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Lucie Tomas

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UNIVERSITE JOSEPH FOURIER
FACULTE DE PHARMACIE DE GRENOBLE

Année : 2012

N°

LE PRODUCT LIFE CYCLE MANAGEMENT APPLIQUE AU
MARCHE PHARMACEUTIQUE

THESE

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

Mademoiselle Lucie TOMAS

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à Perpignan (66)

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CIH : Centre d'Innovation en Biologie
DPM : Département de Pharmacochimie Moléculaire
HP2 : Hypoxie Physiopathologie Respiratoire et Cardiovasculaire
IAB : Institut Albert Bonniot, Centre de Recherche « Oncogénèse et Ontogénèse »
IBS : Institut de Biologie Structurale
LAFM : Laboratoire Adaptation et Pathogénèse des Microorganismes
LIBA : Laboratoire Bioinformatique Fondamentale et Appliquée
LCBM : Laboratoire Chimie et Biologie des Métaux
LCHB : Laboratoire de Chimie Inorganique et Biologie
LECA : Laboratoire d'Ecologie Alpine
LR : Laboratoire des Radio-pharmaceutiques
TIMC-IMAG : Laboratoire Technique de l'Imagerie, de la Modification et de la Cognition
UVICI : Unit of Virus Host Cell Interactions

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TABLE OF CONTENT

REMERCIEMENTS	5
LIST OF FIGURES	9
LIST OF TABLES	10
LIST OF ABBREVIATIONS	11
RESUME (FRANÇAIS)	12
INTRODUCTION.....	22
CHAPTER I - DRUG DEVELOPMENT AND CURRENT ISSUES	23
1.1. DEVELOPMENT & LAUNCH OF A DRUG.....	23
1.1.1. Drug Discovery & Development	25
1.1.2. Approval	28
1.1.3. Post Authorization Activities	32
1.2. CURRENT ISSUES OF THE PHARMACEUTICAL MARKET.....	33
1.2.1. R&D Productivity	36
1.2.2. Clinical trials constraints	42
1.2.3. Approval	42
1.2.4. Payers pressure	44
1.2.5. Generics and biosimilars	45
CHAPTER II – THE PRODUCT LIFE CYCLE MANAGEMENT, CONCEPT AND	
STRATEGIES.....	49
2.1. PRODUCT LIFE CYCLE	49
2.1.1. Origin & description.....	49
2.1.2. The Technological Life Cycle.....	52
2.1.3. The Product Life Cycle Management.....	55
2.1.4. The PLCM in marketing	56
2.2. STRATEGIES OF THE PLCM	56
2.3. TACTICS APPLIED TO IMPROVE THE PLC	59
2.3.1. New uses	60
2.3.2. Further development of product.....	60
2.3.3. Price reduction	61
2.3.4. Brand loyalty.....	61
2.4. LIMITATIONS OF THE MODEL	62
CHAPTER III – THE PLCM CONCEPT APPLIED IN THE PHARMACEUTICAL AREA:	
SIMILARITY AND SPECIFICITIES	63
3.1. A DRUG, A PARTICULAR PRODUCT	63
3.1.1. A non typical relationship : drug versus patients	63
3.1.2. A drug, a monitored product.....	63

3.2. THE LIFE CYCLE OF A NEW BRAND DRUG	64
3.3. PLCM TACTICS USED TO IMPROVE LIFE CYCLE OF NEW BRAND MEDICINES.....	69
3.3.1. New indications	69
3.3.2. Continual technical improvement of product.....	71
3.3.3. Evolution of price.....	72
3.3.4. Brand loyalty.....	74
3.3.5. Switch to Over-The-Counter drug	75
3.3.6. Fixed-combination medicinal products	76
CHAPTER IV- THEORY VERSUS REALITY: COMPARISON AND DISCUSSION	77
4.1 PRODUCT LIFE CYCLE MANAGEMENT IN PRACTICE.....	77
4.1.1. In pre-marketing	77
4.1.2. In post-marketing	78
4.2 SANOFI'S CASES.....	79
4.2.1. Case of a biologic medicine currently being developed	79
4.2.2. Case of a prescription drug already commercialized :Plavix®'s case	80
4.3 AN ASIDE, THE BIOSIMILARS' COMPETITIVENESS.....	82
4.4 A UNIQUE MODEL OF PLC FOR ANY MEDECINE?	84
CONCLUSION	86
REFERENCES	88
ANNEXES.....	91

LIST OF FIGURES

Figure 1 Current process of development a commercialization of a new drug.....	23
Figure 2 Drug Discovery step.....	25
Figure 3 Preclinical stage.....	25
Figure 4 Clinical Trials.....	26
Figure 5 Drug Development stages.....	28
Figure 6 CTD Triangle	29
Figure 7 Drug Development & Commercialization	32
Figure 8 Evolution of the growth rate of revenues in the main pharmaceutical markets ..	34
Figure 9 Annual growth rate for the index of industrial production (IPI), EU-27, 2011	35
Figure 10 R&D model yielding costs to successfully discover and develop a single NME...35	
Figure 11 Dimensions of R&D Productivity	37
Figure 12 R&D model yielding costs to successfully discover and develop a single new molecular entity.....	38
Figure 13 Pharmaceutical R&D Expenditure in Europe & USA (\$ million), 1990-2011	39
Figure 14 Cost required at each step of the drug development process	40
Figure 15 Attrition rate at each step of drug development	41
Figure 16 Average time span of every stage of drug development	41
Figure 17 Number of New Chemical or Biological Entities, 1992-2011.....	43
Figure 18 NME Applications Filed and Approved by FDA’s Center for Drug Evaluation & Research (1997-2012)	43
Figure 19 Scope of Product Life cycle Theory	50
Figure 20 Typical Product Life Cycle	50
Figure 21 Typical Technological Life Cycle	52
Figure 22 All phases of the product life cycle and beyond life cycle.....	53
Figure 23 Brand Life Cycle	62

