



HAL
open science

Challenges of mature drugs in the pharmaceutical industry: issues of multichannel strategies

Blandine Lasbax

► **To cite this version:**

Blandine Lasbax. Challenges of mature drugs in the pharmaceutical industry: issues of multichannel strategies. Pharmaceutical sciences. 2012. dumas-01435258

HAL Id: dumas-01435258

<https://dumas.ccsd.cnrs.fr/dumas-01435258>

Submitted on 13 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance et mis à disposition de l'ensemble de la communauté universitaire élargie.

Il n'a pas été réévalué depuis la date de soutenance.

Il est soumis à la propriété intellectuelle de l'auteur. Ceci implique une obligation de citation et de référencement lors de l'utilisation de ce document.

D'autre part, toute contrefaçon, plagiat, reproduction illicite encourt une poursuite pénale.

Contact au SID de Grenoble :
bump-theses@univ-grenoble-alpes.fr

LIENS

Code de la Propriété Intellectuelle. articles L 122. 4

Code de la Propriété Intellectuelle. articles L 335.2- L 335.10

<http://www.cfcopies.com/juridique/droit-auteur>

<http://www.culture.gouv.fr/culture/infos-pratiques/droits/protection.htm>



**UNIVERSITE JOSEPH FOURIER
FACULTE DE PHARMACIE DE GRENOBLE**

Année 2012

**CHALLENGES OF MATURE DRUGS IN THE
PHARMACEUTICAL INDUSTRY: ISSUES OF
MULTICHANNEL STRATEGIES**

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

DIPLÔME D'ETAT

Blandine LASBAX

[Données à caractère personnel]

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE PHARMACIE
DE GRENOBLE*

LE : 11 Décembre 2012

DEVANT LE JURY COMPOSE DE

Président du jury : M. Michel SEVE, docteur en Pharmacie, PU-PH à Grenoble

Membres : M. Jean Breton, docteur en Pharmacie, MCU à l'Université Joseph Fourier,
Grenoble

M^{me} Ingrid Collomb-Clerc, PhD en biologie structurale

Sous la direction de : M^{me} Isabelle CHALAMON, PhD en Sciences de Gestion

**La Faculté de Pharmacie de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.*

REMERCIEMENTS

Je tiens tout d'abord à remercier Madame Isabelle Chalamon pour ses conseils sur le choix du thème de cette thèse ainsi que pour ses relectures et ses précieuses informations tout le long de la conception de ce travail.

Je remercie Monsieur Michel Sève, professeur à l'UFR de Pharmacie de Grenoble, d'avoir accepté de présider mon jury. Celui-ci a toujours été présent et m'a encadrée et soutenue durant mes études de Pharmacie. Je tiens aussi à remercier les deux membres de mon jury : Monsieur Jean Breton et Madame Ingrid Collomb-Clerc. Merci d'avoir accepté de siéger dans mon jury.

Je voudrais aussi remercier mes deux maîtres de stage qui m'ont encadré durant mon année passée chez AstraZeneca[®] : Emilie Lavenant et Anne-Charlotte Maury-Bigonnet, toutes les deux pharmaciennes de formation. Celles-ci m'ont permis d'en apprendre beaucoup sur le milieu de l'industrie pharmaceutique et le métier de chef de produit. Leurs précieux conseils m'ont donc été d'une grande utilité lors de la rédaction de ce document.

Je remercie enfin mes parents et ma sœur pour leur soutien infini depuis toujours. Cette thèse marque l'aboutissement d'une formation universitaire qui n'a été possible que grâce à leurs encouragements et leur soutien indéfectible.

INTRODUCTION	7
FRENCH SUMMARY	10
PART 1: MATURE DRUGS IN THE PHARMACEUTICAL INDUSTRY: DEFINITION, CURRENT ISSUES AND IMPLEMENTED SOLUTIONS.....	17
1. Drug life cycle and definition of the maturity of a product	17
1.1- Mature product or “Cornerstone”: definition, turnovers and examples.....	17
1.2- Life cycle of products: concept, model and considerations	19
1.2.1- General products life cycle: definition, features and key considerations for successful life cycle management.....	19
1.2.2- Application of product life cycle to the pharmaceutical industry.....	22
1.3- Market limitations and specificities regarding pharmaceutical products: ways of improvement of life cycle for mature drugs.....	24
2. Characterization of drug maturity: what are the current issues facing the pharmaceutical industry?.....	27
2.1- Breathlessness of the pharmaceutical Research & Development due to a tightening of the legislation by the regulatory authorities.....	27
2.1.1- Decrease of the pharmaceutical R&D productivity.....	27
2.1.2- Increase of the Research and Development costs: reasons and strategies.....	29
2.1.3- Increase of the development time frames.....	31
2.1.4- Formerly crowded pipelines become limited and uncertain.....	33
2.2- Strict regulatory framework of drug promotion in France and restrictive changes in 2012	35
2.2.1- Generalities.....	35
2.2.2- Regulatory framework of advertising regarding the types of drug	36
2.2.3- Changes in 2012: a new decree for drug promotion	39
2.2.4- Sales call: definition, numbers and the charter.....	39
2.3- The current patent cliff and the growing pressure of generics and biosimilars	42
2.3.1- A period of massive loss of patents	42
2.3.2- The threat of generics and biosimilars	43
2.3.3- Blockbuster model no longer valid.....	45
2.3.4- Same therapeutic class but a different drug: the increasing number of me-toos	46
2.4- Interesting prices and high level of reimbursement more difficult to obtain	47
2.5- Increase and hardening of investors expectations.....	49
3. Solutions implemented by the pharmaceutical industry to counter these issues...51	51
3.1- Strategic measures realized by the pharmaceutical industry from a product and company point of view.....	51
3.1.1- Product differentiation to counter threat from generic and biosimilar	51
3.1.2- Strategic Mergers and Acquisitions to diversify pipelines.....	56
3.1.3- Alliances and partnerships to share the risks	57
3.1.4- Development of personalized medicine and current progresses	58
3.1.5- Niche indications.....	59
3.1.6- Creation of innovative business models	61
3.2- Changes and improvements in drug promotion.....	62
3.2.1- Communication and promotion: what differences?.....	62
3.2.2- Two types of recipients: healthcare practitioners and patients.....	65
3.3.3- Apparition of new channels of communication: e-detailing, e-learning and partnerships with association of patients	69
3.3.4- Multichannel strategies: prescriber targeting, determination of the favorite channel and advantages of these methods.....	71
3.3.5- Creation of Customer Relationship Management (CRM).....	72
4. Conclusion of the first part	73

PART 2: MULTICHANNEL OPERATION FOR THE PROMOTION OF A MATURE DRUG FROM ASTRAZENECA®: EMLAPATCH 5%®	75
1. Context of the company, presentation of the product and of the Key Performance Indicators	75
1.1- AstraZeneca®: context and issues.....	75
1.2- The product: Emlapatch 5%®: indications, volume of prescriptions, turnovers and targeted physicians	78
1.3- Methodology and presentation of Key Performance Indicators	79
2. Implementation of the multichannel strategy during 2012.....	82
2.1- Overview: a global strategy characterized by a specific program	82
2.2- Targeted operations to specific physicians	85
2.2.1- Phone campaign.....	85
2.2.2- E-mailing.....	86
2.2.3- Mailing and direct marketing directed to physicians.....	87
2.2.4- Face-to-face visit.....	89
2.2.5- Internet campaign realized on specialized websites dedicated to healthcare professionals	90
2.3- Campaign for pharmacists	91
2.4- Campaign on the Internet targeting the patients.....	91
2.5- Some examples of promotional documents with added value to physicians of the « Môme Pas Mal ! » campaign	93
3. Evolution and monitoring of the campaign in real-time: results of re-call test and reporting	94
3.1- Results of quantitative and qualitative KPI in Physicians	94
3.1.1- Phone operation	94
3.1.2- E-mailing/Internet	97
3.1.3- Mailing or direct marketing.....	97
3.1.4- Face-to-face visit.....	98
3.2- Results of quantitative and qualitative KPI in patients	101
3.3- Results of quantitative and qualitative KPI in pharmacists	101
4. Results and conclusion of the campaign: sales volume, turnover and return on investment realized	102
 CONCLUSION	 104
 BIBLIOGRAPHY	 108
 APPENDICES.....	 110

FIGURES, TABLES AND GRAPHS

Figure 1: Product Life Cycle curve showing the five different stages.....	p19
Figure 2: Some LCM strategies to maximize return on investment for pharmaceutical products.....	p25
Figure 3: The “quick win, fast fail” drug development paradigm compared to the traditional method.....	p30
Figure 4: The current development process including the different lengths and number of compounds.....	p32
Figure 5: Generic drug market forecast from 2006 to 2020.....	p43
Figure 6: Packaging of Emlapatch 5%®.....	p79
Figure 7: Logo of the “Même Pas Mal !” program.....	p83
Figure 8: General scheme of the “Même Pas Mal !” program progressing during the year 2012.....	p84
Figure 9: Main feedbacks words acquired during the first phone call.....	p96
Table 1: Features identified regarding the different stages of the product life cycle.....	p21
Table 2: Projected top 5 Oncology products worldwide in 2016.....	p34
Table 3: Type of authorized advertising regarding the kind of people targeted in France.....	p36
Table 4: Main differences between a generic drug and a biosimilar.....	p45
Table 5: Various differentiation strategies and suitability indicators for their implementation.....	p54
Table 6: Rank of DTC spending regarding the product, the therapeutic area, the manufacturer and the launch date in 2010; in black bold, the new products on the list.....	p68
Table 7: Growth comparison between AstraZeneca® and the pharmaceutical industry in general, from August 2011 to July 2012.....	p77
Table 8: Summary of the different KPI used to characterize the multichannel campaign.....	p80
Table 9: Composition of the sample of questioned physicians for the first recall test.....	p81
Table 10: Indicators obtained through regular reports coming from the agency.....	p82
Table 11: Quantitative KPI regarding the first and second phone calls.....	p95
Table 12: Quantitative KPI regarding the emailing campaigns.....	p97
Table 13: Quantitative KPI for direct marketing operations.....	p98
Table 14: Quantitative KPI regarding the face-to-face visit.....	p99
Table 15: Qualitative KPI about face-to-face visits with physicians of services assistants.....	p100
Graph 1: Average success rate and distribution of R&D projects according to the characteristics of the disease targeted, size of organization and research methodology.....	p28
Graph 2: Number of sales reps in the French pharmaceutical industry regarding the year.....	p40
Graph 3: Percentage of investors that could invest in each type of healthcare company in 2012.....	p49
Graph 4: European and US investor’s expectations for R&D spend as percentage of revenues among pharmaceutical companies in 2012.....	p50
Graph 5: Trend of US FDA approval rate of new dosage forms compared to new molecular entities from 1999 to 2008.....	p52
Graph 6: Trend of US FDA approval rate of fixed drug combination and new molecular entities.....	p53
Graph 7: Trend of US FDA approval rate of new indications and new molecular entities.....	p54
Graph 8: Pharmaceutical promotional spending in the world depending on the year.....	p64
Graph 9: Pharmaceutical DTC spending in the world depending on the year.....	p67

ABBREVIATIONS

LCM: Life Cycle Management
PLC: Product Life Cycle
4P's: Product, Promotion, Place, Price
ROI: Return On Investment
OTC: Over The Counter
R&D: Research & Development
POS: Proof Of Success
NME: New Molecular Entity
POC: Proof Of Concept
EMA: European Medicine Agency
FDA: Food and Drug Administration
CNS: Central Nervous System
ANSM: Agence Nationale de Sécurité du Médicament
AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé
DTC: Direct To Consumer
INN: International Nonproprietary Name
LEEM: Les Entreprises du Médicament
GPs: General Practitioners
HAS: Haute Autorité de Santé
PPI: Proton-Pump Inhibitor
HBP: High Blood Pressure
P&R: Pricing and Reimbursement
CEPS: Comité Economique des Produits de Santé
ASMR: Amélioration du Service Médical Rendu
CEO: Chief Executive Officer
M&A: Mergers & Acquisitions
CRM: Customer Relationship Management
DTP: Direct To Patient
COPD: Chronic Obstructive Pulmonary Disease
KPI: Key Performance Indicators
VAS: Visual Analog Scale
INPES: Institut National de Prévention et d'Education pour la Santé
BEH: Bulletin Epidémiologique Hebdomadaire

INTRODUCTION

L'industrie pharmaceutique traverse actuellement de nombreuses incertitudes en rapport notamment avec sa baisse de productivité. La diminution de la R&D pharmaceutique est essentiellement due à une augmentation des ses coûts ainsi qu'à une augmentation des temps de développement. En effet, le coût de développement moyen d'un médicament est aujourd'hui évalué à 1 milliard d'euros^[1] (+60% depuis 2005^[1]). De plus, depuis les années 2000, le temps de développement pour un médicament est passé d'environ 13.9 ans, contre 9.7 ans dans les années 1990^[1]. Les pipelines des grosses entreprises pharmaceutiques sont donc de moins en moins fournis ce qui conduit ces entreprises à des pertes de bénéfices qui ne peuvent plus être comblées grâce aux médicaments blockbusters (médicaments générant plus d'un milliard de dollars de bénéfices).

Les médicaments blockbuster laissent en effet, petit à petit, place au marché des indications niches et de la médecine personnalisée. Ainsi, l'industrie pharmaceutique doit tirer un trait sur les bénéfices venant de ces produits et qui lui permettait jusqu'à présent de financer une partie de sa R&D. En effet, l'industrie pharmaceutique a investi en 2011, 27 milliards d'euros en R&D^[1]. Cela correspond à une augmentation de 6.2% entre 2010 et 2011^[1], principalement due au passage aux biotechnologies. De plus, ce chiffre représente le réinvestissement de 15.9% du chiffre d'affaire de l'industrie pharmaceutique européenne dans la R&D^[1]. Cependant, cette évolution n'est toujours pas suffisante pour palier le manque à gagner induit par les pertes de brevets massives se produisant actuellement.

Enfin, les médicaments obtenant des Autorisations de Mise sur le Marché sont généralement soit peu innovants, soit des me-toos. En effet, il y a actuellement seulement 10 molécules innovantes en phase III dans les pipelines des entreprises pharmaceutiques et biotechnologiques^[1]. Ainsi, il y a donc une réelle nécessité de développer de nouvelles stratégies qui permettraient aux industries de dégager des bénéfices, afin d'investir plus amplement dans la recherche et donc de diversifier leurs pipelines.

Durant mon stage de six mois chez AstraZeneca[©] (Rueil-Malmaison, France) en tant qu'assistant chef de produit, j'ai participé à la mise en place et l'expérimentation de nouvelles voies de communication sur les médicaments matures de l'entreprise. Les médicaments matures s'opposent aux médicaments lancés récemment. Cela veut dire que ces médicaments sont commercialisés depuis une longue période et entament leur phase de décroissance des ventes^[2]. Généralement, ils ont encore au moins l'un de leurs dosages ou l'une de leurs formes galéniques protégés par un brevet. Cependant, ils ne sont plus présentés par le canal principal de promotion de l'industrie pharmaceutique : la visite médicale. Au sein d'AstraZeneca[©], ces produits sont aussi appelés « Cornerstone ». Trois principaux leviers sont actuellement à l'essai chez AstraZeneca[©] : des leviers commerciaux (comprennent essentiellement les stratégies de promotion des produits...), de développement (changement de packaging...) et concernant les produits eux-mêmes (externalisation de la promotion...). Le but de ces stratégies est de relancer la croissance de ces produits matures afin de diminuer la perte de profits induite par la perte de brevet d'une des principales formes du médicament.

Différentes opérations sont donc en cours chez AstraZeneca[©] sur de nombreux produits matures, tels que : Zomig[®], la gamme Atacand/Hytacand[®], Emlapatch[®], Rhinocort[®]... Pour certains produits, ces stratégies sont mixtes et sont basées sur l'utilisation des nouveaux canaux de communication : majoritairement Internet (pour des raisons financières) ainsi que le téléphone, en complément de canaux mieux connus et maîtrisés : la visite face-face ou les marketing directs. De plus, la finalité de ces stratégies est moins basée sur la promotion d'un produit mais plutôt sur la proposition et la présentation de documents à forte valeur ajoutée pour les médecins, appelés services. Ces services peuvent prendre différents formats (principalement papier et digital) et peuvent être distribués par courrier ou grâce à des personnes préalablement formées appelées « attachés de services ». En effet, en parallèle de la visite médicale traditionnelle, un nouveau type de visite est actuellement à l'essai chez AstraZeneca[©]. Différemment des visiteurs médicaux, le but des attachés de services est de transmettre de l'information sur la maladie et son environnement, plutôt que seulement sur le produit.

L'opération la plus intéressante et la plus innovante actuellement en cours chez AstraZeneca[©] est l'opération multicanal se rapportant au produit Emlapatch 5%[®]. Cette campagne consiste à contacter des médecins, définis et ciblés grâce à la spécialité qu'ils exercent ou la patientèle qu'ils voient, grâce à des canaux de communication différents. La

limite d'un contact par mois a été fixée afin d'ancrer cette campagne dans la tête de médecin sans pour autant les solliciter trop souvent. De plus, cette campagne a aussi ciblé les pharmaciens et le grand public. Cette stratégie 360° a été mise en place afin d'augmenter la prise de conscience d'Emlapatch 5%® des différents acteurs impliqués dans la santé. En parallèle, cette stratégie voulait aussi permettre de sensibiliser le grand public à l'environnement autour du produit : prise de sang, vaccins, petits actes chirurgicaux... Cette stratégie multicanal a finalement été évaluée grâce à des indicateurs aussi bien qualitatifs que quantitatifs, chez les trois différentes populations ciblées afin de déterminer son retour sur investissements.

Ce document sera donc découpé en trois grandes parties. La première partie resituera le contexte actuel de l'industrie pharmaceutique avec tout d'abord, la définition d'un médicament mature grâce à l'introduction de la notion générale de cycle de vie d'un produit (ensuite appliquée spécifiquement aux médicaments). Dans un second temps, j'expliquerai les raisons qui conduisent à la maturité des médicaments et ce qui caractérise ces produits. Enfin, j'expliquerai les solutions actuellement développées par l'industrie pharmaceutique pour palier à ces différents problèmes. Dans une seconde partie, j'illustrerai l'une de ces solutions en expliquant la stratégie marketing d'un des produits matures d'AstraZeneca® (Emlapatch 5%®). Enfin, je conclurai par une dernière partie discutant de l'ambivalence et des incertitudes touchant l'industrie pharmaceutique.

FRENCH SUMMARY

L'augmentation de l'espérance de vie de la population mondiale est en partie due à la découverte et l'introduction de nouvelles molécules dans des pathologies chroniques et lourdes, comme notamment les infarctus du myocarde ou les cancers. Cependant, il est de plus en plus difficile, pour les entreprises pharmaceutiques, d'innover en matière de recherche et de développement. En effet, l'industrie pharmaceutique se retrouve actuellement face à de nombreuses problématiques, qui entraînent une diminution de son chiffre d'affaire.

Tout d'abord, le manque d'innovation en matière de recherche et développement entraîne une diminution du nombre de nouvelles molécules commercialisées. Ainsi, de plus en plus de médicaments sont désormais considérés comme matures (i.e. commercialisés depuis de nombreuses années). C'est-à-dire que ces produits ont au moins une de leurs formulations ou dosages déjà tombés dans le domaine public. Ainsi, suite à l'apparition de génériques, les chiffres d'affaire de ces molécules diminuent énormément ce qui constitue un énorme manque à gagner pour l'industrie pharmaceutique.

Le cycle de vie des médicaments est différent de celui des autres produits. En effet, les médicaments doivent être validés par le biais d'essais cliniques afin de prouver leur efficacité, leur innocuité et surtout, leur sécurité. Le bénéficiaire final étant le patient, la sécurité est l'un des paramètres les plus importants à déterminer. Pour les médicaments, la courbe illustrant le cycle de vie est composée de cinq étapes : développement, introduction, croissance, maturité et enfin la phase de déclin. Ces phases ont des durées qui peuvent être très variables dépendamment des médicaments.

Ensuite, le marché des produits pharmaceutiques possède certaines spécificités qui doivent être explorées pour rester compétitif. En effet, les chercheurs de l'industrie pharmaceutique doivent tout d'abord trouver les moyens (à la fois scientifiques et techniques) pour transformer leurs idées en nouveau médicament. De plus, plus le médicament découvert est innovant, plus il pourra être compétitif sur son marché. Cependant, il y a un décalage en terme de besoins et de ressources car l'industrie pharmaceutique préfère généralement se spécialiser dans des aires thérapeutiques à fortes parts de marché, souvent considérées

comme plus profitables. Mais la rapide perte de brevets dans ce milieu devient une vraie limite. C'est pourquoi, des stratégies de management du cycle de vie des médicaments matures sont actuellement à l'essai. Le développement de ces stratégies est une preuve de la forte capacité d'adaptation de cette industrie.

Plus précisément, la maturité d'un médicament peut être définie par les différentes problématiques actuellement rencontrées par l'industrie pharmaceutique. En effet, il y a actuellement un essoufflement de la recherche et du développement dans cette industrie. Cet essoufflement a plusieurs causes. Tout d'abord, une diminution de la productivité de la recherche et du développement se fait actuellement ressentir. La productivité est définie par la relation entre la valeur (médicale et commerciale) créée par un nouveau médicament et les investissements qui ont été nécessaires pour générer ce médicament. Ainsi, l'innovation est devenue clé pour le développement de médicaments à forte valeur médicale ajoutée. C'est pourquoi, relancer la productivité est un des principaux challenges de l'industrie pharmaceutique. Ensuite, l'augmentation des coûts de la recherche et du développement est une autre cause menant à la future maturité de nombreux produits. En effet, le passage des médicaments purement chimiques aux médicaments biotechnologiques a entraîné le besoin de développer des technologies de recherche, développement et production de plus en plus pointues, et donc, coûteuses. De plus, les agences réglementaires en santé demandent de plus en plus d'informations relatives à la future mise sur le marché de produits (des études cliniques de plus en plus complètes avec de nombreuses preuves d'efficacité et de tolérance) ce qui provoque une augmentation des coûts ainsi que des durées de développement. Effectivement, depuis l'affaire Médiator[®], les instances réglementaires sont de plus en plus restrictives et regardantes quant aux essais cliniques réalisés. Ainsi, dans les années 2000, la durée de développement moyenne, depuis l'obtention du brevet jusqu'à la commercialisation du médicament, était d'environ 13,9 ans (par rapport à 9,7 ans dans les années 1990). Ceci représente un énorme manque à gagner et une diminution des chiffres d'affaire pour l'industrie pharmaceutique. Toutes ces raisons mènent à des pipelines plus limités et incertains.

D'un point de vue de la promotion du médicament en France, l'Agence Nationale de Sécurité du Médicament a aussi durci ses conditions. En effet, avant mai 2012, il était possible pour les laboratoires de réaliser des documents promotionnels mentionnant le produit assez facilement. Ces documents étaient déposés à posteriori à l'ANSM pour

relecture. En cas de désaccord de l'ANSM avec le document ou une référence, le laboratoire, après avoir été mis au courant, devait retirer tous les documents promotionnels non conformes sous un délai d'un mois. Cependant, une nouvelle loi parue en décembre 2011 sur la promotion des médicaments a entraîné un changement de ce fonctionnement. Le décret d'application de cette loi, paru en mai 2012, stipule que tous les documents promotionnels (portant un nom de médicament) à l'attention des professionnels de santé et du grand public doivent désormais être déposés à priori à l'ANSM. Pour ce faire, des périodes de dépôts des documents promotionnels ont été déterminées par l'ANSM (deux périodes en 2012 : mai/juin et septembre/octobre). Ces périodes sont de durées variables : de deux semaines à deux mois. Durant ces périodes, les laboratoires doivent transmettre à l'ANSM tous leurs documents nécessitant un accord de diffusion. L'ANSM se réserve ensuite deux mois (à partir de la fin de la période définie) pour donner son accord ou son désaccord sur le document. Après deux mois, toute absence de réponse correspond à un accord tacite. Cette nouvelle loi a donc des répercussions sur les campagnes de promotion actuelles. En effet, un taux global de 32% de refus a été obtenu après la première période de dépôts (*source : LEEM*). L'anticipation et l'adaptation sont donc devenues primordiales.

De plus, dans cette période de diminution des dépenses, la visite médicale n'est pas épargnée. Celle-ci constitue le premier moyen de promotion des médicaments en France. Cependant, une diminution constante du nombre de visiteurs médicaux est en cours depuis 2005. En effet, le rapport bénéfice/dépenses est désormais en leur défaveur c'est pourquoi leur nombre ne cesse de diminuer. L'industrie pharmaceutique est donc en recherche active de nouveaux moyens de promotion des médicaments moins chers, tout en restant efficaces.

La principale caractéristique des produits matures est leur perte de brevet très proche. Ainsi, l'industrie pharmaceutique se retrouve actuellement devant une perte de brevets massive, généralement sur des médicaments avec des chiffres d'affaire élevés. En effet, au jour même de la perte du brevet, de nombreux génériques moins coûteux sont disponibles et entrent donc en directe compétition avec la spécialité princeps. De plus, le modèle du médicament blockbuster (plus d'un milliard de dollars de bénéfices) n'est plus valide. En effet, il y a actuellement un regain d'intérêt pour les marchés niches et la médecine personnalisée. Le but final des industriels du médicament et de la médecine serait d'avoir un médicament pour chaque type de patients (ou un médicament par patient). Ceci permettrait de diminuer les effets indésirables et d'augmenter la sécurité d'utilisation et l'efficacité. C'est

pourquoi une partie des médicaments en cours de développement est plus spécifique et cible une population moins grande que, par exemple, le fameux Tahor[®] (*atorvastatine*) de Pfizer[®]. L'autre partie correspond principalement à des me-toos. Il s'agit de médicaments appartenant à une même classe thérapeutique que d'autres médicaments déjà commercialisés. Ils s'incluent donc dans un marché rempli de compétiteurs et ils sont donc difficiles à différencier de leurs concurrents. Les chiffres d'affaire de ces produits sont donc inférieurs à un médicament first-in-class, mais ils restent profitables à l'industrie pharmaceutique. Ainsi, un des grands enjeux pour l'industrie pharmaceutique serait de trouver des stratégies afin de réussir à diminuer la perte de profit induite par l'apparition des génériques.

Ensuite, les conditions de remboursement sont, elles aussi, de plus en plus difficiles. Les autorités de santé et des instances comme la Sécurité Sociale, demandent des Amélioration de Service Médical Rendu (ASMR) de plus en plus élevées afin d'obtenir un bon remboursement. Le prix d'un médicament est, pour les médicaments disponibles en ville, fixé par le Comité Economique des Produits de Santé (CEPS). Celui-ci se base sur quatre critères différents afin de déterminer le prix d'un médicament. Tout d'abord, l'ASMR est le principal critère : un médicament avec un faible ASMR (niveau V) obtiendra plus difficilement un taux élevé de remboursement et un prix élevé par rapport à un médicament avec un ASMR III, par exemple. Ensuite, le CEPS étudie les prix des autres médicaments de la même aire thérapeutique afin de ne pas créer de déséquilibre. Enfin, sont aussi pris en compte, le volume de ventes espéré ainsi que l'utilisation du médicament par les médecins. Tous ces facteurs entraînent de nombreuses pistes d'incertitudes pour les laboratoires.

Enfin, les investisseurs jouent, eux aussi, un rôle. En effet, ils sont considérés comme les décisionnaires des opérations importantes (comme ceux sont eux qui financent la plupart des opérations). Cependant, leurs attentes grandissent quand au retour sur investissement qu'ils veulent obtenir. Ainsi, les investisseurs préfèrent investir dans certains profils d'entreprise. Par exemple, une entreprise peu diversifiée, avec un pipeline restreint à une seule (voire deux) aire thérapeutique.

Devant toutes ces problématiques touchant des domaines variés (aussi bien la R&D, que la promotion, que la commercialisation en elle-même,...), l'industrie pharmaceutique est actuellement en train d'implémenter des solutions. En effet, il y a un réel besoin d'adaptation de la part de l'industrie pharmaceutique. C'est pourquoi, le but actuel est de développer des

solutions qui lui permettraient de diminuer la perte de profit. Deux types généraux de solutions sont à l'essai : des solutions orientées médicament et entreprise et des solutions marketing.

Premièrement, l'amélioration du cycle de vie du médicament est différente pour un médicament chimique et un médicament biotechnologique. La différenciation d'un médicament semble efficace pour contrer l'arrivée des génériques (ou des biosimilaires). Les trois principales stratégies pour un produit chimique consistent en : la création de nouvelles formulations, l'expérimentation d'associations fixes de deux médicaments ou encore la recherche de nouvelles indications. Ces trois stratégies ont prouvé leur efficacité car elles permettent des extensions de brevets (ou la création d'un nouveau brevet, pour une nouvelle formulation notamment). Ensuite, pour les médicaments biologiques, les stratégies sont un peu différentes. Il s'agit de la création de nouveaux systèmes de délivrance (car la majorité des médicaments biologiques est administrée par injection), la recherche de nouvelles indications et la création d'associations de molécules.

Ensuite, d'autres stratégies moins communes existent. Par exemple, certains laboratoires investissent dans le générique de leur propre princeps à la tombée du brevet. Cela leur permet de maintenir leurs ventes, et donc, évite une trop forte diminution du chiffre d'affaire. Une autre idée consiste à maximiser la fidélité des patients pour ce médicament (exemple de Zomig[®], *zolmitriptan*). Ensuite, certains laboratoires jouent sur un réalignement des prix de leur spécialité après la perte de brevet. En effet, une diminution du prix, permettant de concurrencer celle des génériques, permet de diminuer l'impact de l'arrivée de ceux-ci. Certains médicaments de classes thérapeutiques maintenant bien connues (notamment les inhibiteurs de la pompe à protons) deviennent médicament OTC (à la place d'éthique). Cela permet à l'industrie pharmaceutique de fixer elle même le prix de sa spécialité. Enfin, certains laboratoires expérimentent la cession de droits d'une spécialité, à un laboratoire de génériques par exemple, juste avant la fin du brevet.

