1st January 2012 and the 31st December 2012.

Today, the draft decree states that industries will have to publically disclose every advantage given to HCPs in form of money or goods if its value is equal or superior at 60€. Every company will have to disclose all the advantages provided to HCPs on its website every six months (1st January and 12st July).

4.1.4.2. Sanctions³⁴

The sanctions applied to HCPs or student for accepting advantages from the Industry, prevented by the anti-gift law, is set by the article L4163-2 of the Public Health Code. The fine is up to 75.000€ the HCP can face a sentence of 2 years of prison. The HCP can also eventually face a temporary prohibition of exerting up to ten years.

³³ <http://www.loibertrand.info/> last consultation on the 2nd of December

³⁴ French Public Health Code, *Code de la Santé Publique* (CSP) Dec 2012

The sanctions for the non-disclosure of links of interests between industry is not yet fixed by the regulation (decree to come) but, as a matter of example, here are the fines applied in the case of the relations between HCPs and French Public Health Agencies (ANSM and HAS).

In the public agencies, French HCPs providing expertise have to publically publish their interests with pharmaceutical industries. If they do not disclose or update them they are liable to a fine of 30.000€. The same fine is applied if they disclose false information. A pharmaceutical company or its nominated agency is liable to a fine of 45.000€ for the same actions.

The fines charged may be accompanied by a loss of civic rights for an HCP and for the company, it is exposed to a prohibition of manufacturing, importing and placing on the market of drugs.

4.1.4.3. “Loi anti-cadeaux”, DMOS law or “Anti-Gift Act”^{35,36}

Before the regulation, pharmaceutical industries were used to offer to HCPs presents like expensive travels with their family in fancy destinations or household appliances.

In France, a law regulates the gifts given to physicians; it is called the “Loi anti-cadeaux”, Loi DMOS or “Anti-Gift Act” (No 93-121 of the Public Health Code) and was issued in 1993. It was then modified by decree in 2002 and more recently with the law No 2011-2012 of December 2011.

The first version of this law (1993 modified in 2002) sets the restrictions of the advantages that can be given to HCPs. First, it forbids the offer of advantages to HCPs from the Industry. It is forbidden to offer it as well as receive it; therefore, both parties could be condemned in case of non-compliance. However, derogation to this law includes the conventions concluded between HCPs and the Industry regarding research activities, scientific evaluation.

³⁵ Maitre Helene Miller, *Les modifications apportées par la loi n°2011-2012 du 29 décembre 2011 au dispositif « anti-cadeaux », Qu’est-ce que le dispositif « anti-cadeaux » ?* Agence Juris Media, April 2012 <http://www.alliancejuris-media.com/2012/04/qu-est-ce-que-le-dispositif-anti-cadeaux/>

³⁶ French Public Health Code, *Code de la Santé Publique* (CSP) Article L4113-6 modified by [LOI n°2011-2012 of 29 Dec 2011 - art. 2](#)

The new Anti-Gift Act planned by the 29th December 2011 law extends the scope of the previous one (L4113-6). It forbids the advantages given to student as well as the ones given to HCPs during their relations with the Industry. This new law also requires the obtaining of the consent of the council of the French Medical Association for every convention concluded between HCPs or student and a pharmaceutical company. The decree of application of that new law has not been issued yet.

4.1.4.4. The French Medical Association (*Ordre National des Médecins* or *CNOM*)³⁷

In France the registration of each physician to the CNOM, the Medical Association is mandatory. For more than twenty years, physicians have to confidentially disclose the advantages they perceive from Industries to the Order. Then, this information is evaluated by a committee within the CNOM in order to ensure professional independency of physicians. But this committee can only give a notice in case of noncompliance of physicians to the law (L4113-6 and L4113-9 of the Public Health Code). They have no rights of sanctions or public disclosure.

4.1.4.5. French Code of Ethic^{38,39}

French HCPs also have to follow the French Code of Ethic or “Code of Déontologie”. These texts are part of the French Public Health Code, Part IV (Health Care Professionals) and state the ethical duty of HCPs. Pharmacist and Physicians have their own codes. The code reminds the interdiction to accept any material advantages during his activity except for his contribution to the invention, the study or the development of drugs, medical devices, appliances laboratory techniques or methods. Also, the HCP has to keep his professional independency and the interest of the patient as his first concern in his medical practice.