Figure 24 Sales & Profit through Product’s Life Cycle Stages	64
Figure 25 Elements which influence prescribed drug’s life cycle.....	67
Figure 26 Life Cycle of Innovator Product	76
Figure 27 Evolution of sales revenues of Plavix® worldwide	82

LIST OF TABLES

Table 1 Summary of the different steps through the development of one new medicine.	24
Table 2 Stage Characteristics of a new product in a new market	51
Table 3 Diagnosis to optimize strategies through Product Life Cycle	58
Table 4 Optimized pathway through the product life cycle	59
Table 5 the Case for Premarketing	65

LIST OF ABBREVIATIONS

BLA – Biologic License Application

BLC – Brand Life Cycle

CTD – Common Technical Document

EMA – European Medicines Agency

EU – European Union

FDA – Food & Drug Administration

IPI – Industrial Production Index

LCM – Life Cycle Management

LCP – Life Cycle Prolongation

MA – Marketing Approval

mAb – Monoclonal Antibody

MS – Market Share

NCE – New Chemical Entity

NDA – New Drug Application

NME – New Molecular Entity

OTC – Over-The-Counter

PLC – Product Life Cycle

PLCM – Product Life Cycle Management

R&D – Research & Development

ROI – Return on Investment

TLC – Technological Life Cycle

US/USA – United States of America

RESUME (FRANÇAIS)

Le développement d'un nouveau produit pharmaceutique est un processus long, complexe et très coûteux. Des organisations professionnelles, telles que l'EFPIA (European Federation of Pharmaceutical Industries and Associations) ou encore le LEEM (Les Entreprises du Médicament), estiment actuellement cette période à une quinzaine d'années en moyenne. Mais ce délai peut varier en fonction des caractéristiques du produit, de l'indication thérapeutique pour laquelle le médicament est initialement développé. Ce processus nécessite un énorme investissement humain et financier dans un secteur industriel considéré depuis quelques années comme peu productif. En 2011, seules 30 nouvelles molécules ont obtenu le statut « New Molecular Entities » (NME) délivré par la FDA alors les dépenses R&D ont dépassé les 70 milliards de dollars.

Différentes causes peuvent expliquer ce manque de résultat auquel les industriels doivent faire face, renforcé par la crise économique actuelle :

- des coûts de plus en plus élevés
- un taux de réussite inférieur à celui des autres secteurs de haute technologie
- un temps de développement qui ne cesse de s'allonger, entraînant par ricochet un temps de commercialisation considérablement réduit
- de fortes contraintes inhérentes aux essais cliniques
- un nombre d'autorisations qui tend à diminuer depuis ces dernières années
- une pression toujours plus importante des agences de santé pour réduire les dépenses liées aux remboursements tout en requérant des produits toujours plus sûrs.

Ces différents challenges ont profondément changé l'environnement et la dynamique du marché pharmaceutique, influençant ainsi les orientations stratégiques des décisionnaires industriels: ces dernières se dirigeront préférentiellement vers :

- le développement de molécules complexes, en particulier la conception de médicaments biologiques

- le traitement de maladies chroniques et/ou pour lesquelles la thérapie est particulièrement lourde,
- la prise en charge d'une pathologie affectant un nombre significatif de patients,

Grâce à ces orientations, les industriels s'attendent à obtenir un **retour sur investissement** (ROI) suffisant.

Ces orientations peuvent être choisies aux dépens d'autres pathologies, notamment les pathologies de courte durée.

En plus de ces challenges liés au développement réussi, les managers industriels doivent également faire face à de nombreux facteurs qui peuvent avoir un impact sur la pérennité du médicament sur le marché : une diminution de la durée de la protection par un brevet, une compétition de plus en plus forte et diversifiée (les médicaments "me-too", génériques et biosimilaires,...).

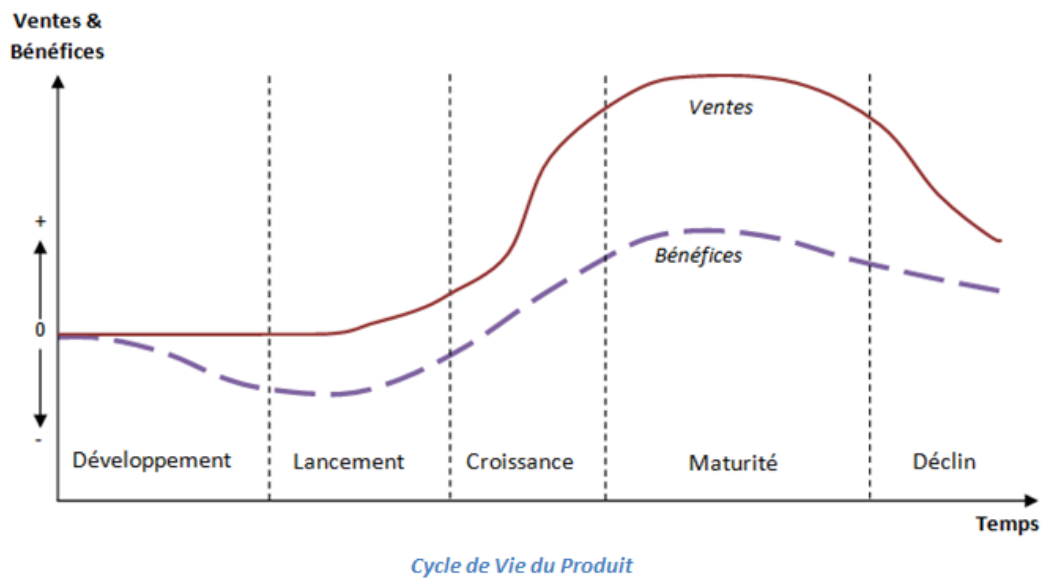
Tout au long des différentes étapes de développement et de commercialisation d'un nouveau produit, les industriels doivent étudier et analyser les influences internes et externes, aussi bien positives que négatives, afin d'augmenter les chances de succès et de réussite commerciale. Une des solutions pour optimiser le retour sur investissement se situerait dans la capacité des industriels à gérer les risques et les opportunités liés au produit et à son marché via son cycle de vie.