D'un point de vue de l'entreprise, la principale stratégie consiste en la réalisation de Mergers and Acquisitions (M&A – fusions acquisitions), permettant de diversifier le pipeline d'une entreprise. Cela permet une consolidation de deux entreprises en une seule. Généralement, les acteurs majeurs sont les grandes entreprises pharmaceutiques, fusionnant avec de plus petites, qui détiennent le savoir-faire et la recherche. Ensuite, de nombreux

alliances et partenariats voient le jour. Ils peuvent prendre différentes formes : une grande entreprise peut devenir partenaire d'une petite qui cherche à se développer ou deux grandes entreprises peuvent s'allier pour, par exemple, la promotion d'un médicament. Ce système permet, entre autres, de créer de la valeur grâce à la promotion de l'innovation, de partager les risques ainsi que de réduire les dépenses. Après, la médecine personnalisée ou la recherche de médicaments pour des indications niches sont en pleine expansion. En effet, les autorités de santé sont très demandeuses de ce genre de médicaments, qui représentent un tournant à prendre dans les années à venir. Enfin, certaines entreprises diversifient leur business model pour essayer de diminuer l'incertitude émanant du système actuel.

D'un point de vue marketing, les solutions sont moins variées. En effet, les dépenses en marketing diminuent continuellement depuis 2007. C'est pourquoi, l'industrie pharmaceutique cherche de nouveaux moyens de promotion de ses médicaments, à moindre coût. Le but est de faire de la communication plus ciblée et plus impactante, pour, à termes, communiquer via le bon canal, au bon médecin, des informations précises et désirées. L'industrie pharmaceutique en est encore à ses balbutiements sur ces points. Ainsi, différentes campagnes de promotion sont actuellement en cours, notamment chez AstraZeneca[®], sur différents produits considérés comme matures. La plupart de ces campagnes reposent sur l'utilisation des nouveaux canaux de communication (i.e. autres que la visite médicale). Ces canaux englobent notamment l'e-detailing, l'e-learning ou encore la réalisation de partenariats avec des associations de patients. Ces nouveaux canaux n'ont, pour le moment, pas un très fort taux de succès. C'est pour cela qu'AstraZeneca[®] essaie de les intégrer dans des stratégies plus globales.

Parmi les nombreuses stratégies actuellement à l'essai dans de nombreuses entreprises, une seule sera développée en détail. Il s'agit de la mise en place d'une nouvelle stratégie marketing pour la promotion d'un médicament mature (encore breveté) : Emlapatch 5%[®]. Cette stratégie est appelée multicanal du fait de l'utilisation, par alternance, des principaux canaux de communication existants à l'heure actuelle. Dans le but de s'inscrire dans une stratégie globale, un fil conducteur a été choisi pour le programme : un logo (un nounours brandissant une épée) et un nom « Même Pas Mal ! ». AstraZeneca[®] veut s'inscrire dans le temps avec ce programme, et créer une relation de confiance avec les médecins ciblés (médecins généralistes à tendance pédiatrique et les pédiatres). En effet, ce programme se différencie des campagnes traditionnelles par le fait que son but n'est pas de promouvoir un

produit. Il prétend plutôt être un programme de services d'aide à la prise en charge de la douleur chez l'enfant. Ainsi, des documents appelés « services » sont remis une fois par mois au médecin, via des canaux différents : marketing direct (voie postale), newsletter (email) et visites face-face (via des attachés de services). Les visites face-face sont réalisées par des « attachés de services ». Ces personnes se différencient des délégués médicaux par le fait que leur principal discours n'est pas à propos produit, mais concerne plutôt l'environnement et la pathologie. Leur rôle est de présenter des services à forte valeur ajoutée, mis à la disposition du médecin. Enfin, cette campagne ne ciblait pas seulement les médecins mais aussi, les pharmaciens et le grand public. Toutes les opérations individuelles menées durant cette campagne ont été surveillées. De plus, ce contrôle a aussi été réalisé globalement afin de déterminer l'impact d'une telle campagne sur les médecins, les pharmaciens et le grand public. Cela a permis d'identifier des pistes de progression pour la mise en place de futures campagnes, comme notamment, une amélioration de l'interactivité entre le laboratoire et les médecins.

PART 1: MATURE DRUGS IN THE PHARMACEUTICAL INDUSTRY: DEFINITION, CURRENT ISSUES AND IMPLEMENTED SOLUTIONS

1. Drug life cycle and definition of the maturity of a product

1.1- Mature product or “Cornerstone”: definition, turnovers and examples

There is no official definition for a mature or maturing drug. We can however say that, essentially, they are the opposite of newly launched drugs. It means that these drugs have been on the market for a long period of time^[2]. Another term used by some companies to characterize these drugs is “Cornerstone”. Indeed, they are sometimes held as the basis of a company. They form a key element of the company, like a foundation, and remain extremely important because, without them, the company would not have been able to establish itself successfully.

However, the pharmaceutical industry regards these drugs with ambivalence. On the one hand, some consider them to be a major reason for the creation of the company. But on the other hand, they can also be forgotten and considered as not useful anymore because of the appearance of new therapeutic options or more efficient drugs. Nevertheless, regarding the current situation and the current issues that are facing the pharmaceutical industry, mature drugs are earning some interest from companies in troubles as well as companies that try to fill their low pipeline. They represent useful drugs that can be a part of a therapeutic strategy for a physician thanks to the therapeutic option that they can offer. Indeed, old does not necessarily mean inefficient.

This category gathers many products with different profiles. First, there are drugs that are still under patent (or that do not have generics or biosimilars) or that have at least one dosage under patent. Among these patented drugs there are two different types: drugs that are still heavily prescribed by physicians and drugs that are forgotten by them. One characteristic that they have in common is that they are no longer promoted by sales calls as well as other

marketing operations. But the end of sales call alone does not explain the steep decrease in the turnover of these drugs. One other reason could be that, as regulation exists for the number of prescriptions that physicians can write, it may not influence sales of newly launched drugs too dramatically. However, it may seriously reduce sales when the drug matures. In fact, in the first months after the launch of a new drug, the volume prescribed by the physician is still low and is intended to be used by the patients that benefit most from this drug^[2].

Most of the time, pharmaceutical firms only focus on products that have higher turnovers or higher potential, in order to obtain the best return on investment. But, they also recently realized that this strategy is increasingly complicated to implement, partly due to more complex regulatory issues. This is the reason why some pharmaceutical companies started to introduce new ideas in order to counter these problems and keep developing the company. One of them is to start over the promotion of mature drugs with new strategies of communication.

Turnovers of these products used to be very high. For instance, Inexium[®] (*esomeprazole*) a proton-pump inhibitor from AstraZeneca[®] that used to be one of their best products with worldwide sales of more than €1 billion in 2010. This product is no longer patented in France since 2011 for the two dosages: 20 mg and 40 mg. However, a pediatric dosage (10 mg) and formulation (individual packaging) is now on the market and is still patented. Even though the turnover of this product is not very high (€3 million), the company hopes to increase it thanks to low-cost marketing strategies [*source: AstraZeneca[®]*].

Another example could be Zomig[®] (*zolmitriptan*) with French turnovers that used to be of almost €50 million before its genericization (in April 2012 in France). After a brief pause from promoting the drug, turnovers decreased. Nevertheless, AstraZeneca[®] has included this product into its new marketing strategy and then, turnovers reached almost €40 million.

To conclude, regarding the current issues facing the pharmaceutical industry, it is essential for it to maximize the income from every drug within its portfolio during this period^[3]. Thereby, Life Cycle Management (LCM) strategies have appeared to be good

initiatives to increase the profitability of the companies, protect their investment and achieve the full value of return^[3].

1.2- Life cycle of products: concept, model and considerations

1.2.1- General products life cycle: definition, features and key considerations for successful life cycle management

Product life cycle (PLC) is a concept that can be applied to many domains like corporate strategy, product development, finance as well as production. Even though it is difficult to define it, we can say that the life of a product (brand as well as a category of product) can be divided into different stages characterized by the revenue generated by the product. That is the reason why the best way to describe it is by using the product life cycle curve [Figure 1].

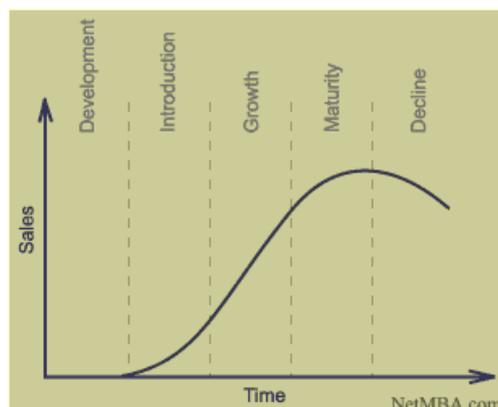


Figure 2: Product Life Cycle curve showing the five different stages^[4]
(Source: <http://www.netmba.com/>)

The PLC curve is divided into five different stages from the product development (and introduction to the market) to the decline of the sales (or the withdrawal). The hypothesis of this model is that sales follow a sequence of stages, beginning with development and product introduction and proceeding with growth, through maturity, and eventually decline of the sales. This curve is presented as a predictive tool in order to forecast marketing requirements as well as help in the long-term product strategies^[4].

To be more precise about the different phases *[Figure 1]*:

- The development stage corresponds to the discovery and development of the product. The firm is preparing its entry on the market, which is why there are no sales.
- During the introduction stage, the product is launched on the market. Sales are slowly increasing due to the rising awareness among consumers. Indeed, during this step, investment cost and advertising are very high because the goal is to improve customer awareness of the product and target early adopters. These high costs added to a low volume of sales result in a low profit period. But one advantage is that the competition is generally very low or even absent. The marketing mix (4P's: Product, Price, Promotion and Place) is generally determined before the introduction stage but it can change all long its life cycle^[4].
- The growth stage is a period of rapid increase in the volume of sales. More customers are aware of the product thanks to the effort of marketing departments. So, the investment and advertising spending are decreasing compared to the introduction stage. On the contrary, competitors start to enter the market as they have noted that more and more customers are interested in the product. To summarize, the goal of this phase is to gain consumer preference and increase the volume of sales of the product (and thereby profits)^[4].
- The maturity stage is the most profitable period of the life cycle of the product. Indeed, volume of sales is maximum (and sometimes keeps increasing slightly during the phase) whereas investment cost is low. However, the competition is also maximum which is the reason why companies maintain a position of aggressive advertising. The difficulty comes from the differentiation between a company's product and that of a competitor. So, the goal is to maintain market share and extend to the maximum the life cycle of the product^[4].
- The decline stage corresponds to the decrease of the volume of sales. Three reasons can explain this phase: the market becomes saturated, the product becomes technologically obsolete (or out off patent) or customer taste changes. Thereby, no

more profit is made^[4]. However, some strategic ideas can be implemented in order to revive the volume of sales during and after the decline stage.

The different stages and features (sales, investment cost, competition, advertising and profit) can be easily summarized [Table 1]. Moreover, the length of the life cycle can be completely different. For example, the maturity stage can be one year for a high-tech product that is going to become obsolete rapidly. It can be 10 years for a pharmaceutical product, or even longer for a domain with few developments.

Identifying features	Stages				
	Development	Introduction	Growth	Maturity	Decline
Sales	None	Low	High	High	Low
Investment cost	Very high	Very high	High	Low	Low
Competition	None	Low or absent	High	Very high	Low
Advertising	Low or absent	Very high	High	High	Low
Profit	None	Low	High	High	Low

Table 2: Features identified regarding the different stages of the product life cycle

In the industry, a process has been created to manage product life cycle. It is called LCM and is defined by the process of managing the entire life cycle of a product, from its conception, through design and manufacture, to service, and disposal. LCM integrates people, data and processes as well as business systems. Moreover, it provides a backbone of product information for companies and their extended enterprises^[5]. In general, LCM strategies are implemented at a global level, but it also may be a regional or local decision depending on the life cycle stage of the product.

In order to obtain a successful LCM, some key considerations must be taken into account such as: governance and organization of LCM, core processes, knowledge and skills to support the process and monitoring and gauging success of the processes implemented^[3].

Indeed, LCM is a long-term process that must be established, managed and monitored thanks to qualified people, concrete actions and sometimes software.

To conclude, product life cycle management is a process of making the right decisions at the right time for each product of the overall product portfolio^[3].

1.2.2- Application of product life cycle to the pharmaceutical industry

In the pharmaceutical industry, things are a little different. The development phase is generally longer than for other products [Figure 1]. Indeed, it has to include another step: the discovery stage. As it is more and more complex to discover new molecules with a high-added medical value, this phase can last from 10 to 15 (or even more) years^[3]. Moreover, it has also to include clinical trials (phases I, II and III) in order to get the approval of the drug. These clinical trials can be very complex and lead to a failure of the drug and thereby no approval and no profit.

The introduction stage for drugs, then, is highly marketing dependent. In the pharmaceutical industry, sales representatives present drugs to physicians. They need communication tools in order to present these drugs. It is the marketing department that creates these tools. Thereby, for pharmaceutical products, a “pre-launch” phase is added before the introduction phase. This phase would include the end of the development phase and the very beginning of the introduction phase. It consists of the creation of communication supports in order to promote the drug. The dilemma of this phase is that sales reps need a great deal of materials and tools to promote the drug, but the marketing service can only produce these documents once the drug has passed the last phase of the clinical trials and had its claims approved. As these supports are very costly to create, this pre-launch phase is a very challenging one. Furthermore, physicians prefer drugs with high added medical value in disease areas with high unmet medical needs. For example, they are more favorable to see entering the market anti-cancer drugs or antibiotics than anti-ulcer drugs (because proton-pump inhibitors are very efficient in this area).

The growth stage encounters similar difficulties. One fear in this phase for pharmaceutical firms is the approval of me-toos. Me-toos are defined as drugs with similar chemical structure or same mechanism of action as a drug already marketed^[7]. Essentially, the marketed drug is the first one entering the market in a specific therapeutic area (first-in-class drug) and competitors come after that. Thereby, it leads to a decrease of market shares for the first-in-class drug^[7]. Moreover, this growth stage also depends on the improvement of medical service of the drug. For example, a drug for orphan diseases will have a rapidly increasing growth stage because of the high unmet needs in these diseases. Physicians are less reluctant to prescribe new drugs in orphan disease because there are no other therapeutic alternatives. However, for crowded therapeutic classes or areas with very efficient drugs, physicians will be more hesitant as the new drug will not necessarily be better than others. This is why the growth stage is less rapid and more time consuming.

For the maturity stage, the curve is much higher than the market share is high. The y-axis indicates the volume of sales. So, for a product with high market shares, the curve will be very high whereas for a product with a small market or a market crowded with competitors, there will be fewer sales. The same problem of me-toos can, then, be responsible of a decrease in profit for the company because of the decrease in market shares. This is why, the goal of this stage is to get an early approval of the first-in-class drug in order to penetrate the market faster and remain without competitors for as long as possible.

Finally, the decline phase is highly patent dependent. This phase corresponds to the arrival of generics on the market. Indeed, molecules patents guarantee exclusivity for a period of 20 years. But, it may take 12 to 15 years to develop a drug (including clinical trials and regulatory approval), leaving only around five to eight years for commercialization and profit^[3]. After the patent loss, generics are allowed to come on the market. One important challenge that the pharmaceutical industry has to face is that generic drugs are entering the market at an earlier stage of the life cycle (and sometimes even prior to patent expiry)^[3]. So, patents are a temporary barrier to genericization.

However, the severe competition in this market leads to different life cycle patterns. Growth phase is immediately followed by the decline without passing through the maturity stage^[7]. Two main reasons may explain this situation. First, innovator products are usually very costly whereas generic ones are not. This is the reason why, if patients have the

opportunity to be treated by generics instead of the costly original molecule, they will switch to generic product if possible^[8]. Second, soon after the patent loss, the market gets crowded with several low-cost generic drugs that compete with each other as well as with the original molecule. This competition leads to a crash of product prices^[8].

To conclude, the concept of product life cycle for pharmaceutical companies is well known for now. They understood that they have to employ specific and timely strategies to maximize the value and reach of a brand before the arrival of me-toos and more importantly generics on the market. This PLC strategy allowed an extension of lifecycle of drugs as much as possible by continuing to be a competitive brand in the face of a market crowded of competitors^[9].

1.3- Market limitations and specificities regarding pharmaceutical products: ways of improvement of life cycle for mature drugs

Pharmaceutical firms are encountering a number of difficulties that do not exist for “general” products. They must take into account many parameters in order to stay competitive. First, scientists have to find the capability to translate their ideas into drugs. Although an idea may be scientifically justified, it can be complicated to realize it technically due to the lack of mediums, techniques and methods^[7]. Then, the drug that scientists are looking for has to be fairly new in order to compete in its own category^[7]. But this novelty has to make sense. For example, the market for cholesterol lowering drugs is crowded with different therapeutic classes and many different drugs in each class. The therapeutic class of Statins (HMG-CoA reductase inhibitors) is considered as very efficient and is generally the first choice treatment chosen by physicians because of their efficacy and good tolerance. Moreover, this therapeutic class includes many different drugs (me-toos). This is the reason why it would not be interesting to come onto the market with a new molecule inside this class.

Another parameter that meets the previous one is the market size. Depending on the disease targeted, the market size may be small (e.g. for orphan drugs) or large (e.g. for anti-hypertensive drugs). In general, large markets are also full of competitors because they are

considered more profitable compared to niche markets. This intense competition leads to a decrease in market shares in these areas due to the apparition of me-too drugs.

Moreover, the fast patent loss for pharmaceutical products is a big limitation for the profit of pharmaceutical companies. This is why they have to find some solutions to maximize their return on investment (ROI) by enhancing the life cycle of mature drugs^[7] [Figure 2]. LCM is very useful and widely used to determine when and how a product will need the implementation of these tactics. However, in order to ensure the success of these management strategies, they must be developed early in the product life cycle, even from the preclinical stage^[3]. A wide range of strategies is available for achieving this ROI once the patent on a drug expired.

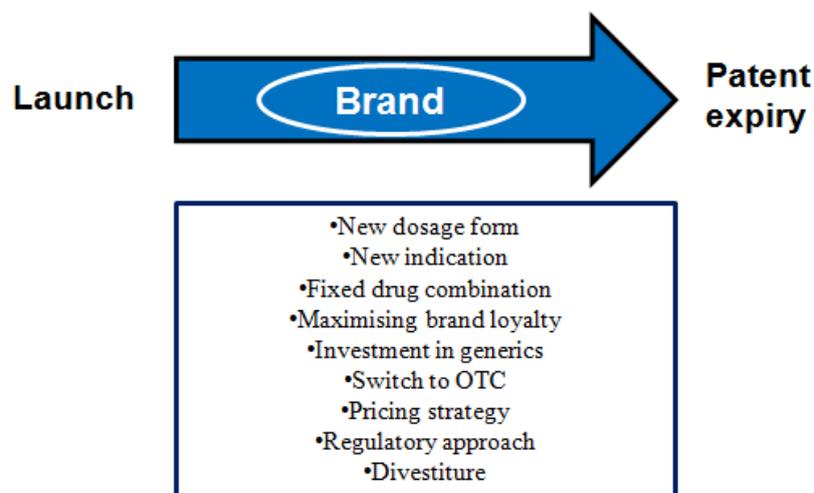


Figure 2: Some LCM strategies to maximize return on investment for pharmaceutical products^[3]
(Source: Journal of Medical Marketing)

The first strategy is the elaboration of new dosage forms of conventional drugs. It is one of the most effective formulas for chemical drugs to enhance the patent length. Indeed, biotech drugs are generally administered by intravenous injections and it is quite complicated to change this formulation^[7]. Another way to increase the time lag to patent expiry would be to find other indications. Pharmaceutical companies have to demonstrate the effectiveness of their drug in pediatric population, related conditions or other disease areas. This strategy leads to a secondary patent that extends the period of exclusivity for the product and thereby delays the generic competition^[3]. In the case of a fixed dose combination, the “new product”

has to be launched for a new indication to be treated as a new agent and to receive significant market exclusivity^[3]. But generally, a fixed drug combination is only protected by the formulation patent of the combination technology. Then, during the period of brand exclusivity, companies invest in marketing with high-profile promotion campaigns, to create a long-term loyalty with their patients. A strong brand name may make it more difficult for generics to enter the market competitively^[3]. However, other companies prefer investing in generics. Indeed, one possibility for research-driven companies is to introduce their own generic drug (of one of their own drug that has lost its patent) or alternatively license the drug to a generic company before the end of the patent in exchange for royalties^[3]. Afterwards, the switch from prescription to Over-The Counter (OTC) status allows an extension of the brand and a reduction of market loss to generic companies^[3]. Pricing strategies are very important to face the threat of less-expensive generics flooding the market. Essentially, three different possibilities can occur: maintain the price (and potentially lower sales volume), reduce the price (to counter the competition) or raise prices (to increase profitability in the short-term). However, government price controls in France may prevent the use of the third solution^[3]. After, the validity of patents is increasingly being challenged to allow launch of generic molecules before patent expiration. This is why litigation is becoming an accepted and necessary part of business for research-driven pharmaceutical companies, even though this solution is costly^[3]. Finally, it is possible to divest a product to someone else. This method involves cutting promotional and research expenses, selling the product or licensing its manufacture once the brand faces direct competition from generics.

Limitations and specificities of the pharmaceutical market must be taken into account. Despite the fact that LCM arrived late, the pharmaceutical industry has successfully proven its high adaptation capacity to current issues and new regulations.

2. Characterization of drug maturity: what are the current issues facing the pharmaceutical industry?

2.1- Breathlessness of the pharmaceutical Research & Development due to a tightening of the legislation by the regulatory authorities

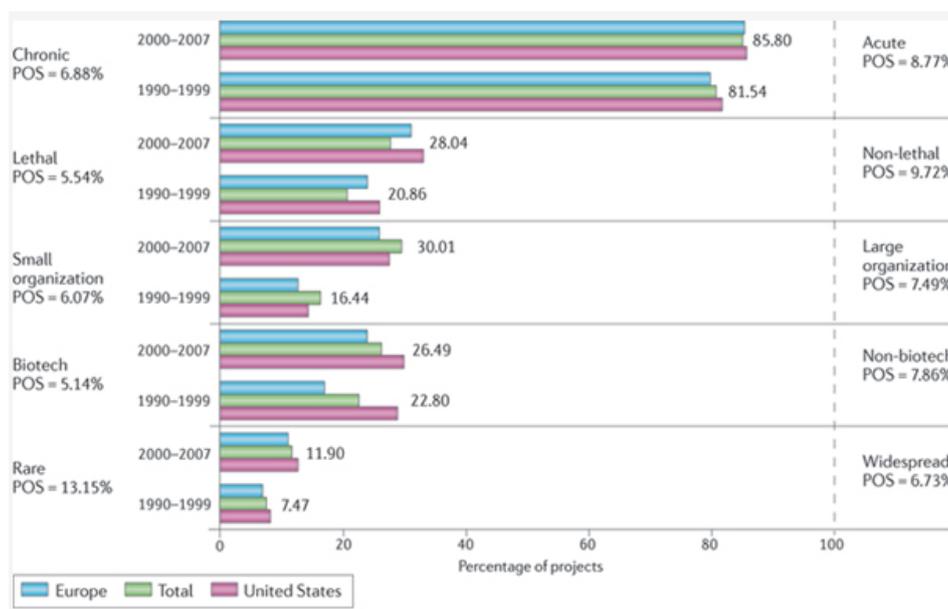
2.1.1- Decrease of the pharmaceutical R&D productivity

Research & Development (R&D) productivity can be defined by the relationship between the value (medical and commercial) created by a new medicine and the investments required to generate that medicine^[10]. However, pharmaceutical R&D productivity is not what it once was. Indeed, between 2001 and 2007, “Big Pharma” R&D productivity declined by 20%^[11]. Another important point is that productivity is higher in Europe than in the United States (US). In fact, there is a higher probability of market launch for compounds entering preclinical stage in Europe^[12].

Some indicators such as the probability of success (POS) of projects, which can also be expressed as attrition rate ($1 - \text{POS}$), can be very helpful in determining this decline. According to Fabio Pammolli and all^[12], the attrition rates of R&D projects have increased, especially in late-phase clinical trials. It means that there is an increase in the number of failed projects entering each phase. This increase is especially high for phase II and III of clinical trials that are key phases for the development of a product as well as the more expensive ones.

The POS is a useful tool to determine whether the project should be continued or aborted. However, since 2000 the pharmaceutical industry prefers to choose projects with low POS (so with a high attrition rate) because they expect a lower number of competitors in this area and thus higher revenues [*Graph 1*]. Research shifted towards developing drugs for chronic diseases (e.g. Alzheimer’s disease, diabetes, obesity...) which have a lower POS compared to acute disease. Moreover, more projects are targeting lethal diseases (e.g. cancer and some infectious diseases like tuberculosis). As we can see in the Graph 1, small organizations also have a lower POS compared to large organizations. The same trend can be observed for biotech and chemical molecules, in favor to biotech drugs. Markets where the POS is higher are those in which there already are effective compounds available^[12]. This is

why, these markets are full of competitors that are trying to improve these already well-known compounds and then develop the drug promotion in order to surpass the other competitors.



Graph 1: Average success rate and distribution of R&D projects according to the characteristics of the disease targeted, size of organization and research methodology^[12]
 (Source: Nature Reviews Drug Discovery)

Another point is that the number of New Molecular Entities (NMEs) approved per year has also decreased^[12]. There currently is an exhausting of chemical molecules. That is why big pharmaceutical companies have to direct them into more complex technologies like biotechnologies. Thanks to the genomic revolution in the 2000s, the pharmaceutical industry thought it could improve how drugs are discovered and so improve its R&D productivity. Nevertheless, genome sequencing leads to a reduction of R&D productivity in the short-term because of the increase of gestation lag between investments and outcomes and also because of the increase of the complexity of the targets^[12].

The pharmaceutical industry then relies on investors (both private and public) to find money to realize their R&D projects. However, these payers discourage incremental innovation^[12]. Essentially, there are two different types of innovation: radical innovation that leads to a major improvement (in the case of the pharmaceutical industry: a NME for

example) and incremental innovation, which corresponds more to an improvement of something that already exists^[13]. Investors in the pharmaceutical industry might consider that incremental innovations are not innovative enough and do not bring enough novelty to be worth the cost. That is one of the reasons why, R&D investments shift toward new therapeutic classes with high uncertainty and difficulty.

“Big Pharma” currently focus on activities with unmet medical needs and complex research areas (high attrition rate areas) because they need a higher medical differentiation to successfully introduce new products into the market^[11]. Moreover, these areas have fewer competitors, which is a great competitive advantage. However, it is more difficult to develop innovative drugs in areas of strong technological uncertainty and high unmet therapeutic need because of the unknown as well as the complexity.

To conclude, innovation is the key to developing drugs that can be of medical value for patients as well as drugs for unmet medical needs. But nowadays innovation has become more difficult to achieve^[11]. However, improving R&D productivity remains one of the most important challenges for the pharmaceutical industry.

2.1.2- Increase of the Research and Development costs: reasons and strategies

In addition to the low productivity, the costs of development of a new drug have increased^[12]. Indeed, in 2010 the average cost for pharmaceutical companies to bring an NME to the market was estimated to be approximately €1,3 billion^[10], against €868 million for a drug developed between 1989 and 2002^[14].

However, some strategies have been implemented to improve the efficacy of the R&D. The clinical studies are the most expensive steps of the drug development, and more precisely the phases II and III with respectively €254 million and €250 million^[10]. These high costs can be explained by the high technical uncertainty associated with these phases. Therefore, a new concept has been introduced: “Quick win, fast fail”^[10]. This strategy mainly relies on two principles: an abundance of drug discovery and an early abortion of the project after the preclinical development if the proofs are not sufficiently reliable.

To achieve this, before entering into the expensive development stages (phases II and III) the establishment of the Proof-of-Concept (POC) is needed in order to decrease the technical uncertainty. After the preclinical development (ideally during a small-scale phase I in well-defined diseases) a hypothesis about the mechanism of action must be determined. This hypothesis allows a demonstration of the therapeutic benefit to patients of the drug. Therefore, if the drug is considered as having a good POC, the other clinical studies will be conducted. This POC leads to a reduction of the number of NMEs passing through phases II and III. But, the ones that advance have higher POS and higher chances of being launched and approved [Figure 3].

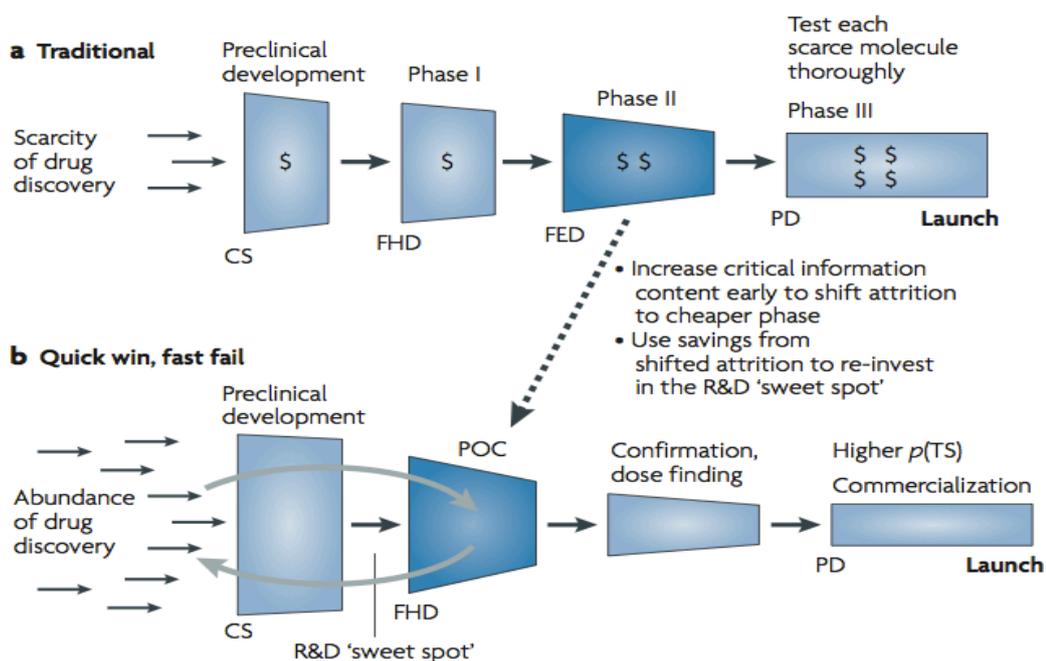


Figure 3: The “quick win, fast fail” drug development paradigm compared to the traditional method^[10]
 (Source: Nature Reviews Drug Discovery)

The savings realized thanks to this method can be reinvested in R&D to find other drugs that will enter into preclinical development. This strategy will allow, in the future, an enhancement of the R&D productivity [Figure 3].