³⁷ *Indépendance professionnelle des médecins – Déclaration d'intérêts : « Sunshine act » à la française*, Ordre National des Médecins, May 2011 <http://www.conseil-national.medecin.fr/article/independance-professionnelle-des-medecins-%E2%80%93-declaration-d%E2%80%99interets-%C2%AB-sunshine-act-%C2%BB-la-francaise-1076>

³⁸ Code de Déontologie des Pharmaciens, Ordre des Pharmaciens, July 2009

³⁹ Code de Déontologie des Médecins, Public Health Code Part IV

4.1.4.6. The French “Charte de la Visite Médicale” or « Charter of Ethics for Pharmaceutical Sales Visits »

All the industries member of the French association of the Industries, the LEEM (see 4.2.1.3), signed the « Charter of Ethics for Pharmaceutical Sales Visits ». This document was adapted in the French Regulatory recommendations in 2009 in a document of reference called “Référentiel de certification de la visite médicale”.

This document applies to any promotional activity by prospecting and solicitation of any health care professional authorized to prescribe or dispense reimbursable medicinal products, but also with nurses, whether performed in the office, in the health facility or remotely (Internet and telephone).

This text states the conditions of certification of companies using Sales Visits in France. The text contains various criteria to be followed like the conditions⁴⁰ of training of Sales Representatives.

⁴⁰ *Référentiel de certification de la visite médicale*, HAS, 2009 http://has-sante.fr/portail/jcms/c_334342/referentiel-de-certification-de-la-visite-medicale

4.2. Industry's self-imposed Rules and guidance

The Pharmaceutical Companies decided to anticipate the law and created broader rules in respect of ethic, integrity, promotion of scientific progress and improvement of health and patient's quality of life.

Therefore, the pharmaceutical companies are working together on core activities on the basis of a general spirit of ethic and efficiency and created Industries federations and associations. These federations are producing sets of codes that the member companies should follow. Also, the firms have their own internal rules to comply with, the Standard Operating Procedures, based on compliance rules, legal texts and Industry codes.

4.2.1. Codes

There is no major code from an international perspective. Apart from the World Health Organization Ethical (WHO) *Criteria for Medicinal Drug Promotion*, Issued in 1988 and never updated, it is focused in the Promotion and Advertisement of prescription drugs.

The major codes concerning relations between HCPs and the Industry in Europe are the FPIA, and the ABPI.

4.2.1.1. Europe: EFPIA

In Europe, there is one major federation: 33 national associations and 37 leading pharmaceutical companies are member of the European Federation of Pharmaceutical Industries and Associations (EFPIA). The EFPIA produced the most used code of practice to be used by industries in Europe, regarding "the promotion of prescription-only medicines to, and interactions with, healthcare professionals". That code was issued in 1991 and is regularly updated since then. The last version was issued in 2008 and contains nineteen articles which cover the promotion of prescription only medicinal products to healthcare professionals and the interactions between healthcare professionals and pharmaceutical companies. This text includes commercial communication, visits and gift. Also, all the different types of medical activities are mentioned including donations and grants, fees for services, sponsorship and non-promotional information disclosure. This

code if more focused on the promotion of medicines and relations compared to the ABPI code which is very developed on that matter. EFPIA code is strongly resting on the European Directive (2001/83/EC).

For example, the Article 14 describes precisely what companies are allowed to do when they are using HCPs as consultants for advisor or speaker services. The content of agreements is described and the condition in which the use of consultants is tolerated. The company should describe the criteria for selecting a consultant, the explanation of the legitimate need for the services of the consultant and the company should also keep records of all interactions engaged with consultants. It also strongly encourage the companies to include in the consultant contract the obligation for the consultant “to declare that he/she is a consultant to the company whenever he/she writes or speaks in public about a matter that is the subject of the agreement or any other issue relating to that company”.

4.2.1.2. UK: ABPI

In the UK, the national Pharmaceutical Industries’ association is the ABPI (Association of the British Pharmaceutical Industry). This association includes all the major research-based industries in United Kingdom including small, middle size and large companies. ABPI produced one of the most accurate codes concerning the interactions between the industry and HCPs, the Code of Practice for the Pharmaceutical Industry. This code was first issued in 1958 and is updated regularly by the ABPI first and by The Prescription Medicines Code of Practice Authority, an independent organism, since 1993. The scope of this code is broader than the EFPIA one and is particularly developed in term of non-promotional communication; all the different types of interactions are regulated in that document with precise ethical and financial guidance regarding promotional and non-promotional communications and events.