Cycle de vie du produit (ou « Product Life Cycle » –PLC-)

Le Concept PLC a largement été décrit et analysé par la communauté scientifique depuis des décennies. Il met en avant les différentes étapes auxquelles est confronté un produit (dans cette situation, le mot « produit » est un terme générique puisque le PLC est également applicable pour une marque, une ligne de produit, un service...) :

- phase de développement
- lancement du produit sur le segment de marché prédéfini,
- phase de croissance (la plus rapide possible),
- stade de maturité (le plus longtemps possible),
- phase de déclin.

La figure ci-dessous représente les différentes étapes du PLC associées aux courbes d'évolution du chiffre d'affaires et du volume de ventes du produit tout au long de son cycle :



Chacune de ces étapes a ses propres spécificités en termes de :

- coûts et dépenses requis,
- possibilité ou non d'un retour financier,
- objectifs stratégiques...

Mais le PLC est en réalité plus complexe que cette « simple » succession de 5 étapes : aujourd'hui les industriels tendent à intégrer des éléments qui ne font pas partie du cycle de vie du produit mais qui dépendent de ce même produit pendant son cycle et au-delà (comme par exemple le développement durable). Ces éléments peuvent être :

- tangibles (ex. gestion des déchets, recyclage,...)
- intangibles (ex. gestion des conséquences sanitaires suite à l'exposition à un produit chimique).

Par ailleurs, dans tous les types de secteurs industriels, un produit est rarement développé et commercialisé seul. La majorité des entreprises possède en effet un portefeuille de produits et/ou de services, implémentés sur différents segments du marché. En outre, ces produits ne sont pas tous au même stade de leur cycle de vie, certains sont une source conséquente de revenus, d'autres, au contraire, nécessitent des

investissements pour réussir ou maintenir leur présence sur le marché. Mais les ressources d'une entreprise, qu'elles soient financières, humaines ou matérielles, ne sont pas infinies. Les industriels doivent donc réfléchir à la répartition desdites ressources afin de maximiser leur performance et ainsi de pérenniser l'entreprise à court et long-terme.

Que ce soit au niveau du portfolio ou plus spécifiquement au niveau d'un produit, différents facteurs apparaissent tout au long du cycle de vie (influençant la R&D, la production, le marketing...). Ceux-ci doivent donc être managés afin de réaliser les objectifs stratégiques sélectionnés par l'entreprise (investir, dégager au mieux des bénéfices, diversifier, "désinvestir",...) : pour cela est utilisée la « gestion du cycle de vie du produit » (Product Life Cycle Management). Dans le secteur industriel, il correspond à un ensemble de processus et d'activités dans le but est de créer un produit et de le maintenir durant tout son cycle de vie, depuis les premiers stades de développement jusqu'à sa fin de vie.

La gestion du cycle de vie du produit peut être scindée en 2 parties distinctes :

- la gestion appliquée à la partie « fabrication » de l'entreprise, comprenant la R&D et la partie production (item non abordé dans ce document)
- le **Product Life Cycle Management** utilisé en marketing (PLCM)

Le PLCM est une succession de stratégies (et tactiques associées) mises en place tout au long du cycle de vie. Les principaux objectifs du PLCM sont d'optimiser la période de commercialisation, réduire les coûts, identifier et se positionner sur les opportunités commerciales...

Les stratégies du PLCM

La planification des stratégies employées dans le PLCM a fait l'objet d'un certain nombre d'études et d'analyses de la part de la communauté scientifique. Dans ces études, certains ont émis l'hypothèse que les variables associées à cette planification étaient identiques à chacune des phases du cycle de vie mais leur importance, elle, varie en fonction des phases du cycle et des objectifs de performance associés.

Ces stratégies sont réalisées par la mise en place d'outils opérationnels de gestion ou tactiques. Ceux-ci présentent deux intérêts majeurs :

- participer et améliorer la différenciation du produit tout au long de sa commercialisation (de son lancement jusqu'à sa phase de déclin),
- augmenter et prolonger la courbe d'évolution du chiffre de ventes durant tout le cycle.

Ces tactiques sont classées en différentes catégories :

- nouvelles utilisations. Habituellement, cette tactique est employée lorsque le produit est déjà « avancé » sur son cycle de vie, généralement durant sa phase de maturité. Si cette tactique réussit, cela aura deux conséquences sur la courbe du cycle :
 - prolongation de la durée de la phase de maturité du produit
 - augmentation du volume des ventes (et par conséquent du chiffre d'affaire) en accroissant la taille de la population ciblée par le produit
- développement de nouvelles variations pour améliorer le produit et/ou diversifier la réponse à la demande. Cette tactique permet notamment de :
 - étendre la protection en additionnant les brevets,
 - maintenir un certain intérêt des consommateurs vis-à-vis du produit grâce à l'attrait de la nouveauté,
 - maintenir un avantage compétitif du point de vue technologique.
- réduction des prix pour faire face à la concurrence et rester attractif (notamment durant les phases de croissance et de maturité, phases durant lesquelles la compétition est la plus forte)
- fidélité à la marque. Tout comme le produit, la marque a un cycle de vie qui lui est propre (développement de l'identité de la marque, reconnaissance, fidélité, déclin). Ce cycle peut aussi avoir un impact sur les différentes étapes du cycle de vie du produit :
 - la reconnaissance d'une marque favorise l'adoption du produit
 - la fidélité peut ralentir le déclin du produit et donc de prolonger au maximum le ROI.