However, one drawback of this paradigm could be that go/no-go decisions^[10] would have to be made early. Thus, some projects can be abandoned whereas they could have been interesting in a longer timeframe.

Another point concerns biopharmaceutical R&D. Developing a chemical drug is less expensive than developing a biotechnology drug^[15]. Indeed, chemistry is a well-known technology whereas biotech is still in its infancy. For example, the cost estimates per approved biopharmaceuticals are €490 million for preclinical studies and €500 million for clinical studies, so a total of almost €1 billion only for the development^[15]. To these numbers, we have to add the cost of research. As the technologies used for this kind of drug are “new”, they are very complex and also expensive compared to the ones used for chemical drugs. Moreover, the development time frames are higher for biopharmaceuticals and more information is needed by the regulatory authorities before launching these drugs on the market^[15]. This also contributes to increase the R&D costs.

2.1.3- Increase of the development time frames

The development time frames are increasing as well. Indeed, the average development length from patent filing to product commercialization is longer for younger products: 9.7 years for products launched before the nineties against 13.9 for products launched after 2000^[12] (study on the United States and the European Union-15). Different parameters have to be taken into account to understand where this increase comes from.

First, because of serious concerns about the industry’s integrity and transparency (among drug safety and efficacy for example), the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) are hardening the drug legislation with more complicated approvals. Indeed, the regulatory agencies are always asking for more and more regulatory requirements and more proofs of the efficacy and the safety of the molecule. Agencies are also raising their regulatory scrutiny by examining several times each information and result and asking for more studies when they think that the current results are not relevant enough^[10].

From the discovery of the molecule to the launch of the product, there are mainly three steps. Currently, the drug discovery and the preclinical studies are taking three to six years, then the clinical trials accounted for six to seven years and finally, the review by the regulatory agencies six months to two years [Figure 4].

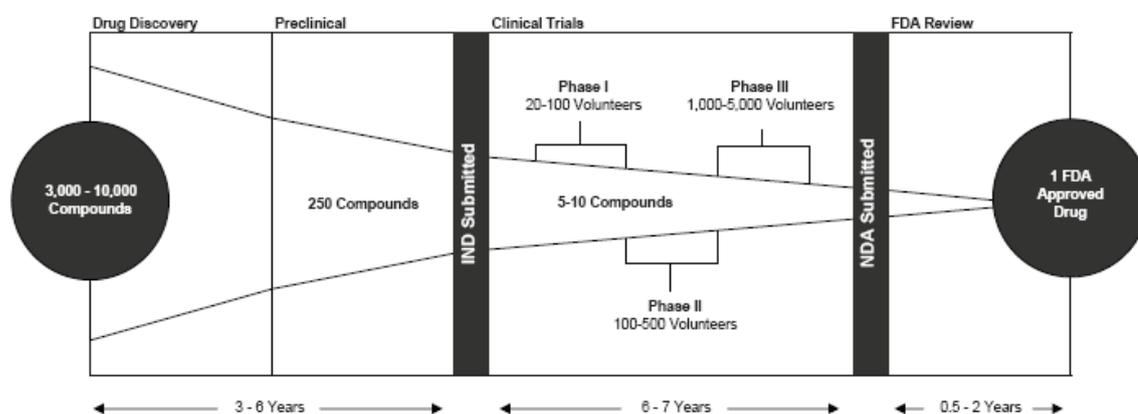


Figure 4: The current development process including the different lengths and number of compounds^[16]
 (Source: Pharmaceuticals & Biotech: Industry Global Report)

By adding the maximum lengths of each step, it leads to 15 years of research, development and approval. Thereby, the pharmaceutical industry has to find some solutions in order to enhance this process and get earlier approvals because of the increasing pressure of the generics immediately after the loss of the patent.

As explained before, there currently is a switch from chemistry to biotechnology. Indeed, as biopharmaceuticals are still complex and “unknown” molecules, regulatory agencies are taking numerous precautions in order to be sure of the added medical value of the product as well as the safety. Thereby, the approval for biopharmaceuticals is more difficult to obtain because of the lack of step back^[15]. The EMA and the FDA do not want to take unnecessary risks partly because of previous scandals that have occurred. For instance, with Thalidomide: a drug commercialized in the sixties as treatment for morning sickness in pregnant women. Actually, this drug had not been tested enough and the associated toxicities had not been determined. Then, it was discovered that it led to birth defects (e.g. phocomelia)^[17].

Therefore, the growing regulatory pressure can be comprehensive because of the issue of drugs on patients. On the other hand, the pharmaceutical industry has to find solutions in order to improve how drugs are discovered and how clinical trials results could be obtained more easily but in a safe way.

2.1.4- Formerly crowded pipelines become limited and uncertain

The pipelines for new drugs in the pharmaceutical industry look uncertain and limited. In fact, Big Pharma failed in developing biotechnologies in their pipelines and focused mostly on chemical drugs. For example, after looking at the pipeline of AstraZeneca[®] [Annex 1], it appears that the future interesting products are still far from going on the market. Most of them are just entering clinical trials (mostly phase I and phase II for the more advanced). Moreover, it does not appear that the drugs currently in development will generate as much revenues as the ones with expiring patents^[18].

Pharmaceutical companies, then, do not innovate enough. For example, in the 1990s, the pipeline for cancer treatments got crowded with pharmaceutical companies developing ever-newer chemotherapies with little therapeutic differences^[16]. This is why some smaller companies decided to enter the biotechnologies market with innovative therapies in unknown and low market shares therapeutic areas. Besides, these companies tried to diversify their pipeline and specialized themselves in therapeutic areas with high unmet medical needs, as well as niche market. For instance, with the increase of the life expectancy, there is an increase of the demand of new treatments in oncology and Central Nervous System (CNS)^[18]. That was the goal of formerly Genentech[®] (which now belongs to Roche[®]) with three products that are projected on the top five of oncology products worldwide in 2016 [Table 2].

Rank	Product	Generic name	Company	Pharma class	Sales		Market share	
					2009	2016	2009	2016
1	Avastin	bevacizumab	Roche	Anti-VEGF Mab	5,744	8,909	0,113	0,122
2	Rituxan	rituximab	Roche + Biogen Idec	Anti-CD20 Mab	5,62	6,788	0,111	0,093
3	Herceptin	trastuzumab	Roche	Anti-HER2 Mab	4,862	6,167	0,096	0,085
4	Alimta	pemetrexed sodium	Eli Lilly	Thymidylate synthase inhibitor	1,706	3,275	0,034	0,045
5	Erbix	cetuximab	BMS + Merck KGaA + Lilly	Anti-EGFR Mab	1,654	2,513	0,033	0,035

Table 2: Projected top 5 Oncology products worldwide in 2016^[11]
(Source: Pharmaceuticals & Biotech: Industry Global Report)

First, Avastin[®] (*bevacizumab*) which is a monoclonal antibody that is used in combination with chemotherapies in some metastatic cancers (colorectal, breast, kidney or non-small cell lung cancers)^[19]. The second one is Rituxan[®] or Mabthera[®] (*rituximab*) which is a murine/human monoclonal antibody used in some lymphoma, leukemia and rheumatoid arthritis^[19]. And finally, Herceptin[®] (*trastuzumab*) used to treat metastatic breast and gastric cancers^[19].

Niche markets have low market shares because of a low prevalence of the diseases. A good example is Genzyme[®] (that now belongs to Sanofi[®]) with its Fabrazyme[®] (*agalsidase β*). This drug is used for Fabry disease^[20], which is a disease that leads to a dysfunctional metabolism of lipids. As the incidence is very low (estimated to be approximately one out of 50,000 live males births^[20]), the pharmaceutical industry thought it was not interesting to enter this market. However, Genzyme[®] business model mainly focuses on orphan diseases with high unmet medical needs^[21]. As the drug is the only therapeutic option for patients with Fabry disease, the drug can benefit more easily from an accelerated approval corresponding to orphan drugs. Moreover, these therapeutic areas have lower competition and some incentives exist for developing an orphan drug.

2.2- Strict regulatory framework of drug promotion in France and restrictive changes in 2012

2.2.1- Generalities

Marketing can be defined as the activity, set of institutions, and processes for creating, communicating, delivering and exchanging offerings that have value for customers, clients, partners, and society at large^[22]. However, the drug marketing is more challenging because the final customer is the patient. Therefore, other parameters must be taken into account: mainly the efficacy and the safety of the product. Moreover, two different types of marketing can be highlighted with two different goals: marketing directed to patients and marketing directed to healthcare professionals.

Drug marketing is more specific than general marketing. Three important parameters have to be taken into account: government regulation, technological innovation and competition^[23]. First, the government regulation is important because the marketing is heavily regulated, specifically in France due to, among other things, stringent reimbursement conditions. Then, pharmaceutical industry is characterized by high expenditures on R&D but has to develop continual innovations in order to always introduce new drugs. Innovation is one of the key word of the pharmaceutical industry even if developments are increasingly lengthy, costly and with significant risks^[23]. Finally, competition can occur on two different levels: the development of new drugs and the sale of drugs. Indeed, companies compete to be the first with a drug designed to treat unmet medical need or with a drug that is safer or more effective at treating a disease than current treatments^[23].

Two types of documents surround drug marketing: environmental documents that deal with the indications of the concerning drug or with medical information that can be useful to physicians, and product documents that are branded with the name of the product. Then, mainly two different types of drugs can be advertised: prescription drugs and OTC drugs. Regarding the public targeted (patients/consumers or healthcare practitioners: mainly physicians and pharmacists), different strategies and legislation are effective in France.

On the one hand, for OTC drugs and the two types of targets, pharmaceutical companies can communicate on the product itself as well as on the disease. On the other

hand, for prescription drugs, firms can only talk about diseases or environment surrounding this drug for patients/consumers and environment or product for healthcare practitioners [Table 3].

	Prescription drugs	OTC drugs
Patients, consumers	Environmental advertising	Environmental and product advertising
Healthcare practitioners	Environmental and product advertising	Environmental and product advertising

Table 3: Type of authorized advertising regarding the kind of people targeted in France

But, for now, the key decision-maker in determining which drugs patients should use, is the physician. Thus, the vast sums of money spent by pharmaceutical companies in drug promotion (including sales rep, samples and all type of advertisements) are basically used mainly for educational campaigns targeted at physicians, designed to encourage them to prescribe a medication for their patients who have a certain condition^[18].

2.2.2- Regulatory framework of advertising regarding the types of drug

Basically, drugs can be separated into two different types: drugs that need a physician’s prescription and drugs that do not. The regulatory framework of advertising depends on this parameter in France.

First, a prescription drug can be defined as a drug that has to be prescribed by a physician in order to be delivered to the patient. According to the article L. 5132-1 from the French Public Health code^[24], prescription drugs include: some substances classified as risky to health, drugs that may pose a direct or indirect danger to health, drugs containing substances whose activity or side effects require medical supervision and more generally, all other product or substance that may pose direct or indirect risks to health. That is the reason why the marketing surrounding these drugs is highly regulated in France.

Advertising about prescription drugs can only target healthcare practitioners [Table 3]. Moreover, a number of conditions have to be met in order to communicate with them. According to the article R. 5122-8 of the French Public Health code^[24], many criteria exist and have to be respected. For example, the document has to include, among other things, the name of the drug, the name and address of the company distributing the drug, the qualitative and quantitative composition of the drug (active substance as well as excipients)... [Annex 2].

Before May 2012, each document branded with the name of the product had to be registered to the Agence Nationale de Sécurité du Médicament (ANSM, formerly Agence Française de Sécurité Sanitaire des Produits de Santé: AFSSAPS) after the release of the document. Indeed, the article L. 5122-9 of the French Public Health code^[24] indicates that "Advertising for a medicinal product to health professionals authorized to prescribe or to dispense drugs or use them, should be, within eight days after its release, deposited to the ANSM". Thereby, in the past years, the ANSM trusted the industry because some documents could be considered as, not in accordance with the legislation, after having been shown to physicians. So, the ANSM was allowed to forbid and withdraw these documents. However the legislation changed during May 2012 and a new decree about advertising related to healthcare professionals is now effective.

Secondly, according to the FDA, OTC drugs are defined as drugs that are safe and effective for use by the patients without seeking treatment by a health professional^[25]. On the contrary, in France, there is no definition of self-medication drugs. Indeed, in the article L. 5132-6 of the French Public Health code^[24], they are defined as "drugs that do not meet the criteria listed for the prescription drugs". According to the article L. 5122-6 of the Code^[24], OTC drugs are considered as: drugs that are not submitted to a medical prescription, drugs that are not registered on the poison list, drugs that are not reimbursed by the Social Security and drugs that do not have any restriction regarding advertising in their approval (the only exceptions are vaccines and drugs to fight against tobacco).

Unlike prescription drugs, OTC drugs can target two different kinds of people: healthcare professionals as well as patients (or people in general). Indeed, as these drugs are not submitted to a medical prescription, laboratories can communicate about the product

itself and not only about the environment or the disease treated [Table 3]. All this communication is called Direct-To-Consumer (DTC) promotion.

However, advertising destined to patients is more regulated. Indeed, this type of advertising has to be controlled before the release of the document to the public in order to obtain a visa that allows the diffusion. The goal of this strict control is to protect consumers. This kind of advertising is defined by the article L. 5122-6 of the French Public Health code^[24] and has to include all the mentions indicated in the article R. 5122-3^[24]: the name of the drug and the INN (International Nonproprietary Name) when the drug contains only one active substance, information for the good use of the drug, an invitation to read carefully the instructions on the leaflet or on the packaging and a caution message that advises to talk first to a pharmacist in case of problems and, if symptoms persist, an invitation to go to the physician.

As the regulation is more and more restrictive for prescription drugs, some “big pharma” diversified them by creating their own OTC branch (e.g. Sanofi[®], Bayer Santé Familiale[®], Bristol Myer Squibb[®]...) in order to increase their turnovers. For example, Sanofi[®] commercializes the famous Doliprane[®] (still not registered in the directory of generics in France despite a variety of competitors on the market) that all alone monopolizes the first place in the ranking of the most prescribed drugs in unit in France^[26].

To conclude, advertising on prescription drugs as well as OTC drugs is heavily regulated in France. However, OTC drugs have a slightly easier promotion process compared to prescription drugs, due to their status of being safe and effective for a use by the patients. Moreover, their promotion can target patients as well as healthcare professionals. In May 2012, a new decree appeared which further hardened the law in the point of view of the pharmaceutical industry.

2.2.3- Changes in 2012: a new decree for drug promotion

On the 29th of December 2011, a new law on strengthening the safety of the drug and health products was created^[24]. One major change in this legislation was about product advertising directed to healthcare professionals as well as patients. Indeed, according to the article L. 5122-8 of the French Public Health code^[24], advertising to public for a drug (ethical as well as OTC drugs) and all advertising campaigns must now be subject to a prior authorization of the ANSM in order to obtain a visa for advertising. Besides, some deposition periods for the document have to be settled on by the enforcement decree.

Thereby, on the 9th of May 2012, the enforcement decree (number 2012-741^[24]) finally came out. It explained that a calendar of the deposition periods has to be introduced before the 1st of November of each year, with at least four periods of one week to two months. If there is no answer from the ANSM after the end of the period, the visa is considered as acquired. This visa is then valid for two years^[24].

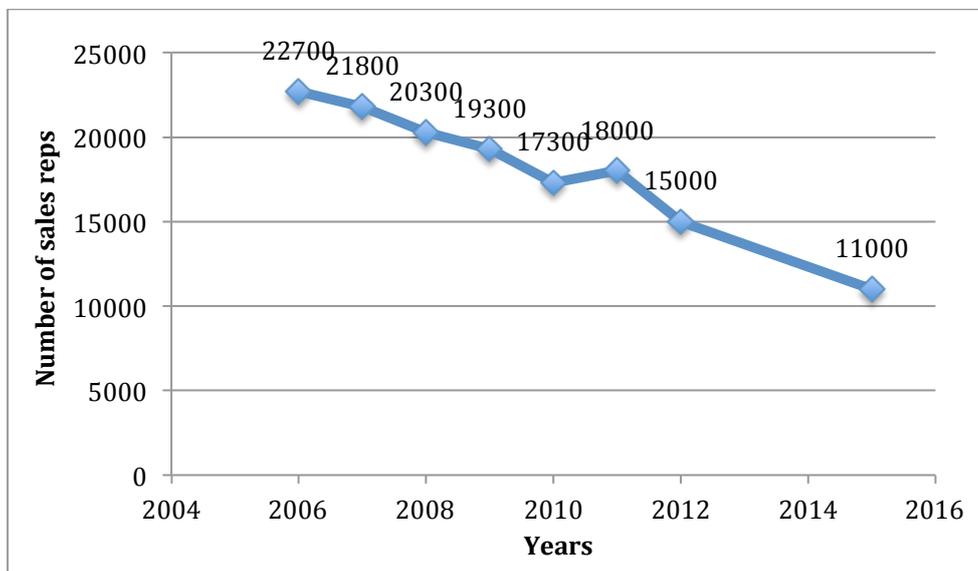
This change will lead to a modification of the organization of the pharmaceutical industry. Even if all the campaigns for the products are planned in advance, the pharmaceutical industry has now to plan even earlier. For example, for a document submitted to the ANSM during the first period (from May until the 15th of June^[24]), the answer will be given in the middle of August. This reform brings laboratories to a global reorganization of the marketing and regulatory units in order to find solutions to improve their efficacy. Moreover, things have to be planned even earlier in order to be sure to have promotional documents for the next campaign. As the seminars initially matched with the ANSM results, they have been moved forward in order to have these results before starting the seminars. This measure means sales reps can be more confident, and the new campaign started calmly.

2.2.4- Sales call: definition, numbers and the charter

Sales call is defined in France by a charter published on the 22nd of December 2004, and then modified by two amendments: on the 21st of July 2005 and 21st of July 2008^[25]. The

main objective of the sales call is to ensure the drug promotion to healthcare professionals in order to contribute to the development of the pharmaceutical industry. Sales call must promote the quality of the medical treatment in the concern to avoid the misuse of the drug, not cause unnecessary expenses and participate in the information of all the healthcare practitioners (physicians as well as pharmacists and in the retail market as well as the hospital)^[25].

In France, the number of sales reps is constantly decreasing. Indeed, according to the LEEM^[26] (Les Entreprises du Médicament) which is considered as unions of the pharmaceutical industry in France, in 2004 there were almost 24,000 sales reps in France compared to 15,000 currently. Moreover, this number should keep declining in the next years. For example, the number of sales reps in 2015 is expected to be around 11,000. It corresponds to a decrease of more than 50% since 2004 [*Graph 2*].



Graph 2: Number of sales reps in the French pharmaceutical industry regarding the year^[26]
(Source: <http://www.leem.org/>)

This decrease might come from different points. First, sales force is very expensive and corresponds to a high spending of the pharmaceutical industry. As each physician deemed important and likely to prescribe the drug must be visited the target is very large. Indeed, in case of a broad pipeline of your company, each specialist and general practitioner

(GP) may be of interest and has to be visited. In France, there are 208,000 physicians divided into 100,000 General Practitioners (GPs) and 108,000 specialists^[27]. With an average of seven visits per day, the pharmaceutical industry has to hire many sales reps in order to visit each targeted physician and thereby realize the desired turnover.

Furthermore, the pharmaceutical industry is now interested by what is called: the new channels of communication^[26]. In fact, this type of communication is less expensive and easier to implement. The product manager creates documents regarding the communication of the product as well as the disease treated by this product. Then, these documents can be sent by mail as well as email, which is a good way to decrease expenses.

Even though the number of sales reps is rapidly decreasing, sales calls are maintained. Indeed, one solution for the pharmaceutical industry to diminish these costs is to hire networks of providers. These networks are less expensive and more efficient because they have an average of nine visits per day because the visit is reduced with only a presentation of generally, a brochure that should be useful to the physician and at the end a little reminder about the product. They do not need to develop all the studies regarding the product like sales reps. However, these two types of visits are complementary. Network of providers alone cannot be enough to communicate heavily with physicians.

Moreover, the sales reps profession is heavily supervised and regulated. A charter has been set up in order to reinforce the role of the sales reps in the proper use of the drug and the quality of the delivered information^[25]. Four main missions are assigned to sales representatives. First, they have to promote drugs in order to enable knowledge by the healthcare practitioners as well as the good use of the drug. Then, they have to inform physicians as well as pharmacists about the regulatory and pharmacological aspects relative to the drug presented. After, the physician has to know the place of the drug into the chosen pathology and the recommended therapeutic strategy (validated by all the authorities: Transparency Commission, ANSM, HAS - Haute Autorité de Santé). Finally, sales rep can also initiate pharmaco-economic analysis or clinical studies^[25]. Some documents have to be necessarily delivered to the physician during the call: the summary of product characteristics, the opinion of the Transparency Commission, the price of the product and its reimbursement conditions (generally indicated on the document branded with the name of the drug)^[25].

As sales representatives are more and more costly to the pharmaceutical industry, companies are currently searching for new channels and ways of communication in order to decrease the costs dedicated to drug promotion. The final goal of these researches would be to find mediums to develop and reorganize drug marketing.

2.3- The current patent cliff and the growing pressure of generics and biosimilars

2.3.1- A period of massive loss of patents

The development timeframes have increased in the pharmaceutical industry while the R&D productivity has decreased. This context leads to major losses of revenue in this sector^[10]. As the drugs come on the market later, they have a less patented timeframe and thereby, they undergo a high pressure from generics. Indeed, the patents of many well-known treatments will expire over the next five years. In addition, 36 treatments that generated nearly €47 billion in 2006 will have to compete with generics^[18].

Moreover, key patent expirations already occurred with for example:

-Tahor[®] (or Lipitor[®] in the US, *atorvastatine*): the famous Statin, best selling product of Pfizer[©] in May 2012 in France^[28].

-Plavix[®] (*clopidogrel*): the blood thinner from Sanofi[©] which used to be the second best selling product in the world, since 2010 in France (and 2012 in the US)^[28].

-Seroquel[®] (*quetiapine*): the drug for bipolar disorders and schizophrenia of AstraZeneca[©] which is off-patent in the US and will lose soon in France^[28].

However, those three products were considered as best-selling products with worldwide turnovers of €8.5 billion, €7.5 billion and €4.2 billion for respectively Tahor[®], Plavix[®] and Seroquel[®] in 2010^[28].

Those high turnovers can be the reason why major pharmaceutical companies used to rely on a small number of high potential drugs for much of their revenue and to ensure their profitability^[18]. However, that business model is no longer valid because of the patent cliff that is currently happening on this market. Pharmaceutical companies do not innovate enough. Indeed, the R&D productivity was higher in the nineties and many useful drugs were

patented in this period^[10]. After an average of 20 years of protection, these drugs are now falling into the public domain and low-cost generics firms are taking advantage of this situation^[10].

To conclude, the expiration of patents on many high revenue drugs over such a short period is an issue because it is still not known how pharmaceutical companies will be able to replace these big losses of revenues.

2.3.2- The threat of generics and biosimilars

The development of generics and biosimilars is currently a high growth rate area^[18]. Indeed, the generic drug sales reached a value of €2.4 billion in 2010 in France (8% of the market by value)^[29]. Moreover, by 2015, sales are expected to increase to €3.24 billion [Figure 5]. This high growth rate could be attributed to the upcoming patent cliff and the subsequent increase in the availability and consumption of generic medicines instead of patented medicines^[29].

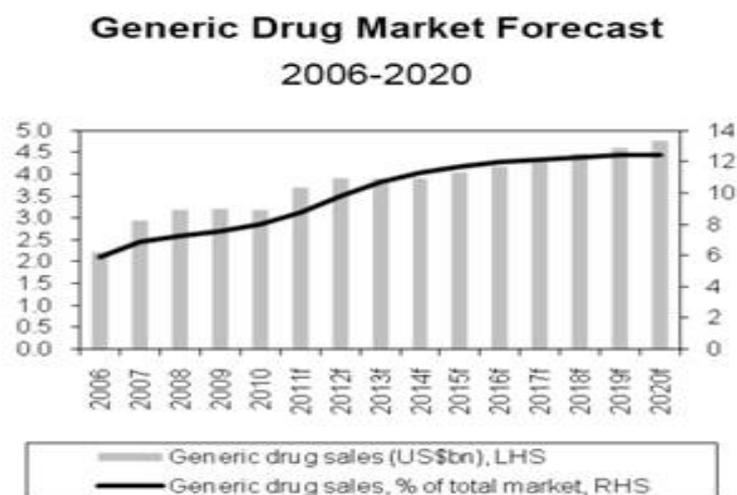


Figure 5: Generic drug market forecast from 2006 to 2020^[29]
 (Source: Business Monitor International's)

Generics are defined as drugs that are comparable to the brand listed drug in dosage form, strength, route of administration, quality and performance characteristics, and intended use^[30]. The only difference between the brand listed drug and its generics is the excipients. That is the reason why, a simple bioequivalence study with 20 patients is sufficient to get a marketing authorization for a generic drug^[16]. Thereby, three years, on average, are enough to develop and get the approval for a generic drug. Moreover, the generic manufacturers do not have high R&D spending and drug promotion compared to brand listed drug manufacturers.

However, for some generic molecules it is more complicated to enter the market because of the notoriety of the brand drug. For example, Zomig[®] (*zolmitriptan*) from AstraZeneca[®] lost its patent on March 2012. Nevertheless, the penetration rate of generics of Zomig[®] is not very high due to the fact that this product had a good renown: patients ask pharmacist not to give them generics.

On the other hand, a biosimilar is considered as a generic of a biotech drug. It is defined as a biological product that is highly similar to a licensed reference biological product notwithstanding minor differences in clinically inactive components and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product^[30].

Biosimilars are currently generating significant interest following the launch of biosimilar recombinant proteins in Europe in 2006. There was also a release of a regulatory approval pathway for these drugs (different from the one of generics)^[31]. However, for biosimilars, the regulatory demand is much higher. They require more exhaustive studies with full preclinical and clinical trials (phases I, II, III) for each production line as small changes in manufacturing can substantially impact the medical outcome^[7, 16]. Indeed, one little change in the processing or dosage form of a biological drug may cause structural or chemical changes that may have a clinical significance. This will make biosimilar development process costlier (compared to simple generics), longer (from six to nine years^[32]) and hence will restrict number of players^[7].

Moreover, another fact may reinforce the safety of biosimilars compared to generics. Although a biosimilar drug may be proven to be comparable to the reference biotech drug, it may not be eligible for an automated substitution, unlike for generics that have to be

substituted^[7]. This parameter may significantly limit the damage to research-driven companies. The main differences between generic drug and biosimilar are exposed in the [Table 4].

	Generic drug	Biosimilar
Production	Chemical synthesis	Biotechnology (use of a specific cell line)
Structure	Simple	Complex
Development time frame	3 years (on average)	6 to 9 years (on average)
Studies needed to get the approval	One bioequivalence study	Exhaustive preclinical and clinical studies
Substitution (in Pharmacy)	Yes	No

Table 4: Main differences between a generic drug and a biosimilar^[32]
(Source: Les Biosimilaires ne sont pas des génériques)

To conclude, legislation makes generic entry easier due to advantageous reimbursement conditions compared to brand listed drugs. However, the pharmaceutical industry found some solutions to counteract this generic competition. One good example is Mopral[®] (*omeprazole*) from AstraZeneca[®], which is their first proton-pump inhibitor (PPI). When the drug fell into the public domain, AstraZeneca[®] marketed its second PPI: Inexium[®] (*esomeprazole*), which is an isomer of the Mopral[®] and then oriented the physicians prescribing Inexium[®]. Finally, when Inexium[®] lost its patent last year, AstraZeneca[®] marketed a pediatric indication with a new dosage and form of Inexium[®]. As generics can be seen as a threat for research-driven companies (because the genericization leads to a rapid sales erosion of innovator brand) biosimilars do not have the same profile^[7]. Moreover, compared to generics, biosimilars are considered as less dangerous because of all the clinical data that are asked for each new batch.

2.3.3- Blockbuster model no longer valid

In recent years, some drugs have been considered as best selling products. Best selling products can be defined as drugs that generate annual sales of at least \$1 billion (or €800 million) for the company that creates it. One example includes Tahor[®] (or Lipitor[®])

from Pfizer[®] that generated €8.5 billion of sales worldwide in 2010^[33]. Blockbuster drugs are commonly used to treat common medical problems like cholesterol increase, diabetes, high blood pressure (HBP), asthma, or cancer...

However, with the increase of biological drugs, niche market and personalized medicine, this strategy is no longer valid. Indeed, drugs are now designed for one patient (or one category of patients) and no more for all the population. This is the reason why, companies using a blockbuster driven strategy tend to be relatively inflexible and slow moving. In fact, these companies need a significant financial investment and these resources are divided between a small numbers of drugs which is not a good investment in case of failure^[31].

Another point is that information on biological targets is available earlier due to recent advances in R&D. Moreover, the information disclosure conveyed by patents induces intense competitive dynamics in R&D^[12]. This is the reason why, challenge of the pharmaceutical industry would be to become more specific in its R&D in order to develop drugs that meet specific therapeutic areas with high unmet needs for example.

2.3.4- Same therapeutic class but a different drug: the increasing number of me-toos

As some therapeutic areas are considered of high potential, each pharmaceutical industry wants to have a product on it. This strategy led to the creation of drugs called “me-toos”. A me-too is defined as a drug with a similar chemical structure or same mechanism of action as a drug already marketed. Basically, there is the first-in-class drug that is the first drug entering one therapeutic class and considered as the breakthrough product. Then, follow-on drugs that are all the other drugs coming on the market in this same therapeutic class^[34].

Regarding the length of time between the approval of the first-in-class drug and the follow-on drugs, it has decreased. Indeed, the period of marketing exclusivity for the first-in-class drug fell from 10.2 years in the 70s, to 1.2 years in the late 90s^[34]. Moreover, most

physicians are refractory to innovation: they prefer drugs that have already proven their efficiency and safety. So, the pharmaceutical industry that commercializes the first-in-class drug has to be sure of the molecule and has to convince physicians of the benefits of the drug.