For example, the ABPI code states very precisely what companies are allowed to do regarding the use of consultants, or for HCPs hospitality and sponsorship. When a company sponsors a meeting, it has to be disclosed in all the documents of the meeting.

In the new version of 2012, a clause was added to the Clause 20 concerning transparency and disclosure obligation of relations between HCPs and the industry.⁴¹

This code also plans sanctions for companies that do not follow the code. The ABPI includes a Panel in front of which a complaint for non-respect of the code can be submitted. After reviewing the case, the commission proposes mediation to both parties.

4.2.1.3. France: LEEM⁴²

In France, the national association of pharmaceutical companies, the LEEM did not issued any formal code of conduct for the companies like the ABPI but helps applying the EFPIA code. It also issued several directives regarding the behavior of French Industries. They produced several repositories, booklets and leaflets about the various activities of the Pharmaceutical Industry, like a Guide for the Medical Visits.

In September 2011, The LEEM created a Committee of Ethic, the Codeem. The majority of the eleven members are external to the industry and its President is member of the French National Ethic Commission (Commission de déontologie de l'Etat). It is designed to operate independently and impartially. It can be invoked by the Leem itself, the Leem members or other stakeholders of the Pharmaceutical Industry like Patient Associations, Health Authorities, HCPs organizations... They can also issue recommendations that Leem members should follow regarding various subjects including: promotion and relationships with health professionals, Sales Rep visits, relationships with patient organizations, continuing medical education (CME), Internet communication, or relations with the press. They issued a recommendation in February 2012 that laboratories should not give more than 4 samples to HCPs during Sales Rep visits. Moreover these samples can be distributed only during the two years following the product commercialization. This law is even stricter than the legal recommendation of the French Code of the Public Health at that time (10 samples in the R.5122-17 article of the Code of Public Health in February

⁴¹ *Code of Practice for the Pharmaceutical Industry*, Second 2012 Edition, The Prescription Medicines Code of Practice Authority

⁴² *Transparence des liens*, Leem, Nov 2011, <http://www.leem.org/article/transparence-des-liens>

2012). Today, modified by the 9th May 2012 Decree, the R.5122-17 article imposes the same amount of four samples a year for each physician.⁴³

Transparency⁴⁴

The Leem also issued a recommendation regarding the disclosure of the links of interest between the industry and HCPs. Waiting for the application decree of the second article of the law of December 2011, the Leem published Guidelines for the companies that would like to start the disclosure of their links of interest with HCPs before the publication of the decree. The Companies that which to start the disclosure of their links of interest with HCPs can publish the following information via the Leem website: identity of the HCP, Location of his activity, the nature of the convention, date and signature. It is interesting to note that it does not include the nature and amount of the eventual advantages given to the HCP. And yet, this information will most likely be mandatory in the coming application decree.

4.2.2. Pharmaceutical industries internal policies: Standard Operating Procedures (SOPs)

Each company has its own Standard Operating Procedures (SOPs) to avoid any risk of conflicts of interest. SOPs are internal rules that describe a procedure for every action performed in or by the company or its nominated agency in order to ensure quality, effectiveness and efficiency. An SOP is a set of written instruction that has to be followed by each employee of the firm. For example, regarding the conduct the firm will follow with HCPs, the SOPs describes precisely what kind of information the employees are allowed to disclose, what they are allowed to do with the HCP or give to him. Like invite HCPs to some events or to the restaurant and in which circumstances. It contains precise figures for example: the company cannot spend more than 40€ for a lunch with an HCP.

⁴³ Leem Press Release, 26th Sept 2011 <http://www.leem.org/installation-officielle-du-codeem-comite-de-deontovigilance-des-entreprises-du-medicament>

⁴⁴ Leem Press Release, 20th July 2011 <http://www.leem.org/transparence-leem-emet-une-recommandation-pour-faciliter-publication-des-liens-d-interet-par-ses-adh>

They are based on the company's everyday practice that is written and approved at different levels of the firm. SOPs are used at every level of the company and for various kinds of activities: from New employee orientation to contract management.

The critical point of SOPs regular use in a company is the control of their applications by all the employees and the follow up and the updates of the documents. Management of SOPs also imply to keep accurate records of all the versions of documents and ensure that the current version of each document is easily and the only one accessible to every concerned employee.