Toutefois, bien qu'utilisé largement dans les différents secteurs industriels, le modèle PLCM doit faire face à certaines critiques :

- les managers pourraient avoir des difficultés–pour déterminer avec précision et fiabilité la place du produit sur son cycle de vie et évaluer quelle sera la durée de chacune des différentes phases.
- Il serait erroné de considérer que tous les produits suivent systématiquement la courbe classique d'évolution des ventes durant le cycle.
- Il se pourrait que dans certaines situations ce soit le management du marketing qui influence le cycle de vie du produit et non l'inverse.

Au final, en regard de ces limites, la stricte application du modèle PLC peut conduire les entreprises vers des décisions stratégiques inappropriées..

Le PLCM appliqué au marché pharmaceutique.

Il est facile d'imaginer que ce modèle puisse être appliqué au secteur pharmaceutique. Le marché pharmaceutique est un marché « comme un autre » : les fabricants vendent leurs produits aux clients tout en œuvrant pour supplanter la concurrence.

Cependant le médicament est un produit particulier :

- Un « client » atypique puisqu'il s'agit d'une « association tripartite » : le médecin qui « choisit » le composé, l'organisme de soins qui le paie et le patient qui finalement le consomme.
- Une surveillance stricte est appliquée. Que ce soit au niveau de son développement, de son lancement et de sa commercialisation, le produit ainsi que son fabricant doivent répondre à un certain nombre de pré-requis établis par des réglementations nationales et internationales.

Ces spécificités n'ont toutefois pas vraiment d'impact sur un changement de modélisation du cycle de vie du médicament. Néanmoins, elles peuvent influencer les différentes tactiques qui seront mises en place afin d'améliorer et de prolonger la courbe des ventes.

N.B : Seul le médicament soumis à prescription sera analysé par la suite.

Éléments influençant le cycle de vie du médicament

Durant le cycle de vie du médicament (après son lancement), différents facteurs peuvent l'influencer :

- certains éléments sont volontairement mis en place par les industriels en charge du produit afin d'optimiser le ROI (par exemple, multiplier les indications, diversifier le dosage et la formulation...),
- mais ils doivent également tenir compte des facteurs externes qui affecteront la croissance et la pérennité du médicament princeps sur le marché (exemple, la compétition liée aux produits « me-too », ou encore celle liée aux génériques et biosimilaires).

Tactiques utilisées pour augmenter le ROI

Ces tactiques devraient être mises en place le plus tôt possible au cours du cycle de vie : plus tôt elles sont implémentées, plus le retour financier sera maximisé.

Il existe un certain nombre de tactiques employées dans le secteur industriel qui peuvent également être utilisées dans le secteur pharmaceutique.

- multiplication des indications,
- amélioration continue du produit,
- évolution des prix,
- fidélité à la marque.

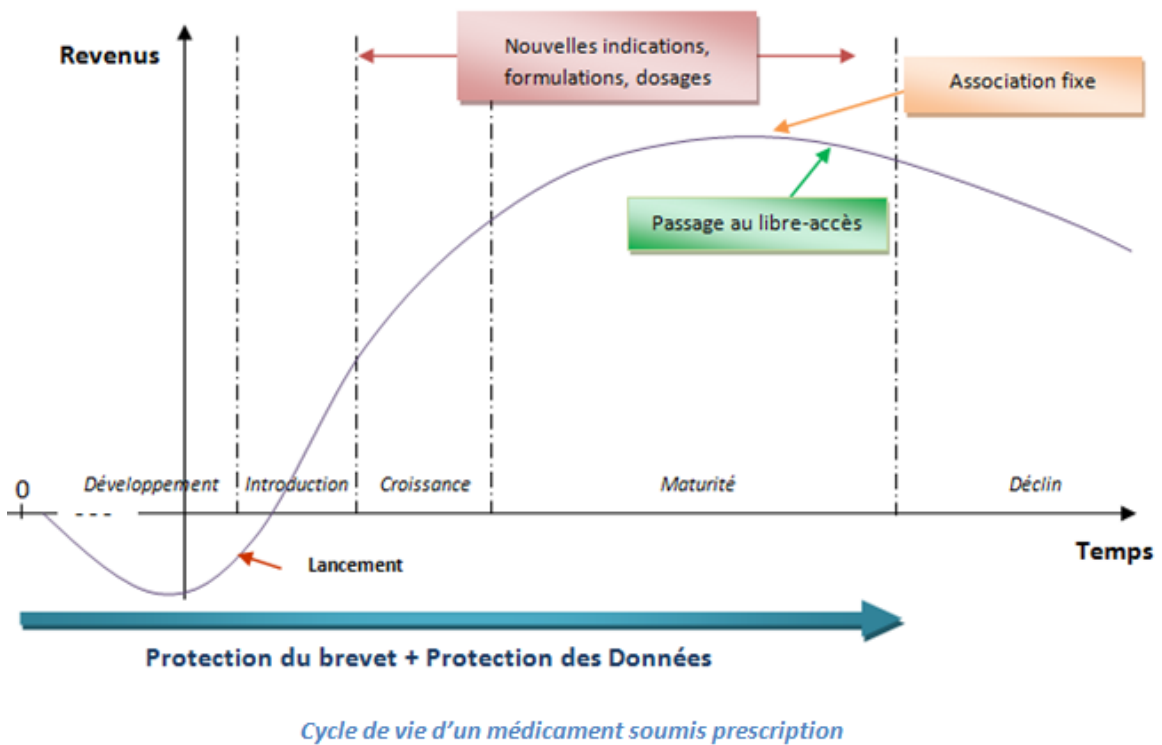
Toutefois, dans ce secteur, certaines d'entre elles ont moins d'influence sur l'évolution de la courbe. Par ailleurs, il existe certaines tactiques spécifiques au marché pharmaceutique :

- passage au libre-accès,
- association thérapeutique.