However, the best-in-class molecule is not always the first-in-class. Indeed, as the priorities are the health and the safety of the patient, the pharmaceutical industry keeps discovering new products until the patients and physicians are totally satisfied^[34]. This strategy increases the competition into specific therapeutic areas where all laboratories want to be. Indeed, the market is more or less always the same size but the more products on it, the less market shares are available^[34].

This strategy can be seen as a useful alternative to enhance therapeutic options for a particular patient (i.e. with different metabolism for instance) as well as to introduce price competition inside one therapeutic area. For example, one major therapeutic area with many me-too drugs is lowering-cholesterol drugs. Many laboratories have their statins: drugs that inhibit an enzyme (HMG-CoA reductase) to decrease the level of LDL-cholesterol. Currently, there are five products on the market in France: *atorvastatine* (Tahor[®]), *fluvastatine* (Fractal[®], Lescol[®]), *pravastatine* (Elisor[®], Vasten[®]), *rosuvastatine* (Crestor[®]) and *simvastatine* (Lodales[®], Zocor[®]) and most of which have generics. As these products do not have major differences (i.e. only pharmacokinetic and pharmacodynamics differences), drug promotion is very important to increase information about the drug and thereby enhance its prescription.

On the other hand, this strategy can also be seen as duplicative and “selfish”. Indeed, the resources used to develop me-toos could have been better used elsewhere (in a therapeutic area with unmet medical needs for example) to help developing more innovative products^[25].

2.4- Interesting prices and high level of reimbursement more difficult to obtain

From a drug developer’s point of view, there is a rising cost pressure from payers. The key word is now: cost containment. Indeed, payers such as social security (in France) and complementary health insurances have increased their reimbursement conditions. The major actor in France is the social security. It is for now vital for pharmaceutical industry

companies to use a robust pricing and reimbursement (P&R) strategy to justify a drug's reimbursement level^[31].

As they are more and more drugs on the market, the social security chooses the reimbursement levels regarding the medical value that the drug can bring to patients. For example, many manufacturers keep developing associated forms of drugs (e.g. statin combined with *acetylsalicylic acid* in Pravadual[®]) to decrease the number of tablets per day. Ten years ago, these medicines did not have any trouble to get the approval and a reimbursement. Nowadays, these medicines are no more considered as having a high medical value so it is more difficult and longer to get a reimbursement.

To be more precise, in France, it is the Comité Economique des Produits de Santé (CEPS) that sets drug prices. According to the article L. 162-16-4 of the Social Security code^[24], the CEPS has to take into account some criteria such as: the improvement of medical service provided by the drug, the other prices of drugs in the same therapeutic area, the sales volume expected or observed as well as predictable and current utilization of the drug. Moreover, an agreement exists between the CEPS and the LEEM. This agreement guarantees that the price of drugs with level I to III of Amélioration du Service Médical Rendu (ASMR) will not be lower than the lowest price between the four major European comparable markets (Germany, Spain, Italy and Great Britain)^[35].

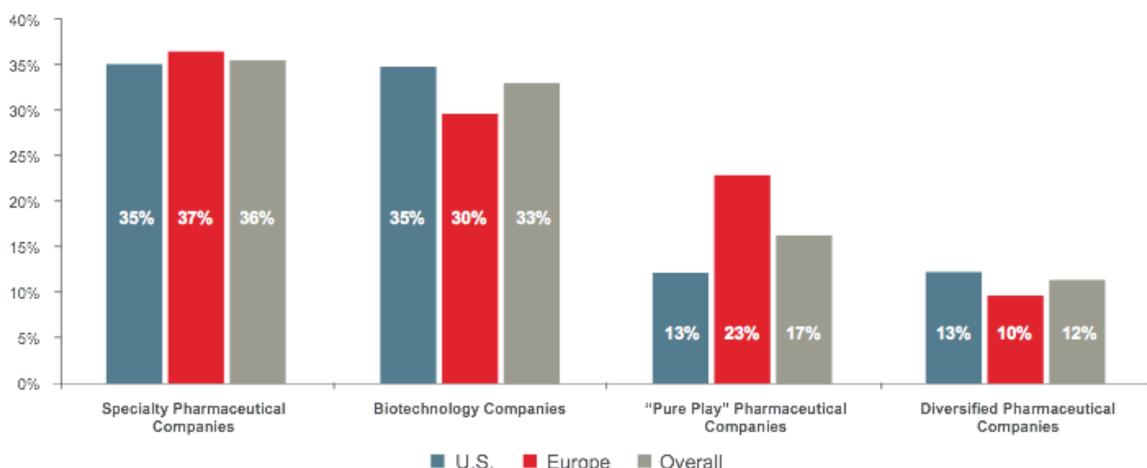
Nowadays, it is more and more complicated to obtain high level of ASMR because of the lack of novelty and innovation of drugs. As the reimbursement environment is becoming increasingly stringent in the major markets (i.e. France, Germany, Great Britain...), one solution could be that companies should find solutions to target specific patient subpopulations that respond better to the drug or for which there is a better safety profile. This method will allow gaining higher reimbursement levels^[31].

On the contrary, generics have an easier legislation process. Indeed, generics have a substantial impact given their effectiveness in terms of containing costs. This is why, they have easier and quicker reimbursement environment^[31]. Finally, these price cuts and reimbursement restrictions continue to limit growth in an environment that needs it^[16].

2.5- Increase and hardening of investors expectations

Investors are considered as the key decision makers for public life sciences companies. As they are the ones that invest money, they want to have high return on their investments. Due to the 2008 crisis, the amount of investments dedicated to pharmaceutical and biotechnologies companies have decreased^[36]. However, in 2012, European investors appear to be more positive and consider the pharmaceutical sector as a more attractive investment opportunity than in the previous years^[36]. The figures show that 53% of these investors agree to say that the recent global economic conditions are increasing appetite for healthcare investments^[36].

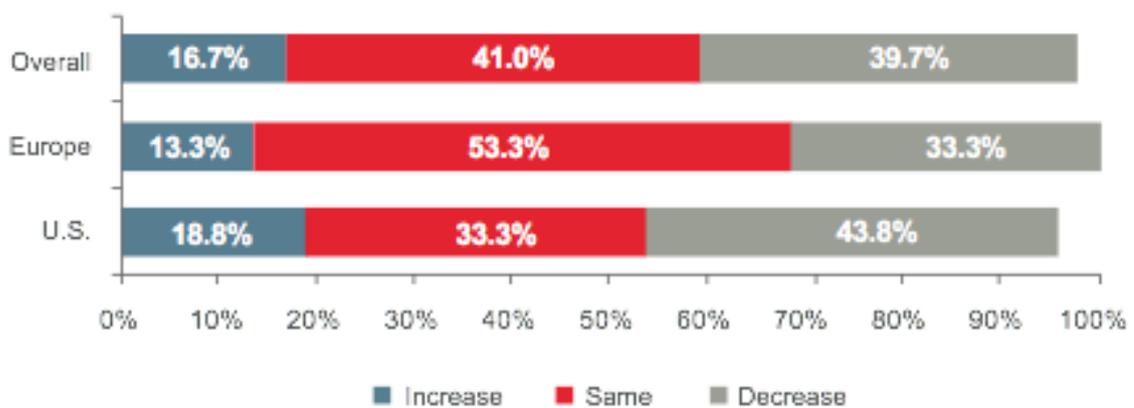
However, investors prefer a certain type of company to invest in. Actually, two out of three investors prefer a well-focused pipeline to a too diversified pipeline strategy. For example, they think that the therapeutic areas that provide the greatest revenue opportunities are: oncology, cardiovascular, autoimmune, infectious and neurological diseases^[36]. This is the reason why investors (USs as well as Europeans) tend to invest more in biotech companies [Graph 3] considered as more specific than conventional “Big Pharma”. But, investments into Specialty Pharmaceutical Companies are also high [Graph 3] because US and European investors express some level of confidence in the decision made by certain pharmaceutical companies to diversify themselves into non-traditional areas such as animal health or generics for example^[36].



Graph 3: Percentage of investors that could invest in each type of healthcare company in 2012^[36]
(Source: Investor expectations for the pharmaceutical sector in 2012)

Nevertheless, when investors are not satisfied with the sales of the company and their return on investments they could become more stringent. A concrete example this year was the resignation of AstraZeneca’s CEO (Chief Executive Officer), David Brennan (pushed out according to the BBC) on April 2012^[37]. Firstly, the company reported a 44% drop in profits in the first of 2012. Then, investors and analysts were frustrated by the failure of the company to achieve an efficient policy of acquisitions and licensing agreements^[37].

Nowadays, investors are controlling companies. But that situation is not necessarily the best one. Investors primarily look for a return on investment whereas pharmaceutical and biotech companies main interest is in the health of the patient. The strategies and returns expected for both are not exactly the same [Graph 4]. Pharmaceutical companies need to diversify their portfolio of drugs and find innovative and new drugs in order to comply with the requirements of investors in terms of ROI and profit. The best way for them to discover new drugs is to increase their R&D spending. However, investor’s (Europeans as well as USs) do not appear to approve this strategy. For instance, nearly 40% of the overall investors think that the R&D spending should decrease for pharmaceutical companies [Graph 4].



Graph 4: European and US investor’s expectations for R&D spend as percentage of revenues among pharmaceutical companies in 2012^[36]
 (Source: Investor expectations for the pharmaceutical sector in 2012)

All these reasons explain why the pharmaceutical industry is currently under a lot of pressure. It has to deal with many different actors to sustain its growth and its revenue. But it has also to find some innovative solutions to counter these issues and keeps investing in R&D.

3. Solutions implemented by the pharmaceutical industry to counter these issues

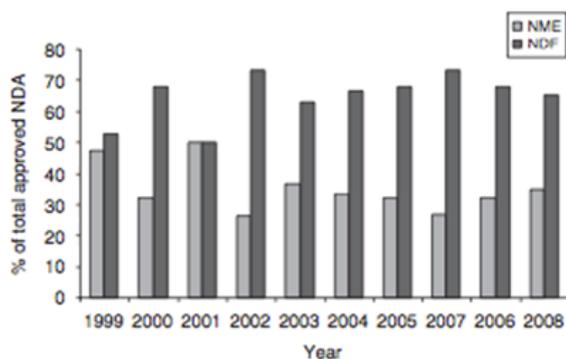
3.1- Strategic measures realized by the pharmaceutical industry from a product and company point of view

3.1.1- Product differentiation to counter threat from generic and biosimilar

Pharmaceutical and biotech industries develop both strategic solutions as well as solutions that directly concerns the drug itself to counter the threat of generics and biosimilars. These solutions are not the same whether they concern a chemical or a biological drug.

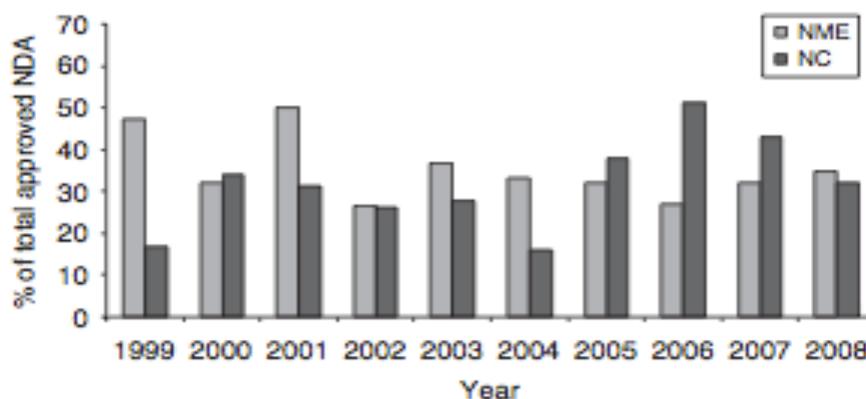
On the one hand, for a chemical drug, the three main strategies that can be used to differentiate the drug from its generics are: the creation of new dosage forms, or fixed drug combinations and the research for new therapeutic indications for an already existing molecule^[8].

First, new dosage form is the most effective tool to enhance the product life cycle of chemical drugs^[8]. During the drug development process, conventional drugs are generally produced in form of tablets or capsules. These forms are the preferred options because of the short development time (because of mature technology and lower challenges), the scalability and the high user acceptance. However, these factors make them vulnerable to a quick genericization. This is the reason why innovative companies are now launching their molecules in new dosage forms that have technical challenges^[8]. That leads to an increase of the number of new dosage forms for the number of new molecules [*Graph 5*]. Significant advantage, these innovative formulations may allow for a secondary patent that extends the period of exclusivity of the product.



Graph 5: Trend of US FDA approval rate of new dosage forms compared to new molecular entities from 1999 to 2008^[8] (NDF: New Dosage Form)
 (Source: <http://www.fda.gov/cder/rdmt>.)

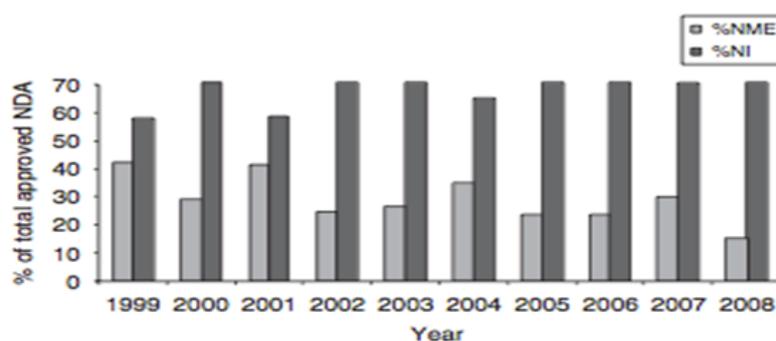
Some innovative dosage forms are under investigations for now. The most preferred choice is the controlled release oral form^[8]. However, this area has been rigorously researched and has little ways for improvement and higher technological differentiation. Thereby, other dosage forms based on new technologies have emerged. For instance, some innovative technologies have already been successfully launched on the market like: timed-release formulations, site-specific drug delivery, depot formulation or inhalation drug delivery^[8]. These technologies have two major benefits. First, they are hitting domains with little knowledge from other companies (in particular generics companies), so it is easier to find a novel and patentable concept. Second, the lack of knowledge from others grants a monopoly on the market for a longer duration. For instance, a new dosage form of *paclitaxel* (Taxol[®]) has been launched on the market. It consists in a nanoparticle-albumin bound with *paclitaxel*^[18]. This new formulation is called Abraxane[®] and is indicated in metastatic breast cancer^[18]. The link to the albumin allows higher concentration of drug to the targeted site.



Graph 6: Trend of US FDA approval rate of fixed drug combinations and new molecular entities^[8]
 (NC: New Combination)
 (Source: <http://www.fda.gov/cder/rdmt>.)

Next, fixed drug combinations combine two or more existing molecules. This strategy has proved to be another winning one and has been steadily increasing from 1999 to 2008 [Graph 6]. This strategy involves the identification of molecules, which, when prescribed and given together, results into better therapeutic effect or tolerability^[8]. The indication of a combination therapy is based on a proven bioequivalence (of this combination) with the two drugs individually. One example could be the famous Pravadal[®] (*pravastatine* and *acetylsalicylic acid*) used to prevent the recurrence of a cardiovascular event^[19]. Combinations may increase the patient compliance to its treatment and thereby diminish the costs for the Social Security. Furthermore, if the combination product is launched in a new indication, the drug can be treated as a new agent and receive significant market exclusivity^[3]. But more commonly, a fixed drug combination is only protected by the formulation patent surrounding the combination technology. One drawback is that the combined drug has to face the competition from the companies producing the individual products^[3].

The last strategy for chemical drugs is the development of new indications for an already existing and patented drug. This strategy involves new preclinical studies to identify new drug targets. Then, clinical trials are performed in order to demonstrate the efficiency and safety in treating human patients suffering from an identified disease^[7]. The number of new indications approvals has been significantly higher, and even, doubled in recent times compared to new molecular entities between 1999 and 2008 [Graph 7].



Graph 7: Trend of US FDA approval rate of new indications and new molecular entities^[8] (NI: New Indication)
(Source: <http://www.fda.gov/cder/rdmt>.)

This tactic allows an increase in the market size due to the expansion of the indicated indications. But it also creates a barrier for the generics entry as such approvals grants three years of market exclusivity^[8]. An indication expansion can be obtained by demonstrating effectiveness in, for instance, pediatric population, other disease areas or different related conditions. However, this strategy requires significant investments in R&D and careful strategic planning^[3]. The different parameters that have to be taken into account for differentiation strategies for chemical drugs can be classified in five categories [Table 5]: cost of formulation development, clinical trial cost, susceptibility to generic competition, complexity to implement and who does it^[8]. These indicators can also be characterized according to the three strategies [Table 5].

Differentiation strategy	Implementation suitability indicators				
	Formulation development cost	Clinical trial cost	Susceptibility to generic competition ^a	Complexity to implement ^b	Who does it
New dosage form	High	Low to medium	Medium to high	Medium	Generic as well as innovators
New combinations	Medium to high	Low (for substitution indication) to high (label claim indication)	Low	Medium to high	
New indications	Low to medium	High	Very low	High	Innovators

^aIndicates generic companies' potential either to develop non-infringing process, or invalidate innovator patent.

^bConsidering proof-of-concept, preclinical and clinical studies.

Table 5: Various differentiation strategies and suitability indicators for their implementation^[8]
(Source: Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing)

As regards biological drugs, things are a little bit different. Indeed, the three strategies used to differentiate them are: identification and creation of new delivery systems, development of new indications, and combination therapies^[8]. For example, new delivery systems consist in prefilled syringes, cartridges or multidose pen. New dosage forms are not interesting for biotech drugs because they are generally administered by the intravenous route. Moreover, few techniques have the potential to change the pharmacodynamics of these drugs^[8]. For instance, pegylation is one of them, and was used for Pegasys[®] (*pegylated α 2a-interferon*). This drug has needed thorough preclinical and clinical evaluation to determine its safety and efficacy. It was then approved through full biologics license application^[8].

Finally, other differentiation strategies exist, even though they are less important regarding the previously ones^[3]. First, some companies facing patent expiration choose to invest in generics by introducing their own generic drug or even license the drug to a generic company short time before the expiration of the patent, in exchange for royalties. Then, a common sense strategy is maximizing the brand loyalty. It means that during the period of exclusiveness, companies have to invest in the brand name to increase the brand loyalty. Indeed, this investment makes it more difficult for generics to enter the market competitively. Regulatory approaches are also more and more present. Litigations have almost become an accepted and necessary part of business models for research-driven pharmaceutical companies. Pricing strategies are also fundamental in order to face the prospect of less expensive generics flooding the market. Three options may be available to companies: maintain, decrease, or increase the price. Maintaining the price may lead to a potential decrease of the sales volume. Increasing the price can increase the short-term profitability (but prices are controlled in some countries). Decreasing the price may be dangerous because it will lead to meet the competition head on. Next, some research-driven pharmaceutical companies choose to switch products from prescription to OTC status. This strategy allows companies to extend their brand and reduce market loss to generic companies. Moreover, OTC drugs benefit of an advantageous status in France, because they can be advertised to patients and prices are fixed by the concerned laboratory. Finally, the last solution to increase product differentiation is the divestiture. Divesting a product involves cutting promotional and research expenses, selling the product or licensing its manufacture (once the brand faces direct competition from generics).

To conclude, there are many ways to improve product differentiation. Their main objective is to face and counter the generics and biosimilars competition. These ways depend on different criteria such as the type of drugs (chemical versus biological) or the overall strategy chosen for the product.

3.1.2- Strategic Mergers and Acquisitions to diversify pipelines

M&A (Mergers and Acquisitions) refer to the consolidation of companies. A merger is a combination of two companies to form a new one. An acquisition is the purchase of one company by another in which no new company is formed^[38]. During the previous years, in the pharmaceutical industry, a series of mergers has created a handful of very powerful players. This is why in 2007, only 10 firms controlled almost 56% of the healthcare market^[18], against 20% in 1985^[38].

Two different actors play a part in M&A: large pharmaceutical companies and small biotechnology companies (usually start-ups). First, the pharmaceutical industry is still research-intensive but there is an evidence of apparently declining R&D productivity in these large firms. In fact, the number of compounds discovered by “Big Pharma” has decreased^[38]. Innovation is the key of R&D nowadays. But, small biotech companies currently detain innovation. This is why M&A could be of interest to pharmaceutical firms in order to develop their pipelines. Thus, for large firms, mergers are frequently the response to fill the gap coming from patent expirations in the product portfolios^[38].

However, for small firms, mergers appear to be primarily an exit strategy (mainly for companies with financial trouble: few products and low cash-sales ratio)^[38]. Most of these small firms do not have marketed products yet but have financial difficulties. These difficulties are more likely to come from high R&D investments and no ROI instead of patent expirations for “Big Pharma”.

Some profitable M&A occurred in the previous years. For instance, there was the acquisition of Genentech[©] by Roche[©] in 2009, for €38,2 billion. This acquisition enabled Roche[©] to acquire biological molecules that have the potential to become (or are becoming)

best selling products like: Avastin[®], Herceptin[®], Rituxan[®] or Tarceva[®]^[39]. Another one in 2011 was the acquisition of Genzyme[©] by Sanofi[©] for almost €15 billion. Genzyme[©] had many products corresponding to niche indications like Fabrazyme[®] (for Fabry disease) or Cerezyme[®] (for Gaucher disease)^[21]. As there is no competition on these markets and easier regulatory approvals, these drugs are profitable.

To conclude, mergers may improve efficiency for “Big Pharma” as well as small biotech companies. Furthermore, gains to shareholders at announcement of a merger reflect improved expectations of future cash flow performance^[38].

3.1.3- Alliances and partnerships to share the risks

One other solution for the pharmaceutical industry to create added value by promoting innovation, sharing risks and reducing costs, is the realization of partnerships. Different types of partnerships can occur. First, “Big Pharma” can create a partnership with small biotech companies or with leading academic institutions in order to acquire for example new technologies or to help in a product development. This solution can be of interest for the big company as it may help to fill the gap in the pipeline, as well as for the small biotech company that will have more cash to realize its projects^[16].

Then, a “Big Pharma” can also partner with another one^[16]. For instance, Bristol Myers Squibb[©] is currently partnering with Pfizer[©] for the development and the launch of a new product: Elikvis[®] (*apixaban*) in the US and in Europe. This is an anti-clotting drug, which is already considered as a future best selling product and that has already obtained its approval on May 2011 in France. As Pfizer[©] lost the patent for its famous Tahor[®] (Lipitor[®]) this year, this molecule with shared risks can be of high interest to help them filling the gap.

As the regulation in the pharmaceutical industry is more and more stringent pharmaceutical companies have to share risks^[16]. Indeed, even for a promising molecule with a high medical need, a long time is necessary to be granted the final approval. This time corresponds to a big shortfall because there is no gain regarding this molecule but you still

need to spend money to realize for example the strategy for the drug promotion or other clinical studies.

Thus, alliances and partnerships are a good opportunity for pharmaceutical and biotechnology companies to develop innovation and fill the gap in the pipeline by sharing the risks and the money together.

3.1.4- Development of personalized medicine and current progresses

Personalized medicine corresponds to the use of information about a person's genetic heritage to tailor strategies for the detection, treatment or prevention of diseases^[40]. This type of medicine is currently spreading because of the advances in genomics. Indeed, there is currently remarkable progress in the field of oncology because of the increase of information about the genetic origin of disease in this domain^[40].

However, some companies missed the opportunity of developing the pharmacogenomics tests linked to these drugs. One example might be AstraZeneca[©], with its famous Iressa[®] (*gefitinib*). This drug was firstly indicated for cancer treatment, more precisely non-small-cell lung cancer. Iressa[®] is an inhibitor of the EGFR (Epidermal Growth Factor Receptor), a growth factor overexpressed in several tumor types including head, neck, breast, gastric, colorectal, pancreatic or non-small-cell lung. Iressa[®] was found to be highly efficient in some patients and ineffective on others. After some researches, responders to *gefitinib* were found to have some specific mutations in the domain containing a pocket targeted by the drug (most often in non-smoker populations and women). But the company did not use this discovery to restrict its indications to patients presenting the mutation. Then, two other companies commercialized two other products: Erbitux[®] (*cetuximab*) for Merck Serono[©] and Tarceva[®] (*erlotinib*) for Roche[©] and seized the opportunity to launch the first EGFR-targeted therapies. To conclude, AstraZeneca[©] missed a golden opportunity to capitalize on pharmacogenomics information from *gefitinib* responders^[40]. However, despite this misadventure, AstraZeneca[©] succeeded in maintaining its sales and turnover regarding Iressa[®].

Personalized medicine could be of interest for pharmaceutical as well as biotech companies. In fact, developing specific molecules that target one category of patients is costly but regulatory authorities are highly demanding this type of drugs. This strategy may, at the end, lead to a decrease of the medical costs. Pharmacogenomics help to determine the basic mechanism of action of the drug and thereby which patient can be treated by which therapy. If the laboratory can prove that this drug is effective on the patients bearing this mutation, physicians can prescribe more easily after determining the mutation status of the patient^[40].

At the end, the objective would be, first, to help the early detection of disease and then, to have one drug designed for one category of patients (and even ultimately for one patient). Moreover, early detection of diseases and treatment with targeted therapies could lead to higher efficient results^[40].

3.1.5- Niche indications

In the 90s, pharmaceutical companies have crowded their portfolios of cancer treatments by developing newer chemotherapies with even little therapeutic difference with the ones already marketed^[16]. But, launching treatments with low medical added value for the patient compared to the previous ones has been considered as not enough profitable by the companies. This is the reason why niche indications are attracting more and more attention^[31]. Indeed, they will help to diversify the risk associated with the over-dependence on a few products.

Niche indication may be defined as an indication with a highly unsatisfied medical need as well as a very low number of patients. It is also related to orphan diseases. Orphan diseases are low prevalence diseases: less than 5 per cent per 10,000 of the population for the European Union^[41]. This is why they had not been adopted by the pharmaceutical industry earlier as they were not considered as profitable enough.

However, some companies have succeeded in this specialization in niche indications like for example: Genentech[©] (which is now belonging to Roche[©]). Genentech[©] focused

mainly on changing the way cancer was treated instead of launching new chemotherapies. Thereby, they commercialized monoclonal antibodies like Herceptin[®] (*trastuzumab*) or Avastin[®] (*bevacizumab*)^[16] that were considered as innovative and efficient drugs to treat cancer. But the most successful company in this area was certainly Genzyme[®] (which is now a part of Sanofi[®]). This company succeeded in launching drugs for very rare cases such as Fabry disease or Gaucher disease^[21]. For instance, Fabry disease corresponds to an increase of the amount of a substance called globotriaosylceramide (or GL-3). This substance builds up in cells lining the blood vessels of the kidneys and certain other cells. Fabrazyme[®] (*agalsidase β*) helps lowering this level. The disease prevalence is very low with one to five patients out of 10,000^[42]. Another useful drug from Genzyme[®] is its Cerezyme[®] (*imiglucerase*) indicated for Gaucher disease^[21]. This disease affects one to nine patients over 100,000^[42]. This drug is a long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher disease with one or more of the following conditions: anemia, thrombocytopenia, bone disease and/or hepatomegaly (or splenomegaly)^[21].

There are some advantages to developing a drug for a niche indication^[31]. First, there is a highly unsatisfied medical need in these areas. So, the development costs are reduced because of the decrease of the time of the clinical trials. Also, the regulatory authorities are more inclined to deliver the approval and to an easier route to higher levels of reimbursement. Then, competitors often tend to regard these indications as not enough interesting. This is why there is a limited competition in this domain. Finally, the marketing strategy is also less expensive because it depends on cost-effective targeted marketing to specific physicians^[31].

For instance, Glivec[®] (*imatinib*) from Novartis[®] is indicated for chronic myeloid leukemia and stromal gastrointestinal tumors. But all the patients cannot benefit from this drug. Indeed, Glivec[®] can be prescribed only when a mutated protein (BCR-ABL) due to a chromosomal translocation between the chromosomes 9 and 22 (called Philadelphia chromosome) is found in the patient. This mutated protein is responsible for the proliferation of malignant cells. So, the prescription of *imatinib* is restricted to patients presenting this protein^[40]. This is why it is considered as a niche indication.

3.1.6- Creation of innovative business models

The pharmaceutical and biotech sector is subject to numerous types of uncertainty previously detailed throughout drug development. In order to counter these uncertainties, some companies decide to change their business models. BioAlliance Pharma[©] is a French listed biopharmaceutical company created in 1997 and specialized in cancer and supportive cares for cancer-associated diseases (complications from chemotherapy, radiotherapy or opportunistic infections in immune-compromised patients)^[43]. This company conceives, develops and partners innovative products dedicated to orphan oncology and specialty pharmaceutical products (niche market). The specificity of BioAlliance Pharma[©] is the development of drugs from already well-known active substances with a safety profile already determined. The objective is to fight drug resistance and improve the health and the quality of life of patients suffering from diseases with high unsatisfied medical needs^[43].

BioAlliance Pharma[©] has a portfolio of five business models: orphan drug business model, proprietary technology platform business model, development (early phase) business model, repurposing business model and drug recycling business model^[43]. These five business models are interconnected all together. First, BioAlliance Pharma[©] has currently four drugs in its pipeline for the treatment of orphan diseases in oncology, including supportive care for cancer-associated diseases. The diseases targeted are considered as the ones with strong unsatisfied medical needs (lethal disease, highly incapacitating conditions...)^[43]. Then, BioAlliance Pharma[©] has two proprietary platforms: Lauriad[™] and Transrug[™]. These platforms are based on innovative drug delivery systems. The Lauriad[™] technology lies in muco-adhesive tablets that allow the immediate release of the active substance at high concentration in the buccal area. On the other hand, the Transdrug[™] technology is a nanoparticulate form of an active substance that has the ability to mask it from cellular components that could contribute to drug resistance^[43]. After, this company has also secured partnerships with public institutions for the development of some drugs. Indeed, their only biotech drug is co-developed with the INSERM (Institut National de la Santé et de la Recherche Médicale)^[43]. The repurposing business model consists in using a well-defined molecule in another indication. For instance *clonidine* (that is still used for the treatment of hypertension), which is off patent, has demonstrated anti-inflammatory properties. So, the strategy is to prescribe it for the treatment of oral mucositis that is affecting almost all patients suffering from cancers and that have been treated with radiotherapy^[43]. The last

business model named drug recycling business model corresponds to the combination of the two technologies developed by BioAlliance Pharma[®] on molecules which are no longer patented (e.g. *doxorubicin* indicated in the treatment of some cancers)^[43].