SOPs concerning HCPs vary from a company to another. But they are all based on the same guiding documents: the EMA European law (2001/83/CE), and the main codes of the industries' associations, if the company is part of them: EFPIA and ABPI.⁴⁵

4.2.3. Audits

The FDA performs regular audits inside the investigators facilities to ensure that the Good Clinical Practices are respected by investigators. Also, they are audits planned in the investigation protocols to ensure the quality of the trials. These audits are planned and performed by the company performing the trial to ensure that the Clinical Research process is not compromised by malpractice.

Pharmaceutical companies usually take constraining measures in their SOPs that are even stricter than the law. They organize as well regular internal audits to ensure that the internal rules are correctly put into practice by all the employees. The audited department is randomly selected and the auditors will control that all the SOPs processes have been applied. For example, for one event, they analyze every agreement made with consultants and control that all internal documents have followed the internal pathway of approval and that the facilities used are complying with the internal conditions. For example, the company decided that any internal meeting can be held in five stars hotels

⁴⁵ Sanjay kumar Jain, *Standard operating procedures (SOP) - Back Bone of Pharmaceutical Industries*, Aug 2008 <http://www.pharmainfo.net/reviews/standard-operating-procedures-sop-back-bone-pharmaceutical-industries>

or that the hotel chosen should not contain another meeting at the same time of another pharmaceutical company.

Discussion

While most of these interactions are needed, however I have some specific caveats.

Communication

Information on the drug and good communication is the cornerstone for the drug usage and the good medical education of the HCPs. The principle seems quite logical: a product has to be known to be used and therefore a Health Care Professional should know very well a drug before prescribing it. Most of HCPs admitted it: they do not find the time to stay informed by themselves and Continuing Medical Education (CME) cannot cover for all the specialties for a General Practitioner or a Pharmacist for example. Then, direct information is needed. As there is a very limited public funding for independent medical education, who else than the pharmaceutical company that found the drug will communicate about it? Facing this evidence the solution is to let the companies communicate themselves and tightly control their actions toward HCPs.

Two different types of communication are used today medical and commercial. These tools explore two different aspects of the communication toward HCPs one is based on the information only about the drug the other one, on the promotion. We do not know the difference of impact on HCPs of these two methods. But the medical one, through Medical Science Liaison (MSLs), more scientific and less promotional than the communication through Sales Rep. As the regulatory environment evolves, the pharmaceutical industry uses more and more the non-promotional channel compared to the promotional one. This could reflect the evolution of the mentality in the industry.

Specific activities with the industry

Having activities with the companies could be a source of conflict of interest. HCP is paid by the industry. He may therefore be inclined to favor this company and its products. When experts are used to interact with many different companies in their area of competencies they are fewer risks to favor one companies or another.

Gifts

The industry has the bad reputation with the public of offering extravagant gifts and creating a climate of duplicity. To limit the risk most of the countries have implemented regulations and guidance based on the principle to limit the support offered by the industry to the strict minimum. But it is very difficult to evaluate what is reasonable to offer and what could be considered as extravagant. As an example, a 50€ present is considered as reasonable in France but not reasonable in other country.

The small gifts given to professionals do not present a major interest for the improvement of healthcare and do not serve any medical interest. However, their distribution was proven as increasing the number of prescription of expensive drugs. Therefore we could question the need for these gifts. In India, for example, their distribution is prohibited by the local law as sales representatives were offering coffee maker and other tools to their best prescribers. Pfizer stopped their distribution in the country to comply with the law.⁴⁶ This kind of communication does not seem essential for the understanding of the drug by HCPs and seem to influence their choice of patient's treatment.

The evolution of the law

In the US and later in France, legislators tried to regulate the offer of gifts to HCPs. However, in both countries, they encountered difficulties for the application. The American law is waiting for two years and the French authorities postponed the decree several times. This phenomenon shows how much it is difficult for the authorities to make a situation change.

The Anti-Kickback Act and the French "Loi DMOS" as well as the two Sunshine Acts are the proof that the regulators thoughts about conflicts of interest are going in the same direction. It brings the possibility of an international harmonization of some fundamental ideas about the regulation of the interactions between the Pharmaceutical Industry and HCPs.