❖ Indication multiple. Si elle est réalisée avec succès, elle apporte plusieurs bénéfices notamment :

- augmentation du volume des ventes en augmentant la population ciblée par ces indications
- prolongation de la période d'exclusivité du marché (période pouvant s'étendre jusqu'à un an)

- ❖ Amélioration continue (ciblant le dosage, la formulation,...). Cela permet notamment de diversifier la réponse à la demande tout en essayant de prolonger la période de protection liée au brevet.
- ❖ Evolution des prix. A la différence d'un produit lambda, le prix associé à un médicament (ainsi que son remboursement) a été négocié et fixé au préalable, avant son lancement sur le marché. Son prix va évoluer tout au long de son cycle de vie, mais selon un calendrier préétabli et agréé par les autorités de santé. Elle n'est donc pas dépendante de facteurs qui pourraient apparaître au cours du cycle. Cette évolution n'a pas d'influence quant à la perte ou non d'attractivité du médicament (à la différence de produits d'autres secteurs industriels).
- ❖ Fidélité à la marque. Tout comme avec l'évolution du prix, l'importance de cette tactique dans la démarche marketing est plus faible comparée à celle des autres secteurs non pharmaceutiques. Ceci peut s'expliquer par :
 - Une limitation réglementaire des actions promotionnelles,
 - Une population avertie (les médecins) également influencée par des directives réglementaires et des consensus professionnels.
- ❖ Passage au libre-accès. Le passage du médicament soumis à prescription au marché du libre-accès génère de profonds changements dans le cycle de vie du médicament et des actions marketings qui lui sont associées :
 - Le PLC n'est plus limité par la fin de la période d'exclusivité du marché suivie de l'entrée inéluctable des génériques,
 - Et la réglementation du libre-accès offre plus de liberté en termes de promotion et d'utilisation des outils publicitaires.
- ❖ Association thérapeutique. Elle permet l'entrée du produit sur un nouveau segment du marché (amélioration de l'observance et/ou de la facilité de prise), tout en offrant des avantages en termes de protection par un brevet. Cependant, cette tactique tend à être abandonnée en raison de la perte d'intérêt des autorités et des professionnels de santé.



La « gestion du cycle de vie du produit » en pratique

En marketing, les différentes tactiques utilisées peuvent être divisées en 2 sous-catégories :

- Le « Life Cycle Management » (LCM) focalisé sur l'élaboration et la mise en place des indications complémentaires,
- Le « Life Cycle Prolongation » (LCP) qui rassemble les autres tactiques.

Toutes sont managées entre deux périodes-clé :

- Le pré-marketing, commencé habituellement lorsque la phase III de l'indication pivot est lancée ;
- Le post-marketing qui regroupe les actions à partir du lancement du nouveau médicament.

Comme indiqué précédemment, ces tactiques devraient être étudiées et instaurées le plus tôt possible au cours du cycle, au cours du pré-marketing. Pourtant, dans la réalité, ces mises en place ne sont pas aussi précoces.

Pour les indications LCM, les décideurs préfèrent attendre un retour suffisant concernant la stabilité et la pérennité du produit sur le marché avant d'autoriser le lancement de nouvelles études dans un souci de rentabilité.

Cette volonté de rentabilité est également avancée pour justifier délai dans l'instauration des tactiques LCP.

Différents moyens qualitatifs et quantitatifs sont utilisés en pré et post-marketing pour mesurer et évaluer la performance des tactiques mises en place. Certaines sont appliquées tout au long de ces deux phases, d'autres sont employées uniquement en post-marketing :

- Outils prévisionnels (prévisions des ventes, calcul de la Valeur Actuelle Nette – VAN,...)
- Outils mesurant la notoriété du produit auprès des professionnels de santé (en particulier auprès des médecins)
- Analyses des ventes, uniquement en post-marketing (unités de volume vendues, chiffres d'affaires, parts de marché, nombre de patients,...)

Certains professionnels du domaine pharmaceutique s'interrogent sur la pertinence de décrire un seul et unique modèle de PLC alors qu'il existe actuellement plusieurs catégories de médicaments qui s'adressent à plusieurs types de marché.

Un second débat tend à s'installer depuis quelques temps parmi les spécialistes du médicament concernant la pérennité du modèle actuel du cycle de vie du produit (de sa phase de développement jusqu'à la fin de sa commercialisation). Celui-ci semble ne plus être parfaitement adapté au regard de son incapacité à répondre efficacement aux challenges actuels malgré des investissements conséquents dans une tentative de « survie » à court terme.

INTRODUCTION

L'industrie pharmaceutique a longtemps été considérée comme un secteur attractif, notamment grâce à un retour sur investissement spécialement significatif. Pourtant, ces dernières années ont particulièrement été difficiles pour le marché pharmaceutique. Les entreprises rencontrent un certain nombre de difficultés qui affectent à la fois leur croissance et leur stabilité sur le marché :

- Un investissement en R&D particulièrement élevé,
- Une réglementation toujours plus contraignante,
- Une pression gouvernementale pour limiter les coûts liés aux dépenses de santé,
- Une perte de brevet des spécialités « blockbuster » induisant une perte conséquente de revenus.

Afin d'optimiser les différentes étapes et les investissements liés au développement et à la commercialisation, les industriels utilisent le « Product Life Cycle Management ». Concept caractérisé depuis longtemps et largement utilisé, il décrit les différents stades du produit tout au long de son cycle de vie. Les managers mettent en place les différentes actions et tactiques afin de réaliser les objectifs stratégiques rattachés à chacune des étapes du cycle.

Le « Product Life Cycle Management » est adapté et appliqué dans différents secteurs industriels. Pourtant, dans le domaine pharmaceutique, il présente des particularités qu'il est important d'identifier. En effet, Le médicament n'est pas un produit comme un autre.

Mais quelles sont ses spécificités et en quoi ont-elles un impact sur le cycle de vie du médicament et son management ?