BioAlliance Pharma[®] possesses an interesting and innovative business model portfolio that reduces the financial as well as the technological risks inherent with the development of drugs. Thereby, it could be interesting for the pharmaceutical industry to diversify itself and to create different strategies with innovative business models.

3.2- Changes and improvements in drug promotion

3.2.1- *Communication and promotion: what differences?*

Communication has many different aspects. In general terms, communication is defined by the imparting or exchanging of information by speaking, writing, or using some other mediums^[44]. The means used to send or receive this information can be declined in various ways: phone calls, mailing, emailing, face-to-face... All those tools are a part of the marketing and the drug promotion.

Communication, which is a component of marketing, plays an essential role in the pharmaceutical industry. Indeed, the drug promotion is an effective way to increase turnovers of laboratories, by improving the knowledge of the healthcare professionals about drugs (and thereby increase the drug sales). But communication is slightly different from drug promotion. Indeed, meeting the 4P's rule (Product, Price, Place, Promotion) is not enough. Companies have to communicate about their product. This means explain what the offer is about. The two key words surrounding communication are: inform and persuade. Indeed, communication in a marketing point of view consists in transmitting messages to the public to change their mental behavior and thereby their effective behavior^[44]. This is why companies have to answer to the four questions before entering into the communication itself:

Why do we want to communicate?

What do we want to communicate?

To whom do we want to communicate?

Which are the mediums that we want to use?

After all the answers to these questions have been determined, the marketing strategy, the means and the insights that will be used can be defined. The more precise you are regarding the people that are targeted, the more effective you will be.

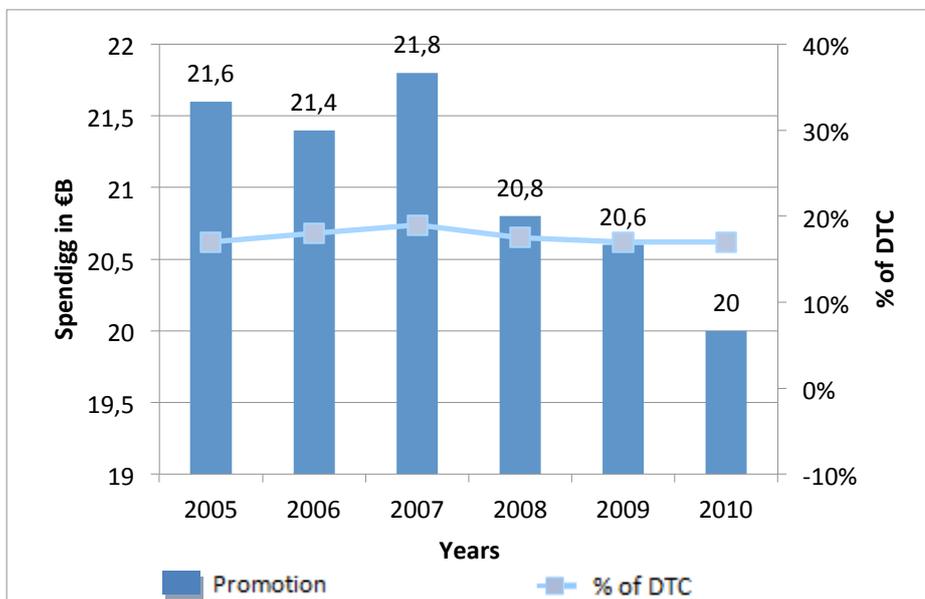
Promotion is a marketing term included in the 4P's rule. More precisely, it is a part of communication. Promotion consists of facilitating or stimulating some effective behavior, including the purchase of a product by any means^[45]. An example commonly used by marketers is a distribution of free samples of a product in order to have it tested by consumers. But, in the pharmaceutical industry this strategy cannot be used. Indeed, as the final consumer is the patient, many other criteria have to be taken into account like mainly the safety of the drug.

The 4P's rule consists of four marketing mix instruments: Product, Pricing, Placement and Promotion^[46]. Essentially, it corresponds to the strategy implemented by the manufacturer (or more specifically the marketer) regarding its market. The Product can be anything that can be introduced on the market with the ability to meet a certain need. For the pharmaceutical products, it is generally linked to "being healthy".

The different variables that have to be taken into account for general Products are: quality, characteristics, brand, size, packaging, guarantee and after-sales service. However, a pharmaceutical product is supposed to primarily benefit to patients but there are also some expectations among prescribers and payers^[46]. This is the reason why, only the quality, the characteristics (e.g. dosage, formulation...), the brand, the packaging and the after-sales service (or pharmacovigilance) are important for drugs. Then, the Price parameter has not to be considered for ethical drugs as prices are only partially determined by the laboratory. The Place of distribution is also easy to determine for pharmaceutical products. Finally, the Promotion point is currently more complicated to clarify. It depends on some factors like the product itself as well as on the company strategy. Moreover, one key promotional parameter for drugs is the sales force dedicated to them. According to the turnover and the strategy of the company there are more or less sales representatives. Nevertheless, nowadays, new and innovative drug promotion methods are emerging.

Pharmaceutical promotional spending used to be very high. They even blew up in 2007 with a total spending in drug promotion of about €22 billion worldwide [*Graph 8*].

However, since 2008, these figures are decreasing (€20.8 billion in 2008 to €20 billion in 2010). The major cause of this decrease could be the worldwide economic crisis of 2008. This was also the period of many losses of patents on blockbuster drugs to the benefit of generics that do not need much promotion.



Graph 8: Pharmaceutical promotional spending in the world depending on the year^[47]
 (Source: [http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan Presentation%20IMS%20Health.pdf](http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan%20Presentation%20IMS%20Health.pdf))

Pharmaceutical companies have high expectations regarding drugs sales. They have high objectives that have to be met in order to reach the desired turnover. To achieve these levels of sales, pharmaceutical companies have to be aggressive in their promotion of drugs^[48]. This is why innovative strategies are implemented through other means of communication. For instance, pharmaceutical marketers are currently demonstrating increasing comfort with online media and Customer Relationship Management (CRM) programming. They are also getting serious about focusing on the retention of patients as well as the acquisition of new ones^[49].

The final outcome of drug promotion would be to obtain better educated consumers because they are more likely to comply with their doctor's prescriptions and orders and thereby persist in taking their medication^[49]. This is why strategies are currently implemented like for example unbranded educational ads targeted towards patients. However, these ads

might only make sense for products with a whole category to themselves (no competition on the market). Otherwise it would be like handing market shares to the competition^[49]. Thereby, drug promotion has to be thought by marketers regarding all these points in order to reach the maximum number of patients and healthcare practitioners.

3.2.2- Two types of recipients: healthcare practitioners and patients

The main targets of the pharmaceutical industry regarding ethical drugs are healthcare practitioners: physicians as well as pharmacists. These people are the ones that are the most implicated in the prescription and deliverance processes. This is the reason why pharmaceutical industries have to be very present in the physician's daily routine in order to increase the knowledge of their brand.

In the case of a market with a limited number of competitors, there are few issues regarding the role of the sales reps. As there are not many therapeutic options, physicians prescribe the molecule that they consider the most efficient for a particular disease. On the other hand, in the case of a market full of competitors, physicians are overwhelmed with information.

One good example could be the market of lipid-lowering drugs. There are different therapeutic classes that can be used for this problem. Moreover, there are about five drugs in each therapeutic class. So many therapeutic solutions exist for this condition. This is why physicians have to be aware of all the existing alternatives in order to improve the quality of life of people suffering from this disease. Laboratories are implied in this process. They have to visit physicians as well as pharmacists to improve the knowledge of their medicines. To achieve that, they have to deliver objective information about their product, on the basis of the studies realized.

However, the attitude of physicians towards promotion vary and do not necessarily match their behavior^[50]. The drug promotion can use different media and each physician has his favorite one(s). For example, the most widespread is the sales call performed by sales reps. At the beginning, this media was very appreciated from physicians. But for now, each

laboratory has a high number of sales reps that have to see a huge number of physicians. Thereby, physicians are tired of these visits. This is why their opinions differ on the value of sales reps and on whether doctors are adequately trained to interact with them^[50]. Some healthcare professionals think information coming from pharmaceutical companies is biased whereas other think it is useful. It depends on the way of thinking of physicians and their availability^[50]. Finally, physicians that tend to rely on drug promotion seem to have generally always the same profile: they are more likely to be older and GPs. But drug promotion is one of the only way for physicians to get to information about new drugs that are coming on the market^[50].

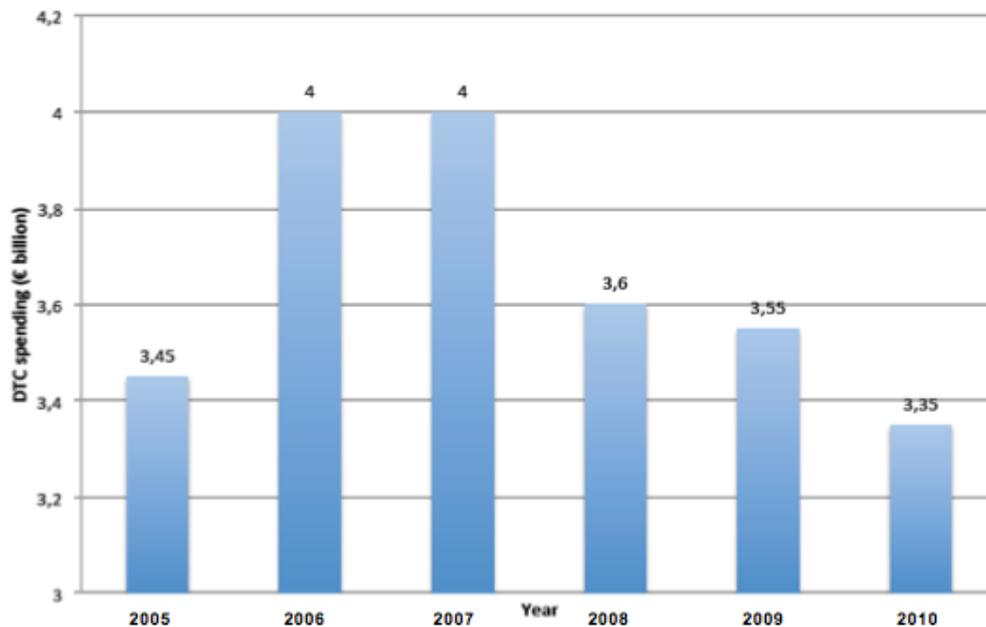
The other target of the pharmaceutical industry is the patient. Pharmaceutical firms have discovered that more and more patients tend to inform themselves about their diseases on the Internet, before and also after having seen a physician in order to auto diagnose themselves. It is a way to get around the process of negotiating with a physician^[49]. This is why pharmaceutical firms want to improve the knowledge of patients by informing them on disease awareness (because they are not allowed to communicate about drugs).

Direct To Consumer (DTC) advertising is defined by the use of mass media (e.g. TV, magazines, newspapers, Internet...) to publicly promote drugs, medical devices or other products which require a prescription and target consumers^[50]. The goal of DTC advertising is to introduce the product to future potential patients.

In France, DTC advertising is only allowed for environmental advertising and not for product advertising (in the case of a prescription drug). There is an increasing pressure from health authorities to convince pharmaceutical companies to advertise in a more responsible way. They are asked to advise about risks more clearly and run more disease-awareness ads^[49]. Trends indicate a shift away from mass-market media ads (like TV or radio) to finely targeted patients, across different channels. The final objective would be to migrate from DTC to Direct To Patients (DTP) advertising.

In the middle of the 2000s, DTC spending has increased because of the born of the “digital patient”. This patient is the one who will check on the Internet all the symptoms of his disease as well as the final diagnostic of the physician. Some of them even visit their physician with their own diagnostic and the treatment that they want to be prescribed. This is

why pharmaceutical industry has highly increased its spending: from €3.45 billion in 2005 to €4 billion in 2007 [Graph 9]. However, after 2007 this figure seems to decrease: from €3.6 billion in 2008 to €3.35 billion [Graph 9]. Even though the raw number is decreasing, by comparison to the total spending in drug promotion, this number is stable (17% of all the drug promotion spending from 2005 to 2010) [Graph 8].



Graph 9: Pharmaceutical DTC spending in the world depending on the year^[47]
 (Source: [http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan Presentation%20IMS%20Health.pdf](http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan%20Presentation%20IMS%20Health.pdf))

Some drugs are more appropriate do DTC advertising than other. For example, the famous Tahor[®] (or Lipitor[®]) from Pfizer[®] is the drug with the highest DTC spending in 2010 and also the drug with the higher sales [Table 6]. Moreover, many drugs in this ranking are considered as drugs used for comfort (e.g. Cialis[®], Chanpax[®], Viagra[®]...). This is a good reason to think that DTC advertising still has good years ahead of him. Then, some newer products have entered the ranking like Pristiq[®] or Simponi[®] for example. These products are biological drugs, it means that even new therapies in areas with high unsatisfied medical needs are more and more present on the DTC advertising [Table 6]. One explanation could be that these drugs generally concern serious diseases highly invalidating so those patients are more implicated in the treatment of their disease compared to small-concern pathology (e.g. flu, cold...). This is why concerns over regulation and the return on investment of DTC advertising are prompting pharmaceutical companies to rethink how they advertise^[49].

DTC spending rank	Brand	Therapeutic area	Manufacturer	Launch date
1	Lipitor	Cardiovascular	Pfizer	Jan 97
2	Advair	Asthma, COPD	GSK	March 01
3	Cialis	Erectile dysfunction	Eli Lilly	Nov 03
4	Abilify	Depression	Otsuka	Nov 02
5	Champix	Smoking cessation	Pfizer	Jul 06
6	Cymbalta	Depression	Eli Lilly	Aug 04
7	Pristiq	Depression	Pfizer	Apr 08
8	Symbicort	Asthma, COPD*	AstraZeneca	Jun 07
9	Plavix	Platelet aggregation inhibitor	BMS-Sanofi	Feb 98
10	Lyrica	Depression	Pfizer	Aug 05
11	Toviaz	Overactive bladder	Pfizer	Mar 09
12	Crestor	Cardiovascular	AstraZeneca	Aug 03
13	Viagra	Erectile dysfunction	Pfizer	Apr 98
14	Singulair	Allergy	MSD	Feb 98
15	Bonviva	Osteoporosis	Roche	Apr 05
16	Spiriva	Asthma, COPD*	Boehringer Ingelheim	May 04
17	Simponi	Rheumatoid arthritis	Merck	Apr 09
18	Lumigan	Eyelash enhancement	Allergan	Dec 08
19	Seroquel	Depression	AstraZeneca	Jul 07
20	Trilipix	Cardiovascular	Abbott	Dec 08
21	Januvia	Diabetes	MSD	Oct 06
22	Zostavax	Vaccine	MSD	Jun 06
23	Lunesta	Insomnia	Sunovion	Mar 05
24	Reclast	Osteoporosis	Novartis	Jun 07
25	Enbrel	Immunomodulator	Amgen/Pfizer	Nov 98

Table 6: Rank of DTC spending regarding the product, the therapeutic area, the manufacturer and the launch date in 2010; in bold black: the new drugs on the list⁴⁷.

*COPD: Chronic Obstructive Pulmonary Disease

(Source: [http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan Presentation%20IMS%20Health.pdf](http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnan%20Presentation%20IMS%20Health.pdf))

DTC advertising spending is maintaining its level in comparison to total promotion spending since 2005. Some new products entered in the ranking of the higher spending in DTC advertising. It means that DTC advertising is a big issue for the pharmaceutical industry and each laboratory has to position itself on this market.

3.3.3- Apparition of new channels of communication: e-detailing, e-learning and partnerships with association of patients

The current objective of the pharmaceutical industry is to reach various audiences in order to increase the knowledge of their brand and thereby the drug sales. To reach their goals, pharmaceutical firms have to innovate regarding the medium used to contact and train physicians (or more generally healthcare professionals).

First, one new channel of communication is e-detailing (or electronic detailing). This concept has been introduced in the last few years by the pharmaceutical industry in order to promote products as well as improve awareness of the diseases of physicians and pharmacists^[48]. There are many definitions of e-detailing. Basically, it is possible to define it by the utilization of a digital technology (such as Internet, video conferences, interactive voice response...) by pharmaceutical firms to target their marketing efforts towards specific physicians with pinpoint accuracy^[48]. Two types of e-detailing currently exist: interactive or virtual e-detailing and video e-detailing. Interactive e-detailing is considered as a self-service product presentation that physicians can access at the time they choose. During this program, physicians are presented with a series of interactive learning exercises in order to reinforce the message coming from the pharmaceutical firm^[48]. On the other hand, video e-detailing is a face-to-face computer-based video conferencing between a physician and a sales rep. This type of e-detailing needs the physician to be fully provided with a webcam and some preloaded applications. Information about the product (indications, efficacy, dosage, side effects...) can appear on the screen while the sales rep guides the physician through the presentation with commentaries^[48]. Video e-detailing is more closely related to traditional detailing (face-to-face between the physician and the sales rep thanks to a visual aid). Specific physicians are targeted through mail, e-mail or through their sales rep. These physicians are chosen depending on their characteristics and practice setting characteristics.

However, in the US, research shows that the rate of adoption of this method among physicians ranges from 25% to 60%^[48].

E-learning is another new channel of communication. This channel looks like e-detailing for the media used but consists of delivering knowledge to physicians for example without talking about the product. It may be considered as continuing medical education^[51]. Indeed, in the modern world, computer-supported education is considered as the main method for training and continuing education of people^[51]. Three reasons might explain this choice. First, in this period of cutting costs for pharmaceutical firms, decreasing the costs of healthcare professionals education is very interesting. E-learning reports a cost reduction of 25 to 35% compared to traditional training methods^[51]. Several expenses may be avoided by switching to learning through a computer screen like travel expenses or salaries of specialized trainers for example. The second reason is the flexibility of education^[51]: physicians can access to e-learning modules at the time they want and when they are available. Finally, it has been proved that e-learning leads to a better and more efficient learning compared to traditional training programs^[51]. Thereby, e-learning appears to be a good compromise for the pharmaceutical industry as well as for healthcare professionals. Moreover, it is important to note that these results have been obtained for middle-aged physicians with no particular computer skills^[51].

Finally, some patients affected by chronic or rare diseases create associations in order to improve the disease awareness of others patients. They can facilitate access to new treatments. Pharmaceutical firms seized this opportunity by creating partnerships with some of these associations to increase the knowledge of their new drugs entering the market. This educational promotion might lead to increase patient compliance and persistence to the brand^[49]. However, unbranded educational ads might also be considered as handing market share to the competition in the case of pharmaceutical products without a whole category to themselves^[49].

Profiles of physicians that are targeted by these methods have been determined including type of specialty, age, gender and volume of prescriptions. These characteristics have a significant influence on pharmaceutical companies' targeting^[48]. Essentially, primary care physicians are more likely to be targeted than other specialties. Being an older male who prescribes more than other physicians is also a criterion of being contacted by pharmaceutical

firms. Furthermore, characteristics of practice setting like frequency of sales representative interaction, peer influence and size of practice were found to have a significant on the choice of targets^[48].

Despite all the mediums engaged by the pharmaceutical industry in order to find new ways to communicate with their audience, the results are still low for this type of communication. Physicians do not feel implicated with e-detailing or e-learning solutions. So, the desire to find an alternative communication channel through which to promote pharmaceutical products is still very present for pharmaceutical firms.

3.3.4- Multichannel strategies: prescriber targeting, determination of the favorite channel and advantages of these methods

Regarding the current high financial pressures in the pharmaceutical industry new strategies of promotion are emerging and are implemented. These strategies are for now mainly tested on mature products whose sales reps are not promoting any longer and whose turnovers are decreasing. As previously discussed, there are many different channels of communication in the pharmaceutical industry. But they are not all adapted to each individual physician. Indeed, the final objective of drug promotion would be to have one channel designed for one physician and which could deliver one targeted and impacting message.

More precisely, there are four main channels used in these strategies: face-to-face, digital information, phone calls and mailing information. The principle is to alternate between the different channels to prevent the physician from being overwhelmed. The major difficulty is to create the interest of the physician without being too insistent. The advantage of alternating channels is the information will reach necessarily the targeted physician. Moreover, it will allow to not solicit too much physicians (especially GPs) because all the others pharmaceutical laboratories also communicate about their products.

Of course, all these actions are monitored. For example, after six months a survey is carried out to determine if the targeted physicians have been satisfied by this campaign. This study, generally performed by phone calls, is the time to ask which channel is the physician's

favorite one. This question will allow determining the appetite of physicians to each channel. This information will be registered and used for others promotional campaigns in order to increase the “transformation rate” of drug promotion. Customer Relationship Management programs are set up in order to manage and follow evolutions of these parameters.

Pharmaceutical companies are currently trying to gather this information to realize complete files. This strategy will allow the pharmaceutical industry being more efficient in giving the right information, to the right doctor through the right channel. This will lead to decrease the costs of the drug promotion for pharmaceutical industry as well as save time for physicians. Indeed, mass-market model is producing diminishing returns. That is why multi-channel approaches might be considered as a necessary evolution in drug promotion^[49].

3.3.5- Creation of Customer Relationship Management (CRM)

CRM is currently booming. Its final objective is to increase productivity, sales and profitability by formulating direct relationship with the customer^[52]. It can be considered as a tool as well as a perspective that involves a long process in developing a true relationship. But in the pharmaceutical industry, the CRM model is more a tool than a true relation. This technology supports relationship marketing and allows management of customer relationships by integrating database management at the customer level^[53].

The growth of the Internet has significantly changed the information circulates and the knowledge available to consumers in the pharmaceutical industry. Pharmaceutical companies have seized this opportunity to introduce specific and privileged relationships with customers (physicians as well as patients). They are creating web activities to build these relationships through Internet-based CRM activities. These activities are incorporated depending on the type of customers wanted by pharmaceutical firms^[52]. Actually, Internet is the only modern accessible media that can create one-to-one relations.

In order to develop such customer centric marketing and sales strategies, two types of techniques are used: push and pull strategy. The push technique consists of communicating

and promoting drugs to physicians, to convince them to become aware of the products and thus increase the propensity of prescribing their products^[52]. On the other hand, the pull strategy is defined by the communication by the firm to patients. This strategy encourages patients to request their physicians for specific pharmaceutical products^[52].

Adoption of CRM depends on the firms. For example, Merck[®] is ranked at the top of the CRM adoption along with Eli Lilly[®] and Novartis[®]. On the contrary, GlaxoSmithKline[®] and Pfizer[®] are at the bottom of the pile^[52].

CRM is still a new strategy that has to be improved before being totally useful. But existing studies perceived the usefulness of the Internet-based strategies on the portfolio of their products for CRM purposes^[52]. Its ultimate goal will be to tie the customer to the brand or the company. For that, an integration of CRM technology into the culture and the behavior of the firm across all functional areas will be more than necessary to implement a successful customer relationship building.

4. Conclusion of the first part

The pharmaceutical industry is currently facing numerous uncertainties and challenges regarding all the R&D steps. In today's market, differentiation is more important than ever. Health practitioners care about two criteria: health outcomes and affordability of the drug. Pharmaceutical firms have implemented a certain number of solutions in order to decrease the technical and financial uncertainty as well as the risk incoming. That could be why, the number of drug candidates successfully reaching phase I has increased recently. The better preclinical characterization (thanks to the genomic^[21]) will increase this number in the years to come. Recently, investors have restarted to invest money in the healthcare sector maybe due to the end of the 2008 crisis. Healthcare sector is henceforth seen as an added value domain with possible high return on investments.

But currently the number of NMEs approved each year is still very low compared to the previous years. Pharmaceutical firms have to find other means to increase their turnovers. This is why mature products (that are still under patent) have renewed interest for companies

with poor pipelines. Many firms are currently implementing new communication and promotion strategies for these products. The final purpose would be to increase the sales of the product as well as diminish the costs of drug promotion for the firms.

New laws regarding the drug promotion have been published in France. To comply with this new legislation, the pharmaceutical industry has to change its organization and its way of promoting drugs. But the ultimate objective remains to deliver the right message to the right physicians (or healthcare professional) in the manner that he or she prefers. This will be a great challenge for pharmaceutical firms because, for now, they mainly “flood” the physicians with much communication on their products by different channels that are not always adapted.

PART 2: MULTICHANNEL OPERATION FOR THE PROMOTION OF A MATURE DRUG FROM ASTRAZENECA[®]: EMLAPATCH 5%[®]

1. Context of the company, presentation of the product and of the Key Performance Indicators

1.1- AstraZeneca[®]: context and issues

AstraZeneca[®] is a worldwide company that was founded in April 1999. It comes from the merger of Astra AB (a Swedish company) and Zeneca PLC Group (a United-Kingdom company). Both companies had close scientific cultures and shared the same vision of the pharmaceutical industry. The final objective of this merger was to improve the capacity of the newly created company to sustain a long-term growth. This merger has increased the global business operations as well as enabled the creation of a more efficient R&D platform for innovation-based growth. This strategy was introduced in order to diversify the portfolio of drugs of the two companies by increasing their investments in R&D^[53].

This merger led also to an extended coverage of key therapeutic areas, including the field of cardiovascular and respiratory diseases. Indeed, these companies had some complementary products and the merger helped to develop the drugs for General Practitioners and specialists. For example, AstraZeneca[®] is heavily involved in respiratory diseases with:

- Bricanyl[®] (*terbutaline*) for asthma (in association with an anti-inflammatory treatment),
- Pulmicort[®] (*budesonide* administered thanks to a nebulizer) to treat persistent asthma,
- Rhinocort[®] (*budesonide*) to treat allergic rhinitis,
- Symbicort[®] (*budesonide* associated with *formoterol*) for asthma and COPD,

But, it has also many drugs to address cardiovascular conditions like:

- Crestor[®] (*rosuvastatine*), AstraZeneca's best selling product to reduce LDL-cholesterol,
- The brand Atacand/Hytacand[®] (*candesartan cilexetil* associated with *hydrochlorothiazide* in Hytacand[®]) against HBP,

- Avlocardyl[®] (*propranolol*) a beta-blocker,
- Flodil[®] (*felodipine*) a calcium channel blocker predominantly vascular for HBP...

However, AstraZeneca[©] wanted to diversify its portfolio of drugs marketed in hospitals. This is why AstraZeneca[©] developed innovative anti-cancer drugs. The three main ones are:

- Faslodex[®] (*fulvestrant*) indicated for the treatment of metastatic breast cancers,
- Iressa[®] (*gefitinib*), the first personalized therapy for patients with metastatic non small cell lung cancer presenting a mutated protein (EGFR-TK),
- Zoladex[®] (*gosereline*) for hormones-dependent cancers (especially prostate and breast cancers).

Regarding the company's pipeline of drugs [*Annex 1*], a promising product, Brilique[®] (*ticagrelor*), was launched in July 2012 for the prevention of athero-thrombotic events in adult patients with acute coronary syndrome, myocardial infarction (including patients treated with drugs or by percutaneous coronary intervention or coronary artery bypass graft). Moreover, the pipeline contains other new products that should be on the market very soon, such as Komboglyze[®] (*saxagliptine* associated with *metformine*) for the treatment of type 2 diabetes or Zinforo[®] (*ceftaroline fosamil*), a new cephalosporin dedicated to cutaneous and pulmonary infections. In the future, other antibiotics should be launched, as well as new cancer-treatment drugs^[53]. Even though the future pipeline sounds interesting, these products are not willing to become best selling drugs such as Symbicort[®], Crestor[®] or Inexium[®]... As some of these drugs are close to losing their patents in the years to come, AstraZeneca[©] has to find some ways to increase its turnover. Thereby the company has to diversify its strategies and not only focus on high-return drugs.

AstraZeneca[©] had a turnover of \$33.6 billion in 2011 and is currently ranked number six of listed pharmaceutical companies. Moreover, it spends almost \$5 billion each year for R&D^[54]. But the growth of the company is decreasing for almost a year, compared to the general growth of the pharmaceutical industry [*Table 7*]. These growth and turnover decreases could be the reason why the company has to find innovative strategies to generate income.

TOP GERS (Sell-out Ph. Ind)		Aug 11	Sep 11	Oct 11	Nov 11	Dec 11	Jan 12	Feb 12	Mar 12	Apr 12	May 12	Jun 12	Jul 12
Ph. Industry	Hospital growth	3.8%	-5.6%	-1.4%	0.5%	-4.9%	7.7%	10.5%	-0.5%	11.2%	2.2%	-2.1%	15.5%
	Retail growth	-1.1%	-2.1%	-1.7%	0.0%	0.1%	-4.4%	0.5%	-2.3%	5.8%	-14.8%	-5.2%	1.7%
	Total growth	-0.1%	-2.7%	-1.6%	0.1%	-0.8%	-1.8%	2.5%	-1.9%	6.9%	-11.5%	-4.6%	4.4%
AstraZeneca	Hospital growth	-18.0%	-18.0%	-28.2%	-38.2%	-11.2%	-16.0%	-11.5%	-13.5%	-13.8%	-15.2%	-5.9%	14.3%
	Retail growth	-12.2%	-15.1%	-15.5%	-19.7%	-14.9%	-22.0%	-11.6%	-22.3%	-17.3%	-10.9%	-11.3%	-9.8%
	Total growth	-12.4%	-15.2%	-16.1%	-20.4%	-14.8%	-21.8%	-11.5%	-22.0%	-17.1%	-11.1%	-11.1%	-9.0%

Table 7: Growth comparison between AstraZeneca[®] and the pharmaceutical industry, from August 2011 to July 2012
(Source: AstraZeneca[®])

On the 26 of April 2012, the AstraZeneca's[®] CEO (David Brennan) abruptly resigned after six years in this position^[36]. Actually, investors and analysts were increasingly frustrated by the failure of the company to run efficiently operations of acquisitions and licensing deals^[36, 53]. For the next five months (from end of April to end of September), the Chief Financial Officer, Simon Lowth, carried out the interim. Then, a new chairman, Pascal Soriot, was appointed and took up his functions on October the first. Pascal Soriot is a French veterinarian, who also graduated from HEC Paris. Previously he headed the Swiss subsidiary of Roche[®].