⁴⁶ Frederik Joelsing, *Exclusive: Abbott suspends giving gifts to doctors in India*, Reuters, Oct 2012
<http://www.reuters.com/article/2012/10/16/us-abbott-india-doctors-idUSBRE89F1N820121016>

Harmonization

These country regulations are well defined but the challenge is that the rules apply locally only. Therefore, there is no harmonization of the law around the world and this is difficult from an international point of view, as most of the companies are present worldwide. Therefore, one company has to comply with multiple texts at the same time. The set-up of international guidelines could facilitate coordination and transparency of the industry's actions.

As for the International Conference on Harmonization (ICH) that already produced Guidelines for the production and the development of a drug, it could be possibility to build an international guideline based on the existing texts and the laws in France and in the US.

Research and Development

The development of a medicine is largely based on the involvement of HCPs. With their advisor and investigator role, HCPs are pivotal in the development of a medicine. It was shown that the funding by industries contributes to a better design but may also have impact on the results.⁴⁷

However the funding of clinical research by the industry cannot be avoided, as they are the only available to finance these trails. The conduct of trails is already a very highly regulated process for obvious reasons of safety and also to guarantee the quality of the drugs that are approved by authorities. Because it is already very highly regulated, there is not really room for improvement.

Transparency

The best way to minimize the risk of COI is to increase the transparency between the industry and HCPs. The Sunshine Act in the US or Loi Bertrand in France are based on the same principle: the disclosure of the advantages given to HCPs. If an advantage is given, whatever it is, it will be publicly known.

⁴⁷ Pr Patrice JAILLON, *Gestion des conflits d'intérêt*

<http://www.snmrhp.org/Data/ModuleGestionDeContenu/application/495.pdf>

Ridker and Torres, *Reported outcomes in major cardiovascular clinical trials funded by for-profit and not for-profit organizations: 2000-2005*, JAMA, 2006 ; 295 : 2270-4

But, as we explained, the presence of a link of interest does not necessarily imply the presence of a conflict of interest. Therefore, transparency has the very important role of informing the public that receive the information and help their critical analysis. However, transparency will not prevent to become conflicts of interest.

Disclaimers

Another dimension of the disclosure issue is the transparency during speeches or in publications. In that case, it concerns the direct relation between the public of congress speeches or professionals reading scientific publications. One of the solutions here is the use of systematic disclaimers. Disclaimers are presented before a speaker's speech and at the end of publications in peer reviewed journals. It contains the links of interest of the speaker in a congress, all the companies the speaker has worked with. In a publication paper, it explains the nature and origin of the founding. Today, the majority of peer reviewed journals have an internal policy requiring the disclosure of the author's links of interests. This rule is also applied in most of the national and international congresses.

Continuing Medical Education (CME)⁴⁸

The CME is not all the time financed by the public funding. Sometimes it is paid with the help of the industry. This situation could bring bias in the transmission of the information to HCPs learning during these CME, as the industry organizing it could be tempted to favor its products compared to the others.

Therefore, it could be a solution to rely on an independent organization that could be founded by companies with the funds they usually allocate to CME. This organization could be controlled by the regulatory agencies or the companies associations and would organize the CME with far less risks of bias.

⁴⁸ Jeffrey R. Binder, *Does industry funding of Continuing Medical Education (CME) and Graduate Medical Education (GME) create bias?*, Nov 2010
<http://www.biomet.com/corporate/ceoblog/postdetail.cfm?postid=61>

Conclusion

Les interactions entre l'industrie pharmaceutique et les professionnels de santé restent largement débattues dans la presse et les revues scientifiques car elles sont un challenge pour les deux parties ainsi que pour les autorités régulatrices.

Dans la mesure où elles sont indispensables, les interactions de l'industrie avec les Professionnels de Santé seront toujours un challenge pour les deux parties ainsi que pour les autorités régulatrices. En effet, les risques de dérives sont constants et existent de part la nature de l'homme : la confrontation de son devoir professionnel face à son intérêt personnel. Cette dualité existe dans toute les professions à ceci près que le professionnel de santé est lui, très impliqué dans la santé du patient. Chaque patient lui fait confiance dans la prise de décisions le concernant sa santé.

Le professionnel possède donc un pouvoir immense d'où l'importance qu'il garde l'intérêt du patient comme objectif premier en toute circonstance.