Après avoir identifié les différentes caractéristiques du médicament, du marché pharmaceutique et leur impact sur le marketing, deux mises en situation seront décrites : 2 exemples de management marketing sur 2 médicaments développés et commercialisés par l'entreprise Sanofi®.

CHAPTER I - DRUG DEVELOPMENT AND CURRENT ISSUES

1.1. DEVELOPMENT & LAUNCH OF A DRUG

The drug development is a long and complex process. To commercialize only one drug, 10,000 compounds were tested and removed through process. The various steps of the development are numerous and long: from the start of drug discovery to the commercialization, fifteen years (on average) are necessary.¹

This figure below describes simply the overall traditional process of a drug development from the first step of discovery until the post-marketing phase. More exactly, this description represents the development process of the classic new drugs, the **New Chemical Entities** (NCE) or the **New Molecular Entities** (NME). According the official definition of human medicine “Any substance or combination of substances – of human, animal, vegetable or chemical origin, presented as having properties for treating or preventing disease in human beings” (European Directive 2001/83/EC), other types of products are currently considered as a medicine: biologic medicines (“substances produced by living systems”) and biotherapies (“advanced therapy medicinal products”). For both of them, the discovery and development parts of process are different and more complex.

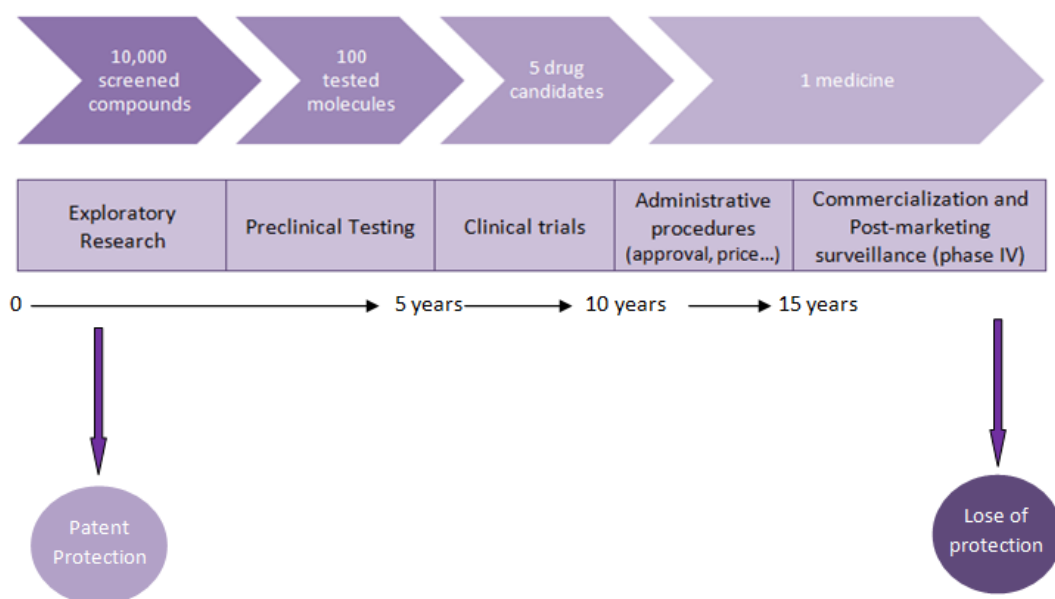


Figure 1 Current process of development a commercialization of a new drug (LEEM 2012)

The development of a new drug requires incredible resources (human, material and financial). Which is characterized the pharmaceutical market is not only the significant investment put in any drug development (on average, more than 15% of revenues of the biggest pharmaceutical companies³) but also its large cycle time of development (around 10 to 15 years on average), starting with the discovery and ending with the launch of product on the market.

The average cost to the **Research and Development** (R&D) of a successful drug is usually estimated to be around \$1 billion to \$2 billion. This includes the cost of thousands of failed drug candidate. For every 5,000-10,000 compounds that will be analyzed and tested in the R&D, only one will be approved by the health authorities.

The number of candidates, the timeframe to develop and commercialize only one drug seem enormous but can be explained when we analyze the R&D process.

The table below summarizes the different main steps realized through the drug development process and highlights the key elements which describe each of them:

	Discovery/Pre-clinical Testing		Phase 1	Phase 2	Phase 3		EMA/FDA	Phase IV
Years (average)	6.5		1.5	2	3.5		1.5	
Test Population	Laboratory and animal studies	File at EMA/FDA	20 to 100 healthy volunteers	100 to 500 patients volunteers	1,000 to 5,000 patients volunteers	File at EMA/FDA	Review process/ approval	Additional post-marketing testing required by EMA/FDA
Purpose	Assess safety, biological activity, and formulations		Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use			
Success Rate	5,000-10,000 compounds evaluated		5 enter trials				1 approved	

Table 1 Summary of the different steps through the development of one new medicine⁴

1.1.1. DRUG DISCOVERY & DEVELOPMENT

Drug discovery

The discovery process includes all early research to identify a new drug candidate and testing it in the research laboratory. The process takes approximately 3 to 6 years. By the end, the ideal situation is to be able to propose a candidate drug to test in people.



Figure 2 Drug Discovery step⁵

This part can be divided into different steps:

1. target identification,
2. target validation and
3. drug discovery.

The two first steps aim to identify and target an element involved in the mechanism involved in the disease. After this identification, the next step is to find a promising molecule (a “lead compound”) that may act on this target and then may be able to modify the disease course. There are few ways to find a lead compound:

Non clinical trials

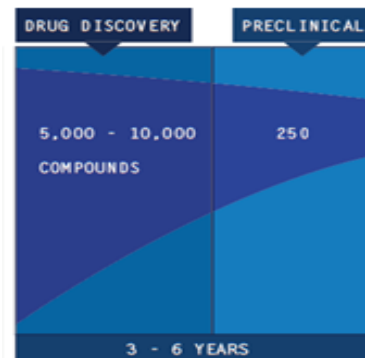


Figure 3 Preclinical stage

This step gives information about the safety, toxicity, pharmacokinetics and metabolism profile of this NCE thanks to lab and animal testing. These parameters have to be assessed prior to human clinical trials. Another major objective of the preclinical phase of drug development is to make a recommendation of the dose and schedule of administration which are used the first time in the first phase of the human clinical trial. It is called "first-in-man" or First Human Dose.