Regarding the different issues that AstraZeneca[®] is facing, a solution (among others) is currently implemented. It consists on the promotion of mature products (i.e. products still patented) with less costly options than traditional promotion. Indeed, AstraZeneca's[®] portfolio of mature drugs is composed of many products in different therapeutic areas. Various approaches are currently underway. For instance, innovative strategies of low-cost promotion are ongoing for Zomig[®], Atacand/Hytacand[®], Emlapatch[®].... Then, the cardiology portfolio (composed of many drugs such as: Flodil[®], Logimax[®], Tenordate[®]...) is licensed to another company in charge of its promotion. Finally, the OTC rights and commercialization of Inexium[®] are conceded to Pfizer[®]. The strategy currently implemented on Emlapatch[®] seems to be the most interesting. Indeed, a multichannel program has been introduced on this drug. The objective of this multichannel program is to raise physician's awareness on the drug. Indeed, Emlapatch[®] has a positive image and a good reputation among physicians but suffers from a lack of awareness.

1.2- The product: Emlapatch 5%[®]: indications, volume of prescriptions, turnovers and targeted physicians

Emla[®] is composed of *lidocaine* (0,0250 g) and *prilocaine* (0,0250 g)^[55]. This drug is being commercialized since January 1998. Both molecules are local anesthetics: they cause a local loss of sensation and sensibility, which allows small local surgery for instance. Local anesthetics act directly on nerves by blocking specific, complete, and reversible nerve conduction. Emla[®] has two different formulations: cream and patch. The cream has already many generics on the market, which is, partly, why it is no longer promoted. Indeed, *lidocaine* and *prilocaine* patents expired three years ago. However, the patch is still under patent until 2015. Actually, Emlapatch[®] is currently patented on the model and the drawing on the patch [Figure 6]. Because both molecules are well known and widely used since the nineties, Emla[®] is considered as a safe and efficient product. The drug promotion (by sales calls) on Emla[®] is over since July 2010. Before that date, it was presented through reduced networks of sales calls. All these features can explain its status of mature drug within AstraZeneca[©].

Emlapatch 5%[®] is indicated for topical anesthesia on healthy skin (e.g. before venous and subcutaneous punctures or before superficial skin surgery: instrumental or by laser beam) [Annex 3]. Basically, it is mostly used before vaccinations or taking blood samples in children. This product is very easy to use on adults as well as on children. Indeed, the adhesive bandage has to be applied on a clean and dry surface, at least 30 minutes (depending on the age of the patient) before the intervention of the physician. At the end of the exposure time, the residue of the product is carefully removed with a compress. Anesthesia lasts for up to two hours^[55].

Then, the number of patches to be used depends on the size of the area that has to be treated: one patch for a 10 cm² anesthesia. However, the size of the patch may not be convenient for applications in newborns or infants. Emla[®] is generally well tolerated and does not have a lot of contra-indications (i.e. hypersensitivity to local anesthetics, congenital methemoglobinemia or porphyria). Furthermore, drug interactions are low and limited to others local anesthetics (to avoid a potential additive toxicity) and drugs that may induce methemoglobinemia (like sulfonamides, *dapsone*, *metoclopramide*, *flutamide* and *sodium nitroprusside*) [Annex 3].



Figure 6: packaging of Emlapatch 5%®
(Source: AstraZeneca®)

In the past few years, the turnover of Emla® (all forms included) was €35 million per year in France. This figure decreased since the genericization of the cream formulation because of the increasing generics penetration rate. It will even be considered to be lower in 2013. Moreover, there are many disparities in term of market shares between the cream and the patch and also between hospital and retail sales. In fact, the cream represents 20% of the total turnover whereas the patch is 80%. This is another reason why AstraZeneca's® program focus exclusively on promoting the patch. The main prescribers of Emla® are GPs involved in children health and pediatricians who practice retail market. Indeed, they are more prescriptions in retail market than in the hospital: 60% of prescriptions against 40% in hospitals.

To conclude, Emlapatch 5%® is a good candidate to implement a new promotional strategy. Even though this product is no longer promoted, the sales volume almost persists. Moreover, the targeted physicians are not very solicited so they might be more interested by pharmaceutical industries communication than GPs who are targeted by all pharmaceutical companies. The final objective of this campaign is to limit the decline in turnover of Emlapatch 5%® by increasing physician's awareness about this drug.

1.3- Methodology and presentation of Key Performance Indicators

To measure the efficiency of the campaign, Key Performance Indicators (KPI) must be introduced. These KPI can be divided into two types: results and key success factors,

which are also subdivided into qualitative and quantitative KPI [Table 8]. Indicators on results measure the impact of the campaign (e.g. increase in market shares or in return on investment). In this example, ROI will be determined at the end of the campaign (i.e. February 2013). Results can be of two natures, qualitative or quantitative, according to the criterion studied. Success factors are the last category and gather many different elements, which in most cases are qualitative (in the AstraZeneca’s[©] case, they are only qualitative). For example, it may include the physician's opinion (acquired during the recall tests: qualitative) or the number of physicians who were contacted by phone (quantitative). We will detail the multichannel program later. These criteria will help in analyzing the results.

KPI	Results	Success factors
Qualitative	Yes	Yes
Quantitative	Yes	No

Table 8: Summary of the different KPI used to characterize the multichannel campaign

In the case of AstraZeneca[©], qualitative parameters were obtained through tests of recall. The first test occurred three months after the first phone call (i.e. the beginning of the campaign). The next one was then carried out five months later. The tests were realized by a communication agency, specialized in strategic marketing and market surveys, among GPs and pediatricians. The objective was to evaluate the memorizing, the perception of the campaign and the evolution of prescription intentions. The first test took place from the 2nd of July to the 26th 2012. The methodology was conducted by phone interviews of 150 physicians: 100 with GPs and 50 with pediatricians. These 150 physicians were considered to be representative of the French national physician’s population. The composition of the sample interviewed is presented in the Table 9. The sample was chosen by the market survey agency in order to be specific, uniform and characteristic. The physicians’ answers were analyzed through statistical methods (Khi² for percentages and Fisher-Snedecor for mediums) to determine if they were significant (determination of p).

		GP's	Pediatricians
Gender	Male	49%	48%
	Female	51%	52%
Age	< 40 years	6%	-
	40 to 50 years	43%	20%
	> 50 years	50%	80%
Patients	< 60 patients	5%	18%
	60 to 100 patients	26%	40%
	> 100 patients	69%	42%
Location	Paris	21%	2%
	North-East	38%	8%
	South-East	41%	16%

Table 9: Composition of the sample of questioned physicians for the first recall test (Source: AstraZeneca®)

Then, quantitative KPI were measured with regular reports on the ongoing and finished operations. Those parameters were acquired throughout the campaign by the communication agency in charge of carrying out all the main operations (such as phoning, mailing and emailing). It had to monitor each ongoing and realized operation with efficient and precise indicators. The choice of these indicators depends on the type of operation. Indeed, more quantitative data are available and can be monitored through phone interviews than through emailings or direct marketings [Table 10]. These data are directly gathered and analyzed by the agency. At the end of each operation, a report with precise information is sent to marketing teams of AstraZeneca®. The analysis of the reports helps to orienting the future operations. For emailings and direct marketings, the number of quantitative data to be monitored is relatively limited. First, emails cannot be fully tracked so the only parameter available is the number of emails sent. Then, direct marketings are monitored with the number of realized mailings. Some letters are returned to AstraZeneca® because of their wrong addresses. Finally, face-to-face interviews mainly leads to qualitative parameters. The only quantitative one is the number of contacts realized [Table 10]. Moreover, some indicators allow the calculation of rates. These rates are useful to compare the results of the operations with the objectives.

	Indicators
Phoning	Number of agents
	Number of contacted physicians
	Number of realized calls
	Number of rejected calls
Emailing	Number of Emails
Direct marketing	Realized mailings
Face-to-face	Realized contact

Table 10: Indicators obtained through regular reports coming from the agency (Source: AstraZeneca®)

2. Implementation of the multichannel strategy during 2012

2.1- Overview: a global strategy characterized by a specific program

Emlapatch 5%[®] was promoted through a multichannel strategy during 2012. This program was based on alternating channels of communication used in the pharmaceutical industry (e.g. mailing, emailing/Internet, phoning and face-to-face visit). Moreover, it had two different targets: healthcare professionals (GPs involved in children health, pediatricians and pharmacists) as well as patients information [Figure 8]. Ten thousand physicians were targeted on average. An impacting logo was designed to make the program more attractive [Figure 7]. Its purpose was to realize a common thread throughout the campaign. This logo represents a teddy bear with a sword. It was decided the logo should have a pediatric connotation in order to be more easily memorized by physicians. Furthermore, a name for the program was chosen: “Même Pas Mal !”. Finally, this program was qualified as a program of services that may help physicians in the pain management for children. Indeed, an important information is that this campaign was less product oriented compared to the classical and original ones. AstraZeneca’s[®] first objective would be to become a physician’s partner in the pain management for children.



Figure 7: Logo of the “Même Pas Mal !” program
(Source: AstraZeneca©)

The “Même Pas Mal !” program was designed as a program which could deliver useful services to physicians instead of product information. This innovative strategy was introduced and implemented in order to deliver value to physicians. Its final objective was to be adopted by physicians and especially be present in a large time frame. In order to be recognized and memorized by physicians, a flyer of the program was made (*cf part 2.5*). This flyer explains that the campaign will use different channels of communication and last from the beginning to the end of 2012. Furthermore, the three main pillars of the campaign were prevention, diagnostic, support and advice. Finally, the flyer illustrates that three types of services could be delivered: to patients, parents and physicians.

The part of the program regarding physicians began at the end of March 2012. Until December 2012, an alternation of phoning, mailing, emailing/Internet and face-to-face visits was carried out. The campaign was subcontracted to two agencies selected at the beginning of the operation. One agency was selected because of its skills in face-to-face visits with physicians. The second was in charge of all other channels. For instance, it had to have its own call center to be independent and was not allowed to subcontract the tasks it was responsible for.

Regarding the general program [*Figure 8*], there was an alternation between all the channels. The goal was to have one contact with each targeted physician, at least once a month. For this, three phone calls, five direct marketings, four newsletters and three face-to-face visits (some physicians only) were set up during the 10 months. Moreover, the only specific campaign talking about the product was realized on a specialized website dedicated only to physicians during September and October. On the other hand, campaigns for patients

and pharmacists were created. The patient’s campaign was primarily focused on the environment of the product (children pain, vaccination...) and was mainly targeting mothers of children under seven years old. Finally, the campaign towards pharmacists was only based on sending documents via direct sales.

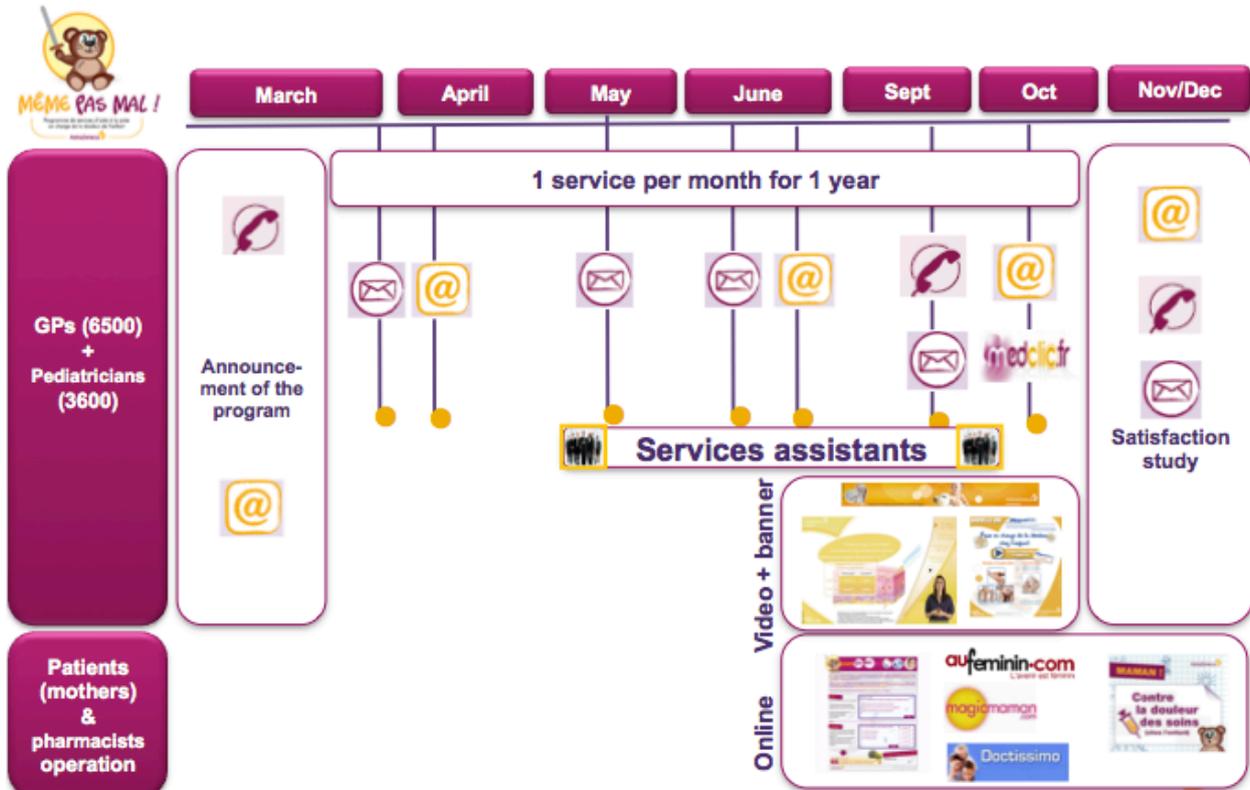


Figure 8: general scheme of the "Même Pas Mal!" program progressing during the year 2012 (Source: AstraZeneca©)

The global campaign required a significant investment of €400,000 for the year 2012. But after a few months the campaign was profitable. It means that the campaign seems impacting and efficient. To be more precise, all the different operations will be detailed in the next chapters.

2.2- Targeted operations to specific physicians

2.2.1- Phone campaign

The program was launched in March 2012 with an announcement made by phone realized by professional operators. These people were trained on AstraZeneca's[©] specific issue and on the product. The primary purpose of this phone call was to announce the launch of the "Même Pas Mal !" program and the different operations that would be organized over the coming next months. Incidentally, one of the most difficult things, if not the most, was to pass the secretary dam in order to speak directly to the physician. The easiest way was to make a phone appointment with the physician to have more time to speak with him and to explain the program. Operators did not have to speak about the product because the purpose of the program was to offer services to help physicians with management of pain. Another purpose of this first phone contact was to collect physician's email addresses to prepare the first coming emailing. Finally, the phone contact was concluded by informing physicians about the next operation to come.

The second call was carried out by the end of September. Like the first one, it had different purposes. First, it had to take some news about the physician's vision of the program, for instance: how did he perceive the program and what he would like to change. The main body of the call was the presentation and explanation of the next two services that would be provided to the physician.

The third and last phone call took place by the end of November and beginning of December. Its first mission was to announce the end of the "Même Pas Mal !" campaign and to collect comments on the quality of the program and suggestions for improvement. In this purpose, a specific questionnaire was created by the agency in charge of the campaign. Moreover, it also informed physicians of the sending of the last services of the campaign.

Regarding all the different phases of the phone campaign, the agency had to establish and communicate regularly reports of the current operations as well as those already realized. For the first two calls, it was essentially a quantitative reporting with for example: the number of calls realized and having succeeded, the number of physicians interested in the campaign,

the number of physicians who did not want to be contacted anymore... For the last call, a qualitative part was added thanks to the analysis of the results of the questionnaire.

2.2.2- E-mailing

During April, the first email of the “Même Pas Mal !” program was sent to all the physicians who accepted the continuation of the program. Actually, this email was a newsletter that presented the latest knowledge about pain. It was entitled “News in pain”. For example, it contained information on how to reduce pain with hypnosis in children with chronic pain or some means to distract children before and during a medical act in order to reduce anxiety. Incidentally, it also provided a link to Medcliv (the AstraZeneca’s[©] website in restricted access to physicians who are registered). This website contains all the promotional documents about AstraZeneca’s[©] products. Many different features are available such as: consult, order, ... the documents.

The second newsletter was sent in early June. It announced the partnership between AstraZeneca[©] and Sparadrap, a patient organization dedicated to children and more precisely to the pain of children. This organization helps parents to take care of their children in the case of a chronic disease as well as an acute pain. The first part of the letter was dedicated to the description of a method to reduce the pain associated with the vaccination of children. A link to Medcliv was also available to order services from previous operations. Finally, a screen pub was available for download. This screen represented the mascot of the campaign (the teddy bear) who walked through the screen by writing all the letters of “Même Pas Mal !” with its sword.

The next newsletter was sent in November and contained new information about pain, as well as a video. This video was realized by physician’s experts in the field of pain (chronic as well as acute). It contained information on the pain of children and how to reduce it.

Finally, the last newsletter, sent in December, contained a satisfaction survey. This survey targeted the physicians that were not available through the last phone call. It referred

to the whole “Même Pas Mal !” program. Its objective (like the phone call) was to gather feedbacks and opinions on the campaign as well as the future needs of physicians regarding the program. The questionnaire used was the same as the one of the last phone call. A reply coupon was added to this questionnaire in order to receive the physician’s answers. This questionnaire then resulted in a qualitative analysis of the campaign.

To send these newsletters, email addresses collected during the first phase of the phone campaign were used. Besides, for the first operation professional databases were rent to increase the number of physicians to contact by e-mails.

2.2.3- Mailing and direct marketing directed to physicians

Throughout all this campaign, five different mailings were sent. The objective of the campaign was to deliver services of high added value to physicians. This is why conception and realization had to be fully designed by the marketing teams of AstraZeneca[©].

The first mailing was sent in April. It included: the flyer announcing the program (*cf part 2.5*), a cover letter, a promotional leaflet about Emlapatch 5%[®] and a booklet with post-it notes. More precisely, the first part of the cover letter explained the enrollment of the physician into a program that would last until December 2012. Then, it detailed the service (booklet of post-it notes) included in the envelope. This booklet contained post-it sheets explaining to parents how to apply a local anesthetic. The last document in the envelope (i.e. promotional leaflet about Emlapatch 5%[®]) was very important to help the physician remembering how to use the product as well as the proper use of Emlapatch 5%[®].

The second mailing took place in May. The envelope contained: the flyer announcing the program, a cover letter, a promotional leaflet about Emlapatch 5%[®] and two scales of pain for children. The first three documents were the same in all the mailings, except for a few minor modifications on the cover letter (mainly on the description of the two services available in the envelope). The two scales of pain for children (*cf part 2.5*) were fully realized by the marketing teams of AstraZeneca[©]. The first was a Visual Analog Scale (VAS or French acronym EVA, that stands for “Echelle Visuelle Analogique”). The second one was a

scale of six Smiley Faces (or “Echelle des 6 visages” in French). Both scales are widely used in the daily practice of physicians. This is why they were considered as services with high added value.

The next mailing was launched before the summer holidays. It consisted of: the flyer announcing the program, a cover letter, a promotional leaflet about Emlapatch 5%[®], a booklet about the 2012 vaccination schedule and a widget with the full 2012 vaccination schedule. The idea was to target physicians as well as the parents of children. Actually, the booklet was mainly intended for parents. Indeed, it was possible to specify on the booklet sheets the date of the next children appointment and the type of vaccine to be realized. This leaflet was realized thanks to information of the Institut National de Prévention et d’Education pour la Santé (INPES). So these information were easily understandable and accessible to everybody. On the other hand, the widget was more complete and was based on the Bulletin Epidémiologique Hebdomadaire (BEH). Thus, this one was fully intended for physicians. Basically, a widget is a small program that can be downloaded on the physician’s computer to help him during his daily practice.

By October, the last but one mailing was sent. It contained: the flyer announcing the program, a cover letter, a promotional leaflet about Emlapatch 5%[®], a booklet explaining the relationship between fear and pain in children and a brochure about vaccination. First of all, the purpose of the booklet was to point the fact that children are more sensitive to pain than adults. Besides, it explained that a first painful medical procedure would increase anxiety for the future acts. Basically, fear increases anxiety and anxiety increases pain, even for minor procedures. Finally, the brochure about vaccination was written by a medical organization (Sparadrap). This brochure was intended for children and described the process of vaccination to dedramatize it. It was designed in the form of a comic strip with a lot of drawings.

Finally, the last mailing was sent on mid-December. It included: the flyer announcing the program, a cover letter, a promotional leaflet about Emlapatch 5%[®], a booklet including a comic strip. The cover letter was a little bit different as it announced the end of the “Même Pas Mal !” program. This letter was thanking physicians for their attention and involvement. The last service was a booklet with a comic strip. It targeted physicians, parents and children. Actually, its purpose was to distract the child during the medical procedure. This action

should be performed jointly between physician and parents in order to obtain an optimum result.

All those direct marketing actions were followed by detailed and precise reports to allow a close monitoring of the campaign. They were very useful to determine the possible changes that could improve the coming operations as well as the whole campaign.

2.2.4- Face-to-face visit

For almost five months, some people also presented the services (these people are called “services assistants”). They should not be confused with sales representatives. Indeed the first mission of sales reps is to provide medical information about one or several products that may be of interest to physicians. Instead, services assistants were mainly visiting physicians in order to present a service that can bring them an added value. The final objective would be that doctors are able to make the difference between sales reps and services assistants.

More precisely, the visit of a services assistant was divided into two parts. First of all, the services assistant had to explain the document(s) to the physician: why it could be useful for him, how it had to be used and other features. This part of the visit was the longest and the most important in order to have physicians to differentiate them from traditional sales reps. Possibly, the second step of the visit consisted in mentioning the product if further information was needed. As these special sales reps had been trained by AstraZeneca[®], they were able to talk about the drug and give a promotional leaflet to physicians. In order to help them during their daily work, they were fitted with pockets with two emplacements. The left one included the promotional leaflet of Emlapatch 5%[®] and the leaflet with the recommendations from the Transparency Commission. The right emplacement allowed putting documents (i.e. services) that had to be presented to physicians.

As regards the “Même Pas Mal !” program, three visits were carried out throughout the campaign by 20 dedicated services assistants. The first visit began in late April and lasted one and a half month (until early June). The objectives of services assistants were to present

both scales of pain (VAS and Smiley Faces scale). Moreover, this first visit was decisive for an efficient monitoring of the campaign because of the novelty of this type of meetings (for physicians as well as pharmaceutical companies). Next, from mid-June to late July, services assistants had to present the two vaccination schedules of 2012: the booklet including specific sheets for parents and the widget for physicians (that was given on a CD). Finally, the last visit was conducted in the course of September with the presentation of two new services: a booklet explaining the relationship between fear and pain and a brochure about vaccination.

This innovative way of visiting a physician might be of interest for the years to come in order to differentiate AstraZeneca[®] from other pharmaceutical firms. This approach is for now rather well accepted by physicians. But this strategy has been carried out on mature products only and some improvements will be necessary to adapt to the new drugs to come. Indeed, new products have to be more developed (i.e. physicians need more information about the drug as it is a new one compared to a mature drug which is already well-known) to improve the physician's awareness on these drugs (e.g. good use, dosage...). So, maybe two different parts will have to be implemented on new drugs: a first part more product-oriented and another one that would mostly deal with disease awareness.

2.2.5- Internet campaign realized on specialized websites dedicated to healthcare professionals

In order to increase the visibility of the brand, a campaign was realized on websites specifically dedicated to healthcare professionals: www.pratis.com and www.pratispharma.com. These websites are considered as information and training websites and are consulted by physicians (mostly GPs) and pharmacists. The global operation consisted in the creation, realization and diffusion of an Internet banner and an interactive medical video about Emlapatch 5%[®].

First, the interactive medical video was created by the provider (i.e. Pratis). The first part of the video talked about product environment, with a little bit of disease awareness on the pain in children and the vaccination. The second part presented the drug: its main characteristics, the dosage and duration, the mode of action or some general advices

regarding the good use of Emlapatch 5%[®]. Finally, a questionnaire about the drug was following the video. It was available online, on both websites, for two months (from the 1st of September to the 31st of October 2012), on the specific space dedicated to videos.

Besides, Pratis was also in charge of promoting this video. First, once a month, a newsletter was sent to all the subscribers of these websites. These newsletters were only dedicated to the Emlapatch 5%[®] video. Then, a promotional advertisement of the video was inserted into the “Pratis TV” newsletter. Two “Pratis TV” newsletters were released each month. This means that, in addition to the general newsletter, four other “Pratis TV” newsletters were sent in the two months of broadcast. Finally, the video was highlighted in the home page four times a month. All these promotional tools helped in increasing the number of views of the video. Regular reports were asked to Pratis in order to monitor the campaign (with, in particular, the number of views and the number of answers to the questionnaire about the product at the end of the video).

2.3- Campaign for pharmacists

Pharmacists were targeted as well. But they were only the targets of a small operation throughout all the campaign. Two documents were released: a training CD about Emlapatch 5%[®] and some booklets about painful cares in children (e.g. blood samples or vaccination). These tools were designed to assist pharmacists in the appropriate delivery and use of Emlapatch 5%[®]. The booklets were intended for the patients (most of the time parents) that go to the pharmacy. These services were sent through direct sales of Emlapatch 5%[®], between AstraZeneca[®] and the pharmacy. This operation was not the most important one because pharmacists are not the primary targets.

2.4- Campaign on the Internet targeting the patients

Patients were also targeted by a digital campaign to raise awareness on disease. The mothers of children up to seven years were the primary targets. This campaign was based on information about pain in children. Its goal was to raise parent’s awareness to the fact that

pain coming from medical procedures can be avoided. This should help decreasing the fear during the procedures to come.

This campaign was held on specific websites of the Internet: www.magicmaman.com, www.famili.fr, www.journaldesfemmes.com, www.doctissimo.fr, www.aufeminin.com and sante-az.aufeminin.com. It lasted two months: from mid-September to mid-November, which corresponds the vaccination period of children. The mascot of the “Même Pas Mal !” program was inserted into different formats: home page promotional campaign, quiz... For the first two websites (Magicmaman and Famili), the full promotional campaign was available. It means that the home page contained all the promotional tools: banners, tags, quiz and a space with “advertorial” on pain. On the other four sites, the quiz and the pages on pain were removed because the visitors of these websites did not fully correspond to the targets of AstraZeneca[©].

The banners and tags enabled the visitor to reach a specific “mini-website” that hosts the quiz and the specific space on pain. Two different quizzes of five questions each were created in order to change them after one month and attract more visitors. Moreover, five surveys were added to gather opinions. Finally, the full campaign was monitored in order to determine the number of reached visitors.

2.5- Some examples of promotional documents with added value to physicians of the « Mème Pas Mal ! » campaign

MÈME PAS MAL !

Programme de services d'aide à la prise en charge de la douleur de l'enfant

Un service par mois, jusqu'à fin 2012

par courrier par e-mail si vous l'avez accepté ou par téléphone

Pour vous
Information médicale à votre intention

vos patients **et leur entourage**
Outils à destination de l'enfant Information à destination des parents

MÈME PAS MAL !

AstraZeneca

MÈME PAS MAL !

Programme de services d'aide à la prise en charge de la douleur de l'enfant
AstraZeneca

Pour être votre partenaire au quotidien, les services de ce programme s'articulent autour des 3 thèmes suivants :

PRÉVENTION **DIAGNOSTIC** **ACCOMPAGNEMENT ET CONSEIL**

Rendez-vous sur medcliv.fr pour vous inscrire et profiter de tous les services AstraZeneca

AstraZeneca

CEM 1041-2012/02 (M2F24) 2012/02

Flyer of the campaign explaining the multichannel approach and the three main pillars

Echelle Visuelle Analogique (EVA)¹

- Enfants de plus de 6 ans. EVA 5 Outil d'autoévaluation de référence.
- Utiliser un traitant, possible et utiliser l'échelle des 6 visages.
- Enfants de 4 à 6 ans : autoévaluation possible par l'utilisation conjointe de l'EVA et de l'échelle des 6 visages.
- Accès réglementé : prescrire à l'usage Médecin-Evaluateur.

Consignes :

- Présenter l'échelle verticalement.
- Formuler les extrêmes en termes neutres.
- Dire à l'enfant : "Place le doigt sans tout que la douleur est grande".

MÈME PAS MAL !

AstraZeneca

CEM 1044-2012/01

Echelle des 6 Visages¹

- Enfants de plus de 6 ans. EVA 5 Outil d'autoévaluation de référence.
- Enfants de l'enfant, possible d'utiliser l'échelle des 6 visages.
- Enfants de 4 à 6 ans : autoévaluation possible par l'utilisation conjointe de l'EVA et de l'échelle des 6 visages.
- Accès réglementé : prescrire à l'usage Médecin-Evaluateur.

Consignes :

- Les scores sont de gauche à droite : 0 (pas mal du tout), 2, 4, 6, 8, 10 (pas très mal).
- Exprimer clairement les limites extrêmes : "pas mal du tout" et "pas très mal".
- N'utiliser pas les mots "triste" ou "heureux".
- Préciser bien qu'il s'agit de la sensation intérieure, pas de l'aspect affiché de leur visage. "Montre-moi comment tu te sens à l'instant de ta".

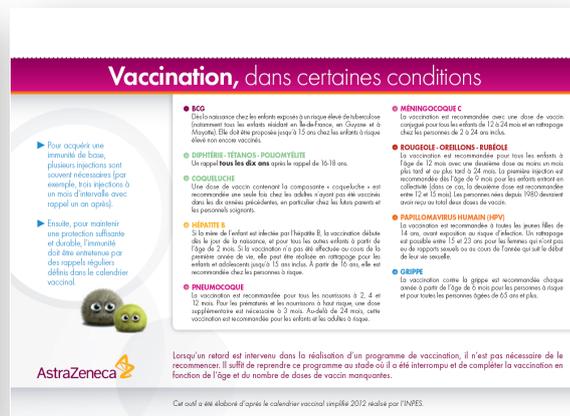
MÈME PAS MAL !

AstraZeneca

CEM 1047-2012/03

Pain scales created for physicians and dedicated to children: on the left, the Visual Analogue Scale and on the right the Smiley Faces scale

The first one must be used alone for children of more than six years old (considered as the reference tool). But it has to be used with the Smiley Faces scale for children between four to six years.



Booklet including nominative sheets with the 2012 vaccination schedule
 This service was sent before the summer holidays because the vaccination period generally arrives on September. This booklet was realized thanks to the INPES information.