Cependant, ce principe peut être remis en cause par l'apparition de conflit d'intérêts. Il est donc essentiel de lutter contre ce risque qui apparait à chaque interaction entre l'industrie et les professionnels de santé.

Mais l'interdiction de ces interactions n'est pas une solution applicable pour résoudre les problèmes de conflit d'intérêt. Des mesures claires doivent donc être mises en œuvre et respectées.

De nombreuses mesures ont été prises au cours des vingt dernières années pour encadrer les interactions entre l'industrie et les professionnels de santé. Des lois et des codes ont été publiés à la fois par les autorités régulatrices et par les industries elles-mêmes. Mais il n'existe pas de réelle harmonisation entre les différentes autorités à travers le monde à ce sujet et les compagnies peuvent donc s'adapter différemment. Il en résulte une disparité d'action entre les firmes.

De plus, la frontière entre l'éducation médicale et la promotion d'un médicament reste mince et certaines interactions peuvent parfois prêter à confusion. L'implication d'organismes indépendants pour ce type d'événement, financés en partie par les compagnies, permettrait de s'assurer d'une objectivité renforcée vis-à-vis de chaque produit. Cela est déjà développé aux États-Unis et mériterait d'être plus appliqué en Europe.

La littérature et les textes de lois placent la transparence vis-à-vis des avantages reçus par les médecins comme l'une des principales mesures de lutte contre les conflits d'intérêt.

La transparence vis-à-vis des intérêts d'un professionnel de santé est un élément clé pour l'information du public et des autres professionnels de santé. Cela permet de savoir qui est l'émetteur de l'information et permet aussi à celui qui la reçoit de la situer dans son contexte. En revanche cette transparence des liens d'intérêt ne prévient pas la modification de l'opinion du professionnel au sujet de l'information traité.

Aujourd'hui, la lutte contre les conflits d'intérêts est un enjeu majeur dans le domaine pharmaceutique et on observe un renforcement, en particulier en France, des lois de prévention des conflits d'intérêt. Mais la législation évoluant vers des règles éthiques plus contraignantes, on observe une tendance des laboratoires à initier eux-mêmes une évolution de leurs pratiques concernant leurs interactions avec les professionnels de santé.

Ainsi, les autorités se penchent de plus en plus sur le problème des conflits d'intérêts dans l'industrie pharmaceutique et les laboratoires n'ont plus les mêmes droits qu'il y a dix ans. Les règles ne cessent d'évoluer dans l'optique d'une meilleure prévention de ces conflits. Mais le risque existera toujours et la vigilance est de rigueur dans l'application des lois et dans le contrôle de leur application.

Enfin, cette lutte contre les conflits d'intérêt ne doit pas venir seulement des autorités et des compagnies pharmaceutiques. Elle doit aussi reposer sur l'éthique individuelle de chaque professionnel de santé. Pour cela, chacun doit être en mesure d'identifier un potentiel conflit d'intérêt ou être capable d'opposer un jugement critique aux informations qui lui sont données. On pourrait suggérer une sensibilisation des professionnels de santé aux risques de conflits d'intérêt au cours de leur formation afin de renforcer leur sens critique vis-à-vis des informations qu'ils reçoivent.

(*) THESE SOUTENUE PAR : Sarah COHEN

(*) TITRE :

**LES INTERACTIONS ENTRE L'INDUSTRIE PHARMACEUTIQUE ET LES
PROFESSIONNELS DE SANTE : UN CHALLENGE PERMANENT**

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(*) VU ET PERMIS D'IMPRIMER

(*) Grenoble, le 20 Décembre 2012

(*) LE DOYEN

(*) LE PRESIDENT DE LA THESE



A handwritten signature is written above the printed text. The printed text reads: "UFR Pharmacie", "Département Mécanismes Biologiques", "des Maladies et Traitements", "Université Joseph Fourier", "Grenoble".