In vitro and *in vivo* tests are used during this phase. The competent health authorities require exhaustive data, in particular about the safety profile of candidates, before the candidate drug will be authorized to be studied in humans.

During this stage researchers also have to formulate the process necessary to the production of large enough quantities of the drug for clinical trials. Techniques for producing a drug in the laboratory on a small scale do not translate easily to larger production. This is the first scale up.

Drug Development

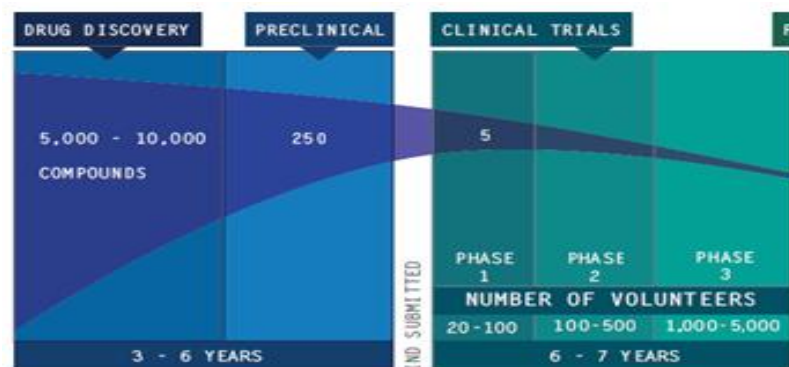


Figure 4 Clinical Trials

A candidate drug must go through extensive studies in humans, and it must prove to be safe and effective before being submitted and approved by the health authorities. This process involves a series of clinical studies, each with its own specific goals and requirement.

The clinical trials process is both expensive and time-consuming and has a high level of attrition rate. From start to end it, this process takes an average of 6-7 years.

During all the clinical phases, the company sponsoring the research must provide regular reports to the health regulatory agencies and the official institutions giving the authorization for the medical institutions to perform clinical studies.

Phase 1 Clinical Trial:

The aim of this phase is to perform initial human testing in a small group of healthy volunteers.

In Phase 1 trials the candidate drug is tested in human population for the first time. These studies are usually conducted with about 20 to 100 healthy volunteers. The main goal of a Phase 1 trial is to determine if the drug is safe in humans.

The pharmacokinetics properties of the drug are also studied. This trial is closely monitored to help to determine what the safe dosing range is and if it should move on to further development.

Phase 2 Clinical Trial:

Test in a small group of patients

Phase 2 trials are designed to determine the candidate drug's effectiveness and evaluated in about 100 to 500 patients affected by the disease or condition under study, and analyze the potential short-term side effects (adverse events) and risks associated with taking the drug.

They also try to answer these questions: Is the drug working by the expected mechanism? Does it improve the condition in question? Researchers also determine optimal dose and schedules for using the drug. If the drug continues to show promise, they prepare for the much larger Phase 3 trials.

Phase 3 Clinical Trial:

Test in a large group of patients to show safety and efficacy

In Phase 3 trials the drug candidate is tested in a larger number of patients (about 1,000-5,000) to generate statistically significant data about safety, efficacy and the overall benefit-risk relationship of the drug. Phase 3 is the key step of drug development in determining if the drug candidate is safe and effective. It also provides the basis for labeling instructions to give advice and recommendations to ensure proper use of the drug (e.g., contraindications, information on potential interactions with other medicines...). Phase 3 trials are both the costliest and longest trials.

1.1.2. APPROVAL

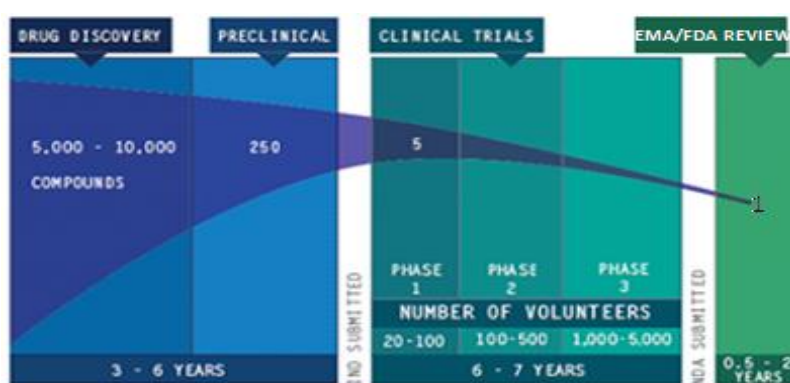


Figure 5 Drug Development stages

At the end of the drug development and if the data resulting of this process are considered as satisfactory by the company sponsoring the drug candidate, application to market is submitted. An official document is drafted: the **Common Technical Document** (CTD). It is a set of specification for application dossier for the registration of medicines. It is used across Europe, Japan and the United States (US). This application document must present substantial evidence about the characteristics of the drug: it has to contain obviously safety and efficacy data of the drug candidate but also all the information collected during the drug development process (conditions of use, recommendation about the prescription...).