3. Evolution and monitoring of the campaign in real-time: results of re-call test and reporting

3.1- Results of quantitative and qualitative KPI in Physicians

3.1.1- Phone operation

For the phoning there were quantitative and qualitative KPI. Indeed, a reporting of the operations was regularly sent by the agency in order to monitor the campaign. Qualitative KPI were obtained through to recall tests.

- Quantitative KPI

While the campaign is not completely finished, all the results are not available yet, but those available are already significant. The results of the first phoning are acquired. They

consist in the number of contacted physicians, the number of reached phone calls, the number of collected emails and the number of rejected calls [Table 11]. The intended targeted population was composed of 10,321 physicians. For the first phoning, all the physicians had to be contacted to determine if they could be interested by the program, and if they agreed on being contacted by phone the next times. This is why the coverage rate is 100%. Then, reach phone calls (i.e. successful phone calls) are defined by the number of phone calls during which the agent really spoke to the physician. After, the number of visits realized corresponds to an explanation of the program by the agent to the physician. On the contrary, the number of realized phone calls is defined by the phone calls during which the agent succeeded to speak to someone (even the secretary). Thereby the transformation rate is the number of visits realized by phone over the number of realized phone calls.

Activity	1st call	Objectives
# agents	8,1	10
# contacted physicians	10 321	10 321
Covering rate	100%	100%
On the dialed calls		
# realized calls	6 648	6 193
Rate of realized calls	64%	60%
# realized calls/day/agents	30,1	25
# rejected calls	1 809	
Rate of rejected calls	18%	30%
Rate of rejected channel	16%	30%
On the realized calls		
Transformation rate	73%	70%
# Emails	2 493	1 330
Rate of Emails	38%	25%

Table 11: Quantitative KPI regarding the first and second phone calls
(Source: AstraZeneca®)

These results are then analyzed and transformed in percentages in order to be more easily understandable and comparable to the objectives. As we can see on the *Table 11*, all the parameters of the first phone call are beyond the objectives. This reflects the high interest of physicians about this campaign.

- Qualitative KPI

Qualitative KPI were measured indirectly by the number of physicians that did not want to be involved in the “Même Pas Mal !” program. Indeed, only a few physicians refused to be contacted by phone calls, some others refused the whole program and concept. It means that they were not interested by the campaign and they considered it as not attractive enough. Nevertheless, during the first phone call feedbacks were received from the physicians. They seemed to be rather encouraging. Some words come back very often like: adapted, coherent, full, original, interesting, innovative, regular, services, parents, AstraZeneca[®], useful, pain, children, partnership... [Figure 9]



Figure 9: Main feedbacks words acquired during the first phone call

These first encouraging feedbacks were the proof that physicians are currently looking for new methods of drug promotion as well as a new relationship with the pharmaceutical industry, with more added value.

3.1.2- E-mailing/Internet

- Quantitative KPI

The newsletters were sent to the addresses gathered during the phone campaign. Moreover, for the first emailing a database was rent in order to increase the number of physicians receiving it [Table 12]. The key parameter for this media is the opening rate. In order to be sure that physicians effectively opened the email, clicks were tracked. As seen on the Table 6, the number of realized contacts was decreasing throughout the three operations. Indeed, the second and third mailings were realized only with the email addresses collected by phone and did not make use of the databases. Then, the R/O (Realized over Objectives) ratio was very high. This can be explained by the fact that the objectives were fixed regarding the number of email addresses that would have been obtained after the first phone call. For the second emailing, the R/O ratio lower than 100% might be due to wrong email addresses.

Operation	Date	Objective	Realized	Realized		R/O
				GPs	Ped.	
Emailing 1	March	2500	2595	1747	848	104%
Emailing 2	May	750	741	408	333	99%
Emailing 3	June	750	751	407	344	100%

Table 12: Quantitative KPI regarding the emailing campaigns
(Source: AstraZeneca®)

3.1.3- Mailing or direct marketing

- Quantitative KPI

Direct marketing could only be monitored by quantitative KPI. Indeed, the only parameter that could be followed is the number of mails sent. This number depended only on one item: the number of targeted physicians. Most of the time, pharmaceutical firms hold the physician's addresses in their databases. This is why it is easy for them to realize this kind of operations. The number of targeted physicians is a little bit lower than the first announced one due to the fact that some of them did not want to be contacted anymore [Table 13].

Moreover, very often the databases are not fully up to date so all the physician’s addresses were not accurate. For direct marketing, all the success rates are close to 100%. Indeed, this direct marketing did not need any answer from physicians. So where the R/O is lower than 100% it means that there are a high number of returns because of wrong addresses. Direct marketing is considered as “passive communication”. So, it is not very useful to help monitoring a campaign.

Operation	Date	Objective	Realized	Realized		R/O
				GPs	Ped.	
Direct marketing 1	April	9500	9305	6618	2687	98%
Direct marketing 2	May	7250	7261	5345	1916	100%
Direct marketing 3	June	7250	7209	5231	1978	99%

Table 13: Quantitative KPI for direct marketing operations
(Source: AstraZeneca®)

With this type of channel, qualitative analysis was not directly possible. But, it could be indirectly measured by the number of physicians asking for new services (because they finished their examples or because they found them useful). It means that they thought services interesting.

3.1.4- Face-to-face visit

- Quantitative KPI

There are not so many quantitative KPI for the face-to-face visits. Indeed, the total number of physicians targeted was split into two smaller groups: one priority target and another one, which was secondary. This division was realized by AstraZeneca® and depended of the specialty of the physician. For instance, the priority target contained mainly pediatricians and GPs involved in children’s health. The secondary target was composed of other GPs who were not specifically involved with children. This is why services assistants had to visit in priority the first target more interested in the program than the secondary target. The only interesting quantitative KPI is the number of physicians visited. In fact, for

the first visit, a total of 3,217 physicians were seen (1,536 from the primary target and 1,681 from the secondary one) [Table 14]. The others visits are still ongoing for now so the results are not all available yet.

Operation	Date	Objective	Realized		Total	R/O
			GPs	Ped.		
Face-to-face 1	May/June	5872	2604	613	3217	55%

Table 14: Quantitative KPI regarding the face-to-face visit
(Source: AstraZeneca®)

- Qualitative KPI

On the other hand, qualitative KPI are more accurate and numerous. A feedback test has been performed on 100 GPs and 50 pediatricians. It was conducted by phone through a questionnaire that was created by the agency. The results appear to be interesting and are split into two categories: GPs and pediatricians (to determine if some physician's specialties are more sensitive to this kind of program and communication). Different parameters were studied during this recall test [Table 15]. The most important for AstraZeneca® were: did the physician make the relationship between the product and the program, was the physician satisfied of this program and what was the impact on AstraZeneca's® image?

First, Emlapatch 5%® is associated by physicians to "Même Pas Mal !" in 100% of the cases. This result is very encouraging for an innovative program for which the main mission is to present services. Moreover, with the hardening in legislation on the drug promotion, these results could be capitalized on others drugs. Then, the satisfaction and the positive opinion on the program are high for GPs and less important for pediatricians. GPs are more solicited by pharmaceutical firms than pediatricians. But they are much visited for very common therapeutic areas such as cardiology, gastroenterology... and not as much for pediatric products. So, GPs are not used to have specialized services on this therapeutic area compared to pediatricians. This is why pediatricians may have higher expectations on the quality of the program and of the services. Finally, the positive impact on AstraZeneca's® image is very high which is a proof of a global acceptance of this new strategy.

Percentage of physicians that have...	GPs	Pediatricians
Global memorization of the services assistants	55%	66%
AstraZeneca's [®] memorization	68%	84%
Memorization of presented services	64%	42%
Memorization of the product speech	60%	61%
Positive opinion of the program	76%	57%
Satisfaction	82%	55%
Link between Emlapatch 5% [®] and "Même Pas Mal !"	100%	100%
Positive impact on AstraZeneca's [®] image	89%	79%

Table 15: Qualitative KPI about face-to-face visits with physicians of services assistants
(Source: AstraZeneca[®])

Another indicator of success was to determine if doctors were satisfied by the documents. These figures seem less positive than the previous ones. Indeed, for GPs the services received a grade of 6.6/10 against 4.8/10 for pediatricians. To analyze these grades, a statistical analysis was performed, the results were:

- Grades < 5: disagreement of the sample
- Between 5.5 and 6: mediocre position
- Between 6 and 6.5: moderate or neutral position
- Grades > 7: agreement of the sample
- Grades > 8: high agreement of the sample

Thus, GPs rather agree with the services provided while pediatricians do not feel fully in phase with this concept. This is maybe due to the fact that GPs are more used to receive these types of documents. The new speech focusing on services rather than on products seems well understood by physicians. This is a good argument for AstraZeneca[®] because it was not the case during the previous innovative campaigns (for Zomig[®] and Atacand/Hytacand[®] for instance).

To conclude, there is a better memorization of pediatricians compared to GPs but a higher satisfaction from GPs. It will be interesting to further work on this type of strategies and clearly differentiate specialists from GPs to increase their awareness.

3.2- Results of quantitative and qualitative KPI in patient's campaign

- Quantitative KPI

Quantitative KPI depended only on the number of visitors on the “mini-website”. In addition, the number of people answering to the quiz or the survey is also taken into account. Actually, the more there are visitors, the more the campaign seems to be interesting. However, this Internet campaign is still ongoing so the results are not all known at this time and will have to be refined.

- Qualitative KPI

On the “mini-website” of the campaign dedicated to patients, it was possible to send emails to AstraZeneca[®] marketing teams. Some feedbacks from visitors were received by emails. After one month of campaign, 55 visitors out of almost 5,000 visits sent an email (\approx 1.1%). Most of the time, it consisted of questions about the quiz or the survey. But some of them gave their opinion about the “Même Pas Mal !” campaign. Thus, visitors were mostly satisfied by the campaign.

3.3- Results of quantitative and qualitative KPI in pharmacists

- Quantitative and qualitative KPI

Quantitative KPI were easy to determine for pharmacists as they only depended on the number of orders. But some qualitative KPI could be declined. Actually, if we consider that an increase in the direct sales for a pharmacy corresponds to a pharmacist interested by

the services, qualitative parameters can be indirectly added. As this campaign is still ongoing, the results are not known so far.

4. Results and conclusion of the campaign: sales volume, turnover and return on investment realized

By analyzing the results of the campaign we can say that it seems to be well welcomed and appreciated. Physicians (GPs as well as pediatricians) found it valuable. This is a good point for the image of AstraZeneca's[®] and the partnership that the company wants to set up with physicians. However, there are some points that need to be improved. From a global point of view, for the next operations it will be interesting to better characterize the targeted physicians. This strategy will permit to invest less money and therefore, increase the ROI of the overall operation. Furthermore, each single operation (phone, mail, email...) can also be improved in order to increase the quality of the program. The more interesting is the program, the more physicians will be reached.

Multichannel strategies are innovative and promising. Many actions can be set up during one single program to reach many physicians. But these actions have to be consistent and linked together. There is a necessity to have a thread that binds all the steps of a program in order to get the physician's attention. Physicians have also to identify as fast as possible which pharmaceutical firm is trying to contact them. If one program as a good thread, the physician will directly know who is trying to contact him. Thereby, he will be more able, for instance, to open an envelope of a direct marketing coming from a pharmaceutical company.

The global multichannel campaign corresponds to a substantial investment of €400,000 in 2012. But after a few months the campaign was considered as profitable. Indeed, Emlapatch 5%[®] had a negative growth (-0.5%) at the beginning of the campaign (April). Five months after the beginning (September), the growth was +3.2%. It means that the campaign seems impacting, efficient and appreciated from physicians.

Finally, the campaign has to be interactive. Indeed, pharmaceutical firms have to integrate physicians in their strategy. There is a need for an active communication, instead of

a passive one, between pharmaceutical firms and healthcare practitioners. Pharmaceutical firms have to initiate and maintain a dialogue with physicians and not only deliver an information. In the future, the downward communication will need to be gradually replaced by interactivity. This method will help improving the capacity of the pharmaceutical industry to have an impacting communication, instead of too many communications. This transition will be very complicated to achieve because of its novelty and the changes in mentality that it will imply. This last parameter needs to be more taken into account by AstraZeneca[®].

CONCLUSION

Les produits matures peuvent donc être vus de deux façons différentes : à la fois comme des médicaments plus utiles à la médecine dû au fait de l'apparition de nombreuses nouvelles alternatives thérapeutiques. Mais en même temps, certaines entreprises les considèrent comme les éléments fondateurs, à l'origine de la croissance de leur entreprise. L'ambivalence entourant ces médicaments matures est donc intéressante. En effet, au vu des problèmes traversant actuellement l'industrie pharmaceutique, celle-ci a actuellement un regain d'intérêt pour ces médicaments. Ainsi, de nombreuses stratégies de différenciation pour les médicaments arrivant en fin de vie (ainsi que certains ayant déjà perdu leur brevet) sont donc à l'essai dans de nombreuses entreprises pharmaceutiques. Elles consistent, par exemple, en la création de nouveaux dosages, de nouvelles formulations ou d'associations fixes de deux molécules déjà connues. Cependant, ces solutions permettent seulement de subvenir à des besoins sur du court-terme.

La recherche de nouvelles stratégies de promotion, à l'inverse, aurait pu être la solution pour permettre une croissance sur du long-terme. En effet, la mise en place d'une méthode de promotion à faible coût aurait pu permettre à l'entreprise de rapidement gagner de l'argent pour subvenir à ses dépenses courantes. De plus, sur un plus grand laps de temps cela aurait pu lui permettre de réinvestir dans la R&D et donc de développer son pipeline. En effet, l'industrie pharmaceutique a besoin de s'appuyer sur quelque chose de solide afin de relancer sa croissance. Cependant, de nouvelles lois sur les génériques parues durant l'année 2012 stipulent que désormais, le patient est obligé de se voir délivrer un générique en remplacement du princeps. En effet, tout patient préférant se voir délivrer le princeps du médicament plutôt que son générique se verra refuser le tiers payant de son médicament par le pharmacien (i.e. l'assurance maladie). L'assurance maladie ne rembourse donc plus les princeps, à l'exception d'une ordonnance du médecin précisant la mention NS (Non Substituable). Le pourcentage de mention NS par médecin est contrôlé. Le pharmacien délivrant la prescription doit lui aussi contribuer à ce nouveau système, sous peine de sanctions. Ainsi, la promotion des produits matures ne pourra donc pas être une solution durable pour relancer l'économie de l'industrie pharmaceutique. De plus, ces médicaments

matures nécessiteront d'être mieux définis et ne devront donc pas inclure les médicaments ne possédant plus de brevet.

Néanmoins, les essais d'ores et déjà réalisés sur ces nouvelles stratégies marketing pourront être utiles par la suite. En effet, cette promotion plus ciblée, et surtout moins chère, pourra servir pour la réalisation de futures campagnes marketing plus ciblées. De plus, l'implémentation sur du long-terme de cette promotion plus ciblée permettra à l'industrie pharmaceutique comme à ses cibles (i.e. les professionnels de santé en général) de se mettre d'accord sur une nouvelle façon de travailler ensemble, d'une manière plus proche et avec une plus grande valeur ajoutée pour les deux parties.

Ensuite, les instances règlementaires telles que l'ANSM ou l'EMA jouent aussi un rôle dans cette période noire. Tout d'abord, le renforcement de la loi sur la promotion des médicaments handicape fortement les laboratoires. Ceux-ci doivent donc actuellement faire preuve d'énormément d'adaptabilité. De plus, la mise en place de stratégies (après la première période de dépôts, où certains laboratoires ont été énormément sanctionnés) est à envisager. En effet, certains produits n'ont pas obtenu leurs visas, les délégués médicaux se retrouvant ainsi sur le terrain sans aucun document promotionnel. Ensuite, l'industrie pharmaceutique devra aussi, dans les années à venir, trouver un moyen lui permettant d'augmenter sa probabilité de succès lors du développement de nouveaux médicaments. Enfin, une augmentation du temps de commercialisation grâce à des process de mise sur le marché accélérés pourrait être bénéfique pour cette industrie. En effet, une diminution du temps entre le moment où le brevet sur la molécule est déposé et le moment où celle-ci se retrouve sur le marché permettrait aux laboratoires d'augmenter leur chiffre d'affaire et donc de réinvestir massivement dans la recherche.

Toutes ces problématiques rencontrées par l'industrie pharmaceutique conduisent la plupart des entreprises à réduire leurs dépenses et à trouver des solutions pour réussir à palier les déficits entraînés par entre autres, les pertes de brevets massives, les augmentations de coûts de la R&D et des temps de développement des médicaments et les conditions de remboursement de plus en plus draconiennes. Ces modifications jouent un rôle majeur sur la communication. Ainsi, l'industrie pharmaceutique va devoir apprendre à se différencier pour pouvoir mieux s'adapter à ses nouveaux interlocuteurs. En parallèle, il faudra aussi qu'elle repense sa communication envers ses interlocuteurs habituels : les professionnels de santé.

Le regain d'intérêt de plusieurs firmes pharmaceutiques pour les produits matures est en directe adéquation avec les problématiques entraînant une perte de chiffres d'affaire, énoncées ci-dessus. C'est pourquoi la création de nouvelles stratégies et de nouveaux outils de promotion du médicament, remplissant les conditions énoncées par l'ANSM, deviennent de vrais enjeux. Ainsi, on assiste actuellement à une profonde modification de la communication des entreprises pharmaceutiques, aussi bien dans la forme, que dans le fond. Les entreprises préfèrent désormais utiliser des canaux un peu moins coûteux que la visite médicale et diversifier le type d'informations et de documents présentés. De plus, ce tournant va encore s'accroître dans les années à venir. En effet, le développement de la médecine personnalisée et des médicaments avec des indications niches devra entraîner une spécialisation de la communication. Les spécialistes (hospitaliers et libéraux) deviendront finalement les principaux interlocuteurs de l'industrie pharmaceutique, et remplaceront ainsi les médecins généralistes. Cela aura le mérite de décharger en partie la pression de visite médicale exercée sur les médecins généralistes. En conséquence, la communication vers les médecins généralistes sera donc sûrement basée sur l'utilisation de différents canaux, notamment électroniques, moins coûteux que la visite médicale.

Ainsi, avant période de grands changements, l'industrie pharmaceutique est actuellement en période de transition. C'est pourquoi, de nombreux enjeux reposent en ce moment sur les produits matures car l'industrie pharmaceutique n'est plus capable (ou du moins, il lui est très difficile) de maintenir une croissance positive sur du long terme. La mise au point de stratégies de communication innovantes et moins coûteuses devient donc une nécessité, pour pouvoir réussir à subvenir aux futurs besoins des médecins. Le fait d'implémenter ces stratégies sur les produits matures a donc un double bénéfice. Le bénéfice à court terme correspond à une diminution de la perte de chiffres d'affaire de ces produits, et donc une légère amélioration de la rentabilité de l'entreprise. Deuxièmement, le bénéfice à long terme correspond à la maîtrise de nouvelles techniques de communication innovantes et appréciées, qui pourront être utilisées dans les années à venir.

Ces modifications impliquent une phase d'adaptation et de développement des nouvelles compétences requises. Celles-ci vont être déterminantes pour l'évolution future. Le but final serait d'obtenir le bon message, pour le bon médecin, via le bon canal (i.e. le canal favori du médecin). C'est-à-dire, une communication plus orientée et plus précise, plutôt

qu'une communication disparate et visant tout le monde. Durant cette phase d'adaptation, l'anticipation et la capacité à choisir les bons canaux, thèmes de communication et informations seront des paramètres à ne pas négliger pour assurer l'avenir et la survie des entreprises pharmaceutiques.

BIBLIOGRAPHY

- 1- Les Entreprises du Médicament, 100 questions que l'on nous pose, Juin 2012.
- 2- S. Stremersch, A. Lemmens. Sales growth of new pharmaceuticals across the globe: the role of regulatory regimes. *Marketing Science*, July-August 2009, vol. 28(4): 690-708
- 3- DZ. Kvesic, Product lifecycle management: marketing strategies for the pharmaceutical industry. *Journal of Medical Marketing*, 2008, vol. 8(4): 293-301
- 4- <http://www.netmba.com/marketing/product/lifecycle/> Consulté le 12 juillet 2012
- 5- John K. Christiansen, Claus J. Varnes, Marta Gasparin, Diana Storm-Nielsen, and Erik Johnsen Vinther. Living Twice: How a Product Goes through Multiple Life Cycles. *J Prod Innov Manag.* 2010, vol. 27(6): 797–827
- 6- <http://www.mphasis.com/pdfs/white-papers/introduction-product-lifecycle-management.pdf> Consulté le 17 juillet 2012
- 7- Joseph A. DiMasi & Laura B. Faden, Competitiveness in follow-on drug R&D: a race or imitation? *Nature Reviews Drug Discovery*, January 2011, 10: 23-27
- 8- R. Dubey, J. Dubey. Pharmaceutical product differentiation: A strategy for strengthening product pipeline and life cycle management, *Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing*, April 2009, vol. 9(2): 104-118
- 9- DZ. Kvesic. Adalat—A Lifecycle Managed, *Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing*, July 2009, vol. 9(3): 187-200
- 10- Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR and al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov.*, March 2010; 9(3): 201-14.
- 11- IMAP's Pharmaceutical & Biotech Industry Global Report – 2011.
- 12- Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov*, June 2011; 10(6): 428-38.
- 13- Dewar RD, Dutton JE. The adoption of radical and incremental innovations: an empirical analysis. *Management Science*, November 1986; 32(11): 1422-33.
- 14- Christopher P. Adams, Van V. Brantner. Estimating the cost of new drug development: is it really \$802 Million? *Health Affairs*, 2006; 25(2): 420-28.
- 15- Joseph A. DiMasia, Henry G. Grabowskib. The cost of biopharmaceutical R&D: is biotech different? *Manage. Decis. Econ.*, 2007; 28: 469–79.
- 16- Pharmaceuticals & Biotech: Industry Global Report – 2011
- 17- Michael E Franks, Gordon R Macpherson, William D Figg. Thalidomide. *The Lancet Review*, May 2004; 363: 1802-11.
- 18- M Steiner, D H Bugen, B Kazanchy, W T Knox IV, Margaret V Prentice, L Goldfarb. The Continuing Evolution of the Pharmaceutical Industry: Career Challenges and Opportunities.
- 19- <http://www.vidal.fr/> Consulté le 5 août 2012
- 20- Salviasi, Alessandro, Burlina, Alessandro P., Borsini, Walter. Nervous system and Fabry disease, from symptoms to diagnosis: damage evaluation and follow-up in adult patients, enzyme replacement, and support therapy. *Neurological Sciences*, June 2010, 31(3): 299-306
- 21- <http://www.genzyme.com/> Consulté le 5 août 2012
- 22- <http://www.marketingpower.com/AboutAMA/Pages/DefinitionofMarketing.aspx> Consulté le 21 juillet 2012
- 23- M. Howard Morse. Product market definition in the pharmaceutical industry. *Antitrust Law Journal*, 2003, 2(71): 633-76.
- 24- French code of Public Health: <http://www.legifrance.gouv.fr/> Consulté le 5 août 2012
- 25- Charte de la Visite médicale du 22 décembre 2004, modifiée par les avenants du 21 juillet 2005 et du 21 juillet 2008
- 26- <http://www.leem.org/> Consulté le 31 juillet 2012
- 27- http://www.insee.fr/fr/themes/tableau.asp?reg_id=0&ref_id=NATTEF06102 Consulté le 31 juillet 2012
- 28- <http://www.lenouveleconomiste.fr/lesdossiers/laboratoires-pharmaceutiques-la-falaise-des-brevets-13061/> Consulté le 31 juillet 2012

- 29- Business Monitor International's. France pharmaceuticals and healthcare report Q4 2011
- 30-<http://gabionline.net/Biosimilars/General/FDA-definitions-of-generics-and-biosimilars> Consulté le 31 juillet 2012
- 31- Mark J. Belsey, Drug developer strategies to boost competitiveness. *Nature Reviews: Drug Discovery*, April 2007, 6: 265-66
- 32- J. Beney , V. von Gunten, Les Biosimilaires ne sont pas des génériques. *Caduceus express*, August 2009, vol. 11(6)
- 33-<http://www.bloomberg.com/news/2011-02-10/lipitor-topped-worldwide-drug-sales-in-2010-crestor-gains-most.html> Consulté le 31 juillet 2012
- 34- Joseph A. DiMasi & Laura B. Faden, Competitiveness in follow-on drug R&D: a race or imitation? *Nature Reviews Drug Discovery*, January 2011, 10: 23-27
- 35- Marie-Catherine Chemtob-Concé, La fixation du prix et les modalités de remboursement des médicaments en France. *Bulletin de l'Ordre*, October 2007, vol. 396: 375-380
- 36- Investor expectations for the pharmaceutical sector in 2012: exploring performance outlook, R&D preferences and other critical industry topics, FTI consulting
- 37-<http://www.fiercebiotech.com/story/brennans-ouster-astrazeneca-sets-stage-big-changes-rd/2012-04-26> Consulté le 1er août 2012
- 38- Patricia M. Danzon, Andrew Epstein and Sean Nicholson, Mergers and Acquisitions in the Pharmaceutical and Biotech Industries. *Manage. Decis. Econ.* 2007. 28: 307-328
- 39- <http://www.gene.com/gene/products/information/> Consulté le 3 août 2012
- 40-Million RP, Impact of genetic diagnostics on drug development strategy. *Nat Rev Drug Discov.* June 2006, 5(6):459-62
- 41- <http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf> Consulté le 17 septembre 2012
- 42- <http://www.orpha.net/> Consulté le 17 septembre
- 43- <http://www.bioalliancepharma.com/> Consulté le 4 août 2012
- 44- <http://oxforddictionaries.com/definition/english/communication> Consulté le 18 août 2012
- 45-<http://www.analyse-marketing.com/analyses-marketing/la-communication-marketing.html> Consulté le 18 août 2012
- 46- V. Dickov, B. Kuzman, Specific features of pharmaceuticals marketing mix. *Journal of Management & Marketing in Healthcare*, August 2011; vol. 4(3): 160-167
- 47- <http://blog.advancemarketworx.com/Portals/11876/docs/RameshKrishnanPresentation%20IMS%20Health.pdf> Consulté le 17 septembre 2012
- 48- Alkhateeb FM, Khanfar NM, Doucette WR, Loudon D. Characteristics of Physicians Targeted by the Pharmaceutical Industry to Participate in E-detailing. *Health Mark Q.*, April 2009; vol. 26(2): 98-116
- 49- A. Matthew. Changing channels. *Medical Marketing & Media*, April 2005; vol. 40(4): 34-42
- 50- Norris P., Herxheimer A., Lexchin J. and Mansfield P. Drug promotion: what we know, what we have yet to learn. *Reviews of materials in the WHO/HAI database on drug promotion.*
- 51- PA. Henning, A. Schnur. eLearning in continuing medical education: A comparison of knowledge gain and learning efficiency. *Journal of Medical Marketing*, April 2009; vol. 9(2): 156-161
- 52- MP. Joshi, T. Jambulingam, R. Kathuria. Benchmarking web based CRM strategies of pharmaceutical companies : a competitive analysis using analytic hierarchy process. *Health Care and Pharmaceutical Management*: 417-422.
- 53- WJ. Lundstrom, RF. Wright. The CRM-physician interface: Toward a model of physician relationship building. *Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing*, November 2005; vol. 5(4): 316-323
- 54- <http://www.astrazeneca.fr/accueil/> Consulté le 30 septembre
- 55- Résumé des Caractéristiques du Produit Emlapatch 5%®

APPENDICES

Annex 1

Development Pipeline as at 30 June 2012

Line Extensions

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Cardiovascular								
<i>Axanum</i>	proton pump inhibitor + low dose aspirin FDC	low dose aspirin associated peptic ulcer in high risk CV patients	III		Withdrawn	Launched	1H 2013*	Approved
<i>Brilinta/Brilique</i> EUCLID	ADP receptor antagonist	outcomes study in patients with PAD	III	3Q 2012	2016	2016	2016	2016
<i>Brilinta/Brilique</i> PEGASUS-TIMI 54	ADP receptor antagonist	outcomes study in patients with ACS	III	4Q 2010	2015	2015	2015	2015
<i>Crestor</i> [#]	statin	outcomes in subjects with elevated CRP	III		Launched	Launched		Launched
<i>Forxiga</i> TM (dapagliflozin)/ metformin FDC [#]	SGLT2 inhibitor + metformin FDC	diabetes	III	3Q 2007		3Q 2012		
<i>Forxiga</i> TM (dapagliflozin) [#]	SGLT2 inhibitor	diabetes – add on to DPP-4	III	1Q 2010		3Q 2012		
<i>Forxiga</i> TM (dapagliflozin) [#]	SGLT2 inhibitor	diabetes – add on to insulin and add-on to metformin long-term data	III	2Q 2008		3Q 2012		
<i>Forxiga</i> TM (dapagliflozin) [#]	SGLT2 inhibitor	diabetes – in patients with high CV risk - Study 18 and 19 long-term data	III	1Q 2010		2H 2013		
<i>Forxiga</i> TM (dapagliflozin) [#]	SGLT2 inhibitor	diabetes – triple therapy (dapa+met+SU)	III	1Q 2011		2H 2013		
<i>Kombiglyze XR</i> TM / <i>Komboglyze</i> TM FDC ^{#**}	DPP-4 inhibitor + metformin FDC	diabetes	III		Launched	Approved		Approved
<i>Onglyza</i> TM SAVOR-TIMI 54 [#]	DPP-4 inhibitor	outcomes study	III	2Q 2010	2016	2016		2016

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Gastrointestinal								
<i>Entocort</i>	glucocorticoid steroid	Crohn's disease / ulcerative colitis	III		Launched	Launched	2014	Launched
<i>Nexium</i>	proton pump inhibitor	peptic ulcer bleeding	III		Filed***	Launched		Launched
Infection								
<i>FluMist/Fluenz</i>	live, attenuated, intranasal influenza virus vaccine	influenza	III		Launched	Approved		Launched
Neuroscience								
<i>Diprivan</i> [#]	sedative and anaesthetic	conscious sedation	III			Launched	2H 2013	Launched
<i>EMLA</i> [#]	local anaesthetic	topical anaesthesia	III			Launched	Launched	Launched
Oncology								
<i>Faslodex</i>	oestrogen receptor antagonist	1 st line advanced breast cancer	III		2016	2016	2016	2016
<i>Iressa</i>	EGFR tyrosine kinase inhibitor	treatment beyond progression	III	1Q 2012		2015	2015	2015
Respiratory & Inflammation								
<i>Oxis</i>	long-acting β_2 agonist	COPD	III			Launched	Approved	
<i>Symbicort</i>	inhaled steroid/ long-acting β_2 agonist	asthma / COPD	III	4Q 2011	2014			
<i>Symbicort</i>	inhaled steroid/ long-acting β_2 agonist	COPD	III		Launched	Launched	Filed	Launched
<i>Symbicort</i>	inhaled steroid/ long-acting β_2 agonist	SMART	III			Launched	Launched	Launched