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PROFESSEURS DES UNIVERSITES-PRATICIEN HOSPITALIER (n=6)

CALOP	Jean	Pharmacie Clinique (TIMC-IMAG, PU-PH)
CORNET	Murielle	Parasitologie – Mycologie Médicale (LAPM, PU-PH)
DANEL	Vincent	Toxicologie (SMUR SAMU / PU-PH)
FAURE	Patrice	Biochimie (HP2/PU-PH)
MOSSUZ	Pascal	Hématologie (PU-PH-THEREX-TIMC)
SEVE	Michel	Biochimie – Biotechnologie (IAB, PU-PH)

PROFESSEUR EMERITE (n=1)

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MAITRES DE CONFERENCES DES UNIVERSITES (n=31)

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BRIANCON-MARJOLLET	Anne	Physiologie Pharmacologie (HP2)
BUDAYOVA SPANO	Monika	Biophysique (I.B.S)
CAVAILLES	Pierre	Biologie Cellulaire et génétique (L.A.P.M)
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GEZE	Annabelle	Pharmacotechnie (D.P.M)
GILLY	Catherine	Chimie Thérapeutique (D.P.M)
GROSSET	Catherine	Chimie Analytique (D.P.M)
GUIEU	Valérie	Chimie Analytique (D.P.M)
HININGER-FAVIER	Isabelle	Biochimie (L.B.F.A)
JOYEUX-FAURE	Marie	Physiologie - Pharmacologie (HP2)
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KRIVOBOK	Serge	Biologie Végétale et Botanique (L.C.B.M)
MOUHAMADOU	Bello	Cryptogamie, Mycologie Générale (L.E.C.A)
MORAND	Jean-Marc	Chimie Thérapeutique (D.P.M)
MELO DE LIMA	Christelle	Biostatistiques (L.E.C.A)
NICOLLE	Edwige	Chimie Thérapeutique (D.P.M)
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PEUCHMAUR	Marine	Chimie Organique (D.P.M.)
RACHIDI	Walid	Biochimie (L.C.I.B)
RAVEL	Anne	Chimie Analytique (D.P.M)
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SOUARD	Florence	Pharmacognosie (D.P.M)
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MAITRE DE CONFERENCE DES UNIVERSITES-PRATICIEN HOSPITALIER (n=3)

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PROFESSEUR CERTIFIE (PRCE) (n=2)

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PROFESSEURS ASSOCIES (PAST) (n=4)

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PROFESSEUR AGREGE (PRAG) (n=1)

GAUCHARD	Pierre-Alexis	(D.P.M)
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VAN NOOLEN	Laetitia	Biochimie Toxicologie (HP2-DBTP-BGM)

ATER (n= 6)

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FAVIER Mathieu	ATER	Pharmacologie - Laboratoire HP2 (JR)
HADDAD-AMAMOU Anis	ATER	Laboratoire de Pharmacie Galénique
HENRI Marion	ATER	Physiologie – Laboratoire HP2 (JR)
LEHMANN Sylvia	ATER	Biochimie Biotechnologie (JR)
REGENT-KLOEKNER Myriam	ATER	Biochimie (LECA-UJF)

MONITEUR ET DOCTORANTS CONTRACTUELS (n=9)

CAVAREC	Fanny	(01-10-2011 au 30-09-2014)	Laboratoire HP2 (JR)
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BERTHOIN	Lionel	(01-10-2012 au 30-09-2015) (TIMC-IMAG-THEREX)	Laboratoire
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CHU : Centre Hospitalier Universitaire
CIB : Centre d'Innovation en Biologie
DPM : Département de Pharmacochimie Moléculaire
HP2 : Hypoxie Physiopathologie Respiratoire et Cardiovasculaire
IAB : Institut Albert Bonniot, Centre de Recherche « Oncogenèse et Ontogenèse »
IBS : Institut de Biologie Structurale
LAPM : Laboratoire Adaptation et Pathogenèse des Microorganismes
LBFA : Laboratoire Bioénergétique Fondamentale et Appliquée
LCBM : Laboratoire Chimie et Biologie des Métaux
LCIB : Laboratoire de Chimie Inorganique et Biologie
LECA : Laboratoire d'Ecologie Alpine
LR : Laboratoire des Radio pharmaceutiques
TIMC-IMAG : Laboratoire Technique de l'Imagerie, de la Modélisation et de Cognition
UVHCI : Unit of Virus Host Cell Interactions

Faculté de Pharmacie de Grenoble



Serment des Apothicaires

Je jure, en présence des maîtres de la faculté, des conseillers de l'ordre des pharmaciens et de mes condisciples :

D'honorer ceux qui m'ont instruit dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.

D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.

De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine ; en aucun cas je ne consentirai à utiliser mes connaissances et mon état pour corrompre les mœurs et favoriser des actes criminels.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobres et méprisé de mes confrères si j'y manque.