[#]Partnered product

* Nexium low-dose aspirin indications approved in 1H 2012

**Kombiglyze XRTM US; KomboglyzeTM FDC EU

***2nd CRL received in June 2011

NCEs

Phase III/Registration

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Cardiovascular								
<i>Brilinta/Brilique</i>	ADP receptor antagonist	arterial thrombosis	III		Launched	Launched	1H 2013	Launched
<i>Forxiga™</i> (dapagliflozin) [#]	SGLT2 inhibitor	diabetes	III	3Q 2007	Filed*	Filed**	1H 2013	Filed
Infection								
CAZ AVI [#] (CAZ104)	beta lactamase inhibitor/cephalosporin	serious infections	III	1Q 2012	N/A	2014	2014	2014
Q-LAIV Flu Vac ^{***}	live, attenuated, intranasal influenza virus vaccine (quadrivalent)	seasonal influenza	III		Approved	4Q 2012		
<i>Zinforo[#]</i> (ceftaroline)	extended spectrum cephalosporin with affinity to penicillin-binding proteins	pneumonia / skin infections	III	1Q 2007	N/A	Filed**		Filed
Neuroscience								
naloxegol (NKTR-118) [#]	oral peripherally-acting opioid antagonist	opioid-induced constipation	III	2Q 2011	2H 2013	2H 2013		
Oncology								
<i>Caprelsa</i>	VEGFR / EGFR tyrosine kinase inhibitor with RET kinase activity	medullary thyroid cancer	III		Launched	Launched	2014	Filed
<i>Ranmark[#]</i> (denosumab)	anti-RANKL MAb	bone disorders stemming from bone metastasis	III		N/A	N/A	Launched	N/A
Respiratory & Inflammation								
fostamatinib [#]	spleen tyrosine kinase (SYK) inhibitor	rheumatoid arthritis	III	3Q 2010	2H 2013	2H 2013		2H 2013
lesinurad	selective inhibitor of URAT1	chronic management of hyperuricaemia in patients with gout	III	4Q 2011	2014	2014	2016	2014

[#]Partnered product

*CRL received in January 2012

**Positive opinion received from CHMP in 1H 2012

***sBLA in US, MAA in EU

NCEs
Phases I and II

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Cardiovascular								
AZD4017	11BHS	glaucoma	II	1Q 2011				
AZD2820 [#]	melanocortin receptor type 4 (MC4r) partial agonist peptide	obesity	I	2Q 2011				
Gastrointestinal								
tralokinumab	anti-IL-13 MAb	ulcerative colitis	II	2Q 2012				
Infection								
AZD9773 [#]	anti-TNF-alpha polyclonal antibody	severe sepsis	II	1Q 2008				
CXL [#]	beta lactamase inhibitor/cephalosporin	MRSA	II	4Q 2010				
AZD5847	oxazolidinone antibacterial inhibitor	tuberculosis	I	4Q 2009				
MEDI-550	pandemic influenza virus vaccine	pandemic influenza prophylaxis	I	2Q 2006				
MEDI-557	anti-RSV MAb – extended half-life	RSV prevention in high-risk adults (COPD/CHF/Other)	I	3Q 2007				
MEDI-559	paediatric RSV vaccine	RSV prophylaxis	I	4Q 2008				
Neuroscience								
AZD3241	myeloper-oxidase (MPO) inhibitor	Parkinson's disease	II	2Q 2012				
AZD3480 [#]	alpha4/beta2 neuronal nicotinic receptor agonist	Alzheimer's disease	II	3Q 2007				
AZD5213	histamine-3 receptor antagonist	Alzheimer's disease / ADHD	II	2Q 2012				
AZD6765	NMDA receptor antagonist	major depressive disorder	II	3Q 2007				
AZD1446 [#]	alpha4/beta2 neuronal nicotinic receptor agonist	Alzheimer's disease	I	4Q 2008				
MEDI-5117	anti-IL-6 MAb	OA Pain	I	2Q 2012				

[#]Partnered product

NCEs
Phases I and II (continued)

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Oncology								
AZD4547	FGFR tyrosine kinase inhibitor	solid tumours	II	4Q 2011				
AZD8931	erbB kinase inhibitor	breast cancer chemo. combi./solid tumours	II	2Q 2010				
fostamatinib [#]	spleen tyrosine kinase (SYK) inhibitor	haematological malignancies	II	1Q 2012				
MEDI-551 [#]	anti-CD19 MAb	haematological malignancies	II	1Q 2012				
MEDI-573 [#]	anti-IGF MAb	solid tumours	II	2Q 2012				
MEDI-575 [#]	anti-PDGFR-alpha MAb	NSCLC / glioblastoma	II	4Q 2010				
olaparib	PARP inhibitor	gBRCA ovarian cancer	II	1Q 2012				
selumetinib [#] (AZD6244) (ARRY-142886)	MEK inhibitor	solid tumours	II	4Q 2006				
tremelimumab	anti-CTLA4 MAb	solid tumours	II	3Q 2004				
AZD1208	PIM kinase inhibitor	haematological malignancies	I	1Q 2012				
AZD1480	JAK1, 2 inhibitor	solid tumours	I	2Q 2009				
AZD2014	TOR kinase inhibitor	solid tumours	I	1Q 2010				
AZD3514	androgen receptor down-regulator	prostate cancer	I	3Q 2010				
AZD5363 [#]	AKT inhibitor	solid tumours	I	4Q 2010				
AZD8330 [#] (ARRY 424704)	MEK inhibitor	solid tumours	I	1Q 2007				
MEDI-0639	anti-DLL-4 MAb	solid tumours	I	2Q 2012				
MEDI-3617 [#]	anti-ANG-2 MAb	solid tumours	I	4Q 2010				
MEDI-565 [#]	anti-CEA BiTE	solid tumours	I	1Q 2011				
MEDI-6469 [#]	murine anti-OX40 MAb	solid tumours	I	1Q 2006				
moxetumomab pasudotox [#]	anti-CD22 recombinant immunotoxin	haematological malignancies	I	2Q 2007				
selumetinib (AZD6244) (ARRY-142886) /MK2206 [#]	MEK/AKT inhibitor	solid tumours	I	4Q 2009				
vollitinib [#]	MET inhibitor	solid tumours	I	1Q 2012				

[#]Partnered product

NCEs
Phases I and II (continued)

Compound	Mechanism	Area Under Investigation	Phase	Date Commenced Phase	Estimated Filing			
					US	EU	Japan	Emerging
Respiratory & Inflammation								
AZD2115 [#]	MABA	COPD	II	2Q 2012				
AZD5069	CXCR2	asthma	II	4Q 2010				
AZD5423 [#]	inhaled SGRM	COPD	II	4Q 2010				
AZD8683 [#]	muscarinic antagonist	COPD	II	4Q 2010				
benralizumab [#]	anti-IL-5R MAb	asthma / COPD	II	4Q 2008				
brodalumab [#]	anti-IL-17R MAb	psoriasis / psoriatic arthritis / asthma	II	4Q 2009				
mavrilimumab [#]	anti-GM-CSFR MAb	rheumatoid arthritis	II	1Q 2010				
MEDI-546 [#]	anti-IFN-alphaR MAb	SLE	II	1Q 2012				
MEDI-8968 [#]	anti-IL-1R MAb	COPD	II	4Q 2011				
sifalimumab [#]	anti-IFN-alpha MAb	SLE	II	3Q 2008				
tralokinumab	anti-IL-13 MAb	asthma	II	1Q 2008				
AZD8848 [#]	inhaled TLR7	asthma	I	2Q 2012				
MEDI-2070 [#]	anti-IL-23 MAb	Crohn's disease	I	2Q 2010				
MEDI-4212	anti-IgE MAb	asthma	I	1Q 2012				
MEDI-551 [#]	anti-CD19 MAb	scleroderma	I	2Q 2010				
MEDI-570 [#]	anti-ICOS MAb	SLE	I	2Q 2010				
MEDI-5872 [#]	anti-B7RP1 MAb	SLE	I	4Q 2008				
MEDI-7183 [#]	anti-A4b7 MAb	Crohn's disease / ulcerative colitis	I	3Q 2010				
MEDI-7814	anti-C5/C5a MAb	COPD	I	1Q 2012				
MEDI-9929 [#]	anti-TSLP MAb	asthma	I	4Q 2008				
RDEA3170	selective inhibitor of URAT1	chronic management of hyperuricaemia in patients with gout	I	3Q 2011				

[#]Partnered product

Development Pipeline - Discontinued Projects between 31 December 2011 and 30 June 2012

Cardiovascular

NCE/Line Extension	Compound	Reason for Discontinuation	Area Under Investigation
NCE	AZD2927	Safety/Efficacy	atrial fibrillation

Neuroscience

NCE/Line Extension	Compound	Reason for Discontinuation	Area Under Investigation
NCE	AZD2423	Safety/Efficacy	chronic neuropathic pain
NCE	AZD3839	Safety/Efficacy	Alzheimer's disease
NCE	MEDI-578	Regulatory	OA pain
NCE	TC-5214	Safety/Efficacy	major depressive disorder (monotherapy)
NCE	TC-5214	Safety/Efficacy	major depressive disorder (adjunct)

Infection

NCE/Line Extension	Compound	Reason for Discontinuation	Area Under Investigation
NCE	AZD5099	Safety/Efficacy	serious infections
NCE	MEDI-534	Safety/Efficacy	RSV/PIV prophylaxis

Respiratory & Inflammation

NCE/Line Extension	Compound	Reason for Discontinuation	Area Under Investigation
NCE	AZD1981	Safety/Efficacy	asthma/COPD
NCE	AZD2423	Safety/Efficacy	COPD

Comments

As disclosure of compound information is balanced by the business need to maintain confidentiality, information in relation to some compounds listed here has not been disclosed at this time.

Submission dates shown for assets in Phase III and beyond.

Annex 2

Article R5122-8

Modifié par Décret n°2012-741 du 9 mai 2012 – art. 6

La publicité pour un médicament auprès des professionnels de santé mentionnés à l'article L. 5122-9 est adaptée à ses destinataires. Elle précise la date à laquelle elle a été établie ou révisée en dernier lieu et comporte au moins les informations suivantes :

- 1° La dénomination du médicament ;
- 2° Le nom et l'adresse de l'entreprise exploitant le médicament ;
- 3° La forme pharmaceutique du médicament ;
- 4° La composition qualitative et quantitative en principes actifs, avec la dénomination commune, et en constituants de l'excipient dont la connaissance est nécessaire à la bonne administration du médicament ;
- 5° Les numéros d'autorisation de mise sur le marché ou d'enregistrement ;
- 6° Les propriétés pharmacologiques essentielles au regard des indications thérapeutiques ;
- 7° Les indications thérapeutiques et les contre-indications ;
- 8° Le mode d'administration et, si nécessaire, la voie d'administration ;
- 9° La posologie ;
- 10° Les effets indésirables ;
- 11° Les mises en garde spéciales et les précautions particulières d'emploi ;
- 12° Les interactions médicamenteuses et autres ;
- 13° Le classement du médicament en matière de prescription et de délivrance mentionné dans l'autorisation de mise sur le marché ;
- 14° Le prix limite de vente au public lorsqu'un tel prix est fixé en application des lois et règlements en vigueur, accompagné, dans ce cas, du coût du traitement journalier ;
- 15° La situation du médicament au regard du remboursement par les organismes d'assurance maladie ou de l'agrément pour les collectivités publiques prévu à l'article L. 5123-2 ;
- 16° Pour une spécialité générique, la mention de cette qualité et, si le groupe générique auquel appartient la spécialité comporte une ou plusieurs spécialités de référence, la mention : " Cette spécialité est un générique de ", suivie du nom de la ou des spécialités de référence, de leur dosage et de leur forme pharmaceutique. En ce cas, la publicité comporte également la mention : " Médicament inscrit au répertoire des génériques. Lors de la substitution, consultez la liste des excipients à effet notoire figurant sur l'emballage ainsi que le répertoire des génériques pour prendre connaissance des mises en garde éventuelles y figurant. " Toutefois, pour une publicité sur un support de diffusion radiophonique, seule est requise la mention que la spécialité est générique.

Annex 3

MENTIONS LEGALES COMPLETES

EMLAPATCH® 5 POUR CENT, pansement adhésif cutané

COMPOSITION

Lidocaïne 0,025 g

Prilocaine 0,025 g

Huile de ricin hydrogénée polyoxyéthylénée (Arlatone 289), carbomère (Carbopol 974P), hydroxyde de sodium, eau purifiée qsp, 1 g d'émulsion pour un pansement adhésif cutané* de 10 cm²

Composition du pansement adhésif cutané* : feuille stratifiée (aluminium/plastique), disque absorbant (cellulose), bande circulaire de mousse adhésive (PE), adhésif (acrylate).

FORME PHARMACEUTIQUE

Pansement adhésif cutané

DONNEES CLINIQUES

Indications thérapeutiques

Anesthésie par voie locale de la peau saine, par exemple :

- avant ponctions veineuses ou sous-cutanées
- avant chirurgie cutanée superficielle, instrumentale ou par rayon laser

Posologie et mode d'administration

Le pansement adhésif est appliqué au moins une heure avant l'intervention.

A la fin du délai d'application, le résidu de l'émulsion est soigneusement retiré avec une compresse. L'anesthésie obtenue persiste 1 à 2 heures.

Le nombre de pansements adhésifs cutanés à appliquer dépend de la surface à traiter.

- 1 g (1 pansement adhésif) pour une surface à anesthésier de 10 cm².

La dose maximale théorique est de :

- 50 g chez l'adulte.

La taille du patch peut ne pas être adaptée à l'application sur certaines parties du corps du nouveau-né ou du nourrisson. L'utilisation du patch chez le nouveau-né et jusqu'à 3 mois est réservée à l'application sur une surface maximale de 10 cm².

Age	Durée minimale d'application	Dose maximale Théorique	Durée maximale d'application
<u>Adulte et enfants âgés de plus de 12 ans</u>	1 heure	50 g	4 heures**
<u>Enfant</u>			
De 0 à 3 mois	1 heure	1 g pour 10 cm ² : ne pas appliquer plus d'un patch à la fois - A ne pas renouveler avant 12 heures.	1 heure *
De 3 à 12 mois	1 heure	2 g : ne pas appliquer plus de deux patches à la fois	4 heures**
De 12 mois à 6 ans	1 heure	10 g	4 heures**
De 6 ans à 12 ans	1 heure	20 g	4 heures**
* Dans cette tranche d'âge, une durée d'application supérieure à 1 heure n'a pas été étudiée.			
** Au delà de 4 heures, l'effet anesthésique diminue			

Chez les enfants porteurs de lésions cutanées atopiques : avant curetage de molluscum, un temps d'application de 30 minutes est recommandé.

Coût de traitement pour un patch : 3,45 €.

Contre-indications

- *Hypersensibilité aux anesthésiques locaux à liaison amide ou à tout autre composant du pansement.*
- Méthémoglobinémie congénitale.
- Porphyrries.

Mises en garde et précautions particulières d'emploi

Mises en garde

- Ne pas appliquer le pansement adhésif anesthésique sur l'oeil ou à proximité des yeux, du fait du risque d'irritation marquée.
- L'efficacité d'Emlapatch lors des prélèvements capillaires au talon chez les nouveaux nés n'a pas été démontrée en clinique.
- Le pansement adhésif anesthésique doit être prescrit avec prudence chez les sujets porteurs de lésions cutanées atopiques, en raison de réactions cutanées marquées, mais réversibles, de nature non allergique.
- Avant curetage de molluscum chez les enfants porteurs de lésions cutanées atopiques, un temps d'application de 30 minutes est recommandé.
- Chez le nouveau-né et le prématuré, en raison du risque potentiel de méthémoglobinémie, il est recommandé d'utiliser Emlapatch en milieu hospitalier.
- Il est recommandé de ne pas utiliser Emlapatch chez le nourrisson de 0 à 3 mois présentant un déficit en G6PD connu ou suspecté.
- Il est recommandé de ne pas utiliser Emlapatch en applications répétées, en particulier chez le nourrisson de 0 à 3 mois.
- Utiliser avec précaution chez les enfants (en particulier le nourrisson de 0 à 3 mois) traités par des médicaments méthémoglobiniants (voir rubrique Interactions avec d'autres médicaments et autres formes d'interactions).
- Chez les enfants de moins de 3 mois une augmentation de la méthémoglobinémie transitoire est couramment observée jusqu'à 12 heures après application.
- Ne pas appliquer chez les prématurés de moins de 37 semaines d'âge corrigé.
- L'attention des sportifs sera attirée sur le fait que cette spécialité contient un principe actif pouvant induire une réaction positive des tests pratiqués lors des contrôles antidopages.

-Par mesure de prudence, cet anesthésique ne doit pas être utilisé préalablement pour l'anesthésie de l'injection intradermique d'un vaccin vivant tel que le BCG, en raison des propriétés antibactériennes des principes actifs.

-En raison de la présence de l'huile de ricin, risque de sensibilisation, notamment chez l'enfant de moins de 3 ans.

Précautions particulières d'emploi

Chez le petit enfant, une surveillance particulière est recommandée afin de vérifier le maintien en place du pansement adhésif anesthésique et de prévenir un éventuel risque d'ingestion ou de contact avec les yeux, consécutif à une manipulation du pansement par l'enfant.

- En cas d'utilisation d'Emlapatch précédant une anesthésie régionale, il convient de tenir compte des quantités d'anesthésiques locaux administrés par voie transcutanée.

Interactions avec d'autres médicaments et autres formes D'interactions

Associations à prendre en compte :

+ autres anesthésiques locaux : lors de l'application de doses importantes, l'association avec d'autres anesthésiques locaux peut entraîner un risque additif de toxicité systémique.

+ médicaments susceptibles d'induire une méthémoglobinémie (sulfamides, dapsone, métoclopramide, flutamide, nitroprussiate de sodium), **en particulier chez le nourrisson de 0 à 3 mois** : risque d'addition d'effets méthémoglobinisants.

Grossesse et allaitement

Grossesse

Les études chez l'animal n'ont pas mis en évidence d'effet tératogène. En l'absence d'effet tératogène chez l'animal, un effet malformatif dans l'espèce humaine n'est pas attendu. En effet, à ce jour, les substances responsables de malformations dans l'espèce humaine se sont révélées tératogènes chez l'animal au cours d'études bien conduites sur deux espèces.

En clinique, il n'existe pas actuellement de données suffisamment pertinentes pour évaluer un éventuel effet malformatif ou foetotoxique d'EMLAPATCH lorsqu'il est administré pendant la grossesse.

En conséquence, par mesure de précaution, il est préférable de ne pas utiliser EMLAPATCH pendant la grossesse.

Allaitement

La lidocaïne et la prilocaïne sont excrétées dans le lait, mais l'absorption négligeable des anesthésiques locaux par voie digestive, permet leur administration, en cas de besoin, chez la femme qui allaite.

Effets indésirables

-L'application cutanée ou muqueuse est susceptible d'induire localement un érythème, une pâleur, un prurit, une sensation de brûlure ou un œdème du site d'application. Ces réactions cutanées sont bénignes, toujours réversibles et ne préjugent pas de la qualité de l'anesthésie obtenue.

-Exceptionnellement, réaction allergique voire choc anaphylactique.

-Méthémoglobinémie, particulièrement chez l'enfant de moins de 3 mois, et en cas de surdosage.

-En raison de la présence d'huile de ricin, risque d'eczéma de contact.

-De rares cas de lésions locales discrètes au niveau du site d'application, à type de purpura ou de pétéchies ont été rapportés, notamment après des temps d'application supérieurs à la durée recommandée chez les enfants porteurs de lésions cutanées atopiques ou d'un molluscum contagiosum (voir rubrique Mises en garde).

Surdosage

L'application de doses massives de l'association lidocaïne et prilocaïne pourrait conduire à un surdosage ; en ce cas, une surveillance en milieu spécialisé devra être maintenue durant plusieurs heures après le retrait des pansements adhésifs, en raison de l'absorption retardée des deux anesthésiques locaux.

Les manifestations neurologiques éventuelles (convulsions, dépression du SNC) seront traitées par des moyens symptomatiques (réanimation respiratoire en particulier) et par l'emploi d'agents anticonvulsivants type benzodiazépine ou barbiturique d'action rapide.

En cas de survenue d'une méthémoglobinémie, après confirmation biologique du diagnostic, le traitement comportera l'administration intraveineuse lente de 1 à 2 mg/kg de bleu de méthylène dilué.

Propriétés pharmacologiques

Propriétés pharmacodynamiques

ANESTHÉSISQUES LOCAUX

(N: système nerveux central)

Ce pansement adhésif cutané, contient deux anesthésiques locaux à liaison amide : la lidocaïne et la prilocaïne.

A température ambiante, le mélange, à parts égales de lidocaïne base et de prilocaïne base, forme spontanément une huile.

L'émulsion de cette huile dans l'eau permet le franchissement de la barrière cutanée et procure une anesthésie effective de la peau.

Les anesthésiques locaux agissent de façon directe sur les nerfs en bloquant de manière spécifique, totale et réversible la conduction nerveuse.

Le poids moléculaire de la lidocaïne base est de 234, celui de la prilocaïne base de 220, leur pKa est de 7,7.

Le pH est de 9,2.

Propriétés pharmacocinétiques

Les données de pharmacocinétique reprennent les valeurs enregistrées lors de l'application d'EMLA® 5 % crème sur peau saine.

L'absorption systémique de la lidocaïne et de la prilocaïne est fonction de la dose, de la durée d'application, de l'épaisseur de la peau.

Appliqués sur la peau saine, leur absorption est faible et retardée ; ainsi après 3 heures d'application, elle est de 3 % pour la lidocaïne et de 5 % pour la prilocaïne.

Les taux sériques obtenus sont bas ; une dose très élevée (60 g), appliquée durant 3 heures donne des taux maximum à la 4^{ème} heure de 120 ng/ml pour la lidocaïne et de 67 ng/ml pour la prilocaïne.

Proportionnellement, les taux obtenus chez l'enfant sont un peu plus élevés, mais d'après les études, toujours inférieurs à 450 ng/ml.

Après une distribution tissulaire, fonction du degré de vascularisation, la lidocaïne et la prilocaïne sont métabolisées par le système microsomial hépatique.

Les métabolites obtenus sont pratiquement inactifs et éliminés par voie rénale.

La dégradation de la prilocaïne passe par la formation d'orthotoluidine capable d'induire une méthémoglobinémie, pour une dose de prilocaïne base supérieure à 600 mg pour 70 kg rapidement absorbée, comme, par exemple, au cours d'une infiltration.

Données de sécurité précliniques

L'orthotoluidine (métabolite de la prilocaïne) et la 2,6-xylidine (métabolite de la lidocaïne) ont révélé des propriétés mutagènes in vitro et un potentiel carcinogène à hautes doses au cours des études de toxicologie chronique chez l'animal.

Il n'est pas considéré que ces données impliquent un risque particulier chez l'homme, compte tenu de la voie d'administration, des doses utilisées et de la durée du traitement.

Données pharmaceutiques

Durée de conservation

2 ans.

PRECAUTIONS PARTICULIERES DE CONSERVATION

A conserver à une température ne dépassant pas 25°C.

Nature et contenance du récipient

Le pansement adhésif est composé d'un pansement occlusif contenant 1 g d'émulsion et aluminium/plastique, d'un disque absorbant en cellulose contenant les anesthésiques locaux et d'une bande circulaire de mousse adhésive. Cette bande est du polyéthylène recouverte d'un adhésif en acrylate.

Mode d'emploi, instructions concernant la manipulation

Le pansement adhésif doit être appliqué au moins une heure avant l'intervention.

S'assurer que la surface cutanée à anesthésier est propre et sèche.

Pour ouvrir le pansement adhésif, prendre le coin aluminium prévu à cet effet.

La partie blanche du pansement adhésif contient la crème anesthésique, ne pas la toucher.

Appliquer le pansement adhésif de manière à ce que la pastille blanche recouvre la surface à anesthésier.

Ne pas appuyer sur la partie centrale du pansement adhésif, pour éviter une fuite sous l'adhésif.

Assurer la bonne adhésion du pansement adhésif en appuyant fermement sur le pourtour.

Indiquer l'heure d'application à même le pansement adhésif. Celui-ci doit rester en place au minimum 60 minutes chez l'adulte et l'enfant de plus de 3 mois.

Chez le nourrisson de 0 à 3 mois, la durée d'application maximale est de 1 heure pour une surface de 10 cm² maximum.

PRESENTATION ET NUMERO D'IDENTIFICATION ADMINISTRATIVE - CONDITIONS DE PRESCRIPTION ET DE DELIVRANCE

AMM 3400934000713 : boîte de 1 pansement adhésif cutané

AMM 3400955887591 : boîte de 20 pansements adhésifs cutanés

Liste II.

Prix : 3,45 Euros (1 pansement). Remb. Sec. Soc. à 65%- Agréé collectivités.

Modèle hospitalier : Agréé collectivités.

Exploitant

AstraZeneca

1, Place Renault

92844 Rueil-Malmaison Cedex

Tél : 01 41 29 40 00

DATE D'APPROBATION/REVISION

Janvier 2007 [EMLP 5%/MLC/0112.1]

BLANDINE LASBAX

CHALLENGES OF MATURE DRUGS IN THE PHARMACEUTICAL INDUSTRY: ISSUES OF MULTICHANNEL STRATEGIES

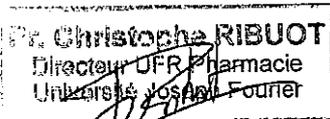
De nombreux enjeux reposent actuellement sur les médicaments matures. En effet, plusieurs problématiques pèsent sur l'industrie pharmaceutique et conduisent à une diminution de son chiffre d'affaire. De plus, une réduction des dépenses est aussi d'actualité afin de palier les déficits engendrés par, entre autres, les pertes de brevet massives, les augmentations de coûts de la R&D et des temps de développement et les conditions de remboursement de plus en plus draconiennes. L'industrie pharmaceutique est donc à la recherche de solutions lui permettant de relancer son économie. Certaines entreprises ont donc choisi de reprendre la promotion de leurs produits matures grâce à des stratégies low-costs. Les chiffres d'affaire ainsi dégagés permettraient à l'industrie pharmaceutique d'investir plus amplement dans la R&D et donc de relancer l'innovation. Ces stratégies en sont pour l'instant à leurs balbutiements. C'est pourquoi le modèle le plus impactant et efficace nécessite encore d'être déterminé.

Many issues currently rely on mature drugs. Indeed, the pharmaceutical industry is currently facing numerous uncertainties that lead to a decrease in its turnover. In addition, a reduction in spending is also occurring to overcome the deficits created by, among others, the massive loss of patents, the cost increases in R&D and development timeframe and the more stringent reimbursement conditions. Pharmaceutical firms are looking for solutions allowing them to boost their economy. Some companies have chosen to promote their mature products through low-cost strategies. Thus, the generated turnovers would allow the pharmaceutical industry to further invest in R&D and thus improve its innovation. These strategies are currently in their infancy. This is why the most effective and impacting model still needs to be determined.

VU ET PERMIS D'IMPRIMER

Grenoble, le 14/01/2012

LE DOYEN



Professeur Christophe RIBUOT

LE PRESIDENT DE LA THESE

A large, stylized handwritten signature in black ink.

Professeur Michel SEVE



Serment des Apothécaires



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'opprobre et méprisé de mes confrères si j'y manque.

CHALLENGES OF MATURE DRUGS IN THE PHARMACEUTICAL INDUSTRY: ISSUES OF MULTICHANNEL STRATEGIES

LASBAX Blandine

Thèse présentée pour l'obtention du titre de Docteur en Pharmacie

Résumé :

L'augmentation de l'espérance de vie de la population mondiale est en partie due à la découverte et l'introduction de nouvelles molécules dans des pathologies chroniques et lourdes, comme notamment les infarctus du myocarde ou les cancers. Cependant, il est de plus en plus difficile, pour les entreprises pharmaceutiques, d'innover en matière de R&D. En effet, l'industrie pharmaceutique se retrouve actuellement face à de nombreuses problématiques, qui entraînent une diminution de son chiffre d'affaire.

Ainsi, celle-ci tente de s'adapter et de mettre en place de nouveaux leviers, aussi bien commerciaux que développementaux, pour relancer sa croissance. Les leviers commerciaux concernent principalement la promotion des médicaments matures. En effet, leur nombre est en constante augmentation à cause du manque d'investissements en R&D des laboratoires. Les médicaments matures incluent ceux arrivant en fin de vie, c'est-à-dire, proche de la date d'expiration de leur brevet et ont donc, généralement, des ventes en décroissance.

Plus précisément, l'un des leviers commerciaux chez AstraZeneca[®] consiste en la mise en place d'une nouvelle stratégie de promotion d'Emlapatch 5%[®]. Cette stratégie se base sur l'utilisation alternée et régulée de différents canaux de communication afin de communiquer avec différents types de médecins. A termes, le but de cette stratégie serait de pouvoir communiquer la bonne information, au bon médecin, via le canal de communication que celui-ci préfère. Cependant, de nombreuses améliorations seront encore nécessaires avant que ce type de stratégie fasse partie du quotidien. Mais cela démontre bien la volonté d'adaptation de l'industrie pharmaceutique.

Mots-clés : promotion des médicaments, nouveaux canaux de communication, stratégie multicanal, médicaments matures

Soutenue à la Faculté de Pharmacie de Grenoble le mardi 11 Décembre 2012 devant le jury composé de :

Président du jury : M. Michel SEVE, docteur en Pharmacie, PU-PH, Grenoble

Membres :

M. Jean BRETON, docteur en Pharmacie, MCU à l'Université Joseph Fourier, Grenoble

Mme Ingrid COLLOMB-CLERC, PhD en Biologie Structurale

Mme Isabelle CHALAMON, PhD en Sciences de Gestion, professeur-chercheur