The organization of the CTD is internationally harmonized. It is divided into five modules⁶:

1. Administrative and prescribing information. This module is not really a part of the CTD because it is specific each country (Europe, US, Japan...)
2. Overview and summary of modules 3 to 5
3. Quality (pharmaceutical documentation)

4. Non clinical data
5. Clinical data

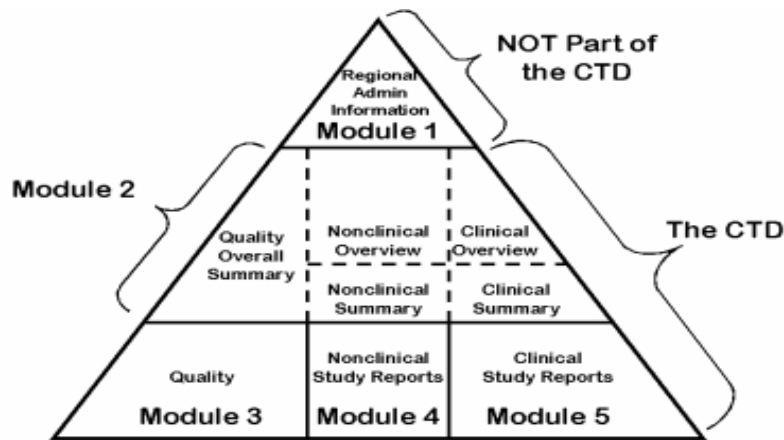


Figure 6 CTD Triangle⁶

The condition and the timeframe to get or not the approval are dependant of the procedure selected for the applicant and the applicable committee which delivers it.

Submit application for approval to Food & Drug Administration (FDA)

If these clinical data demonstrate that the experimental drug is both safe and effective, the company files a **New Drug Application** (NDA) or a **Biological License Application** (BLA) to get required approval to commercialize the drug.

The NDA (or BLA) includes all of the information from the previous years of study, as well as the proposals for manufacturing and labeling of the new medicine.

The application is reviewed by FDA's **Center for Drug Evaluation and Research** (CDER)⁷ which assess all the information included in the file to determine if the demonstration that the medicine is safe and effective is enough relevant and reliable to be approved.

Following rigorous review, the FDA can either:

- 1) approve the medicine,
- 2) send the company an "approvable" letter requesting more information or studies before approval can be given, or
- 3) deny approval.

On average, 6 months are necessary for reviewing priority approval and almost one year in case of standard approvals⁸.

European Medicines Agency (EMA) Drug Approval Process

In Europe, there are four different types of procedure to get the **marketing approval (MA)**⁹:

- National procedure. The procedure for getting approval is submitted to each European Union (EU) member states in which the company expects to commercialize its drug candidate. It is significant time-consuming procedure to get only nationally marketed products.
- Decentralized procedure. It is used for products which fall outside the scope of the EMA centralized procedure. It corresponds to a simultaneous authorization in numerous countries in the EU.
- Mutual recognition procedure. Only one request is submitted to one country in the EU. The final decision will be accepted by the other countries.
- Centralized procedure¹⁰. The EMA has selected a numerous categories of medicines for which this procedure is mandatory: biotechnology products, orphan medicines, and new substances for the treatment of some diseases – oncology, AIDS, diabetes & CNS... One authorization applied to all countries in the EU. The market application is evaluated by the **Committee for Medicinal Products for Human Use (CHMP)** which gives a recommendation to the final decision maker, the European Commission.

According to the characteristics of the drug candidate (chemical characteristic of the Active Ingredient, indication submitted, type of population targeted...) and the strategic plan associated with it (national, international...), the company can choose one of these procedures, national or international.

In 2011, the median time of EMA review process was 250 days (more than 8 months)⁸.

Market Exclusivity

A new brand drug is protected through two different ways which can exist alone but usually combined¹¹:

- Patent protection
- Protection of clinical data, particularly relevant for the off-patent products

The procedures are different between the US and the EU.

❖ United States

- Protection of product. Two elements can be applied: patent (period of 20 years maximum) potentially adjusted by a Patent-Term Extension (PTE) estimated according to some specific requirements¹².
- Marketing exclusivity. The period is between three and five years (new indication/new formulation form and new NME status respectively) from the date of FDA's approval¹³.

❖ European Union

- Protection of product: a 20-year period of patent protection, plus the Supplementary Protection Certificate (SPC) which extends the effective patent life up to a maximum of 15 years from the first approval in the EU, in order to compensate for delays in bringing new products to market caused by regulatory requirements (but does not exceed 5 years after the expiry of patent)¹¹.
- Data protection – 8+2+ (1). Data of the originator product are protected for a 10-year period from the date of the first approval in the European Community (generic company can use these data during the two last years to draft its application file). A one-year period of extension can be approved if a new significant application is approved during the eight first years of exclusivity¹¹.

1.1.3. POST AUTHORIZATION ACTIVITIES

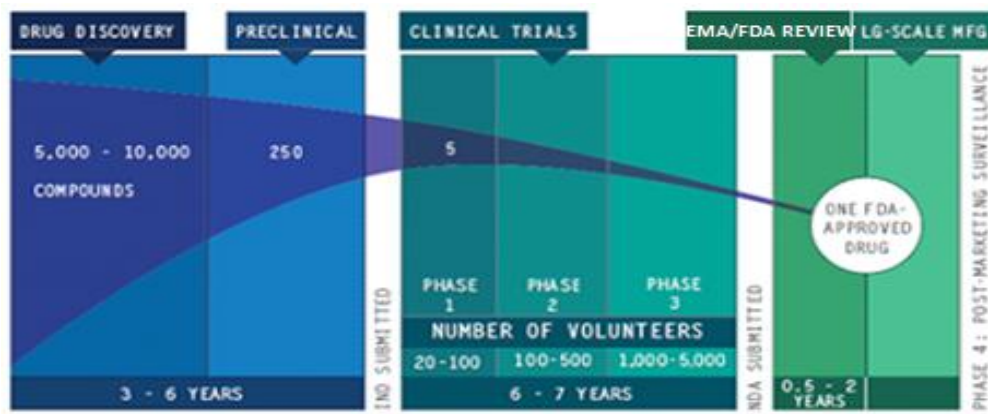


Figure 7 Drug Development & Commercialization

After getting the approval, 2 to 3 years of administrative procedures are needed before drug marketing¹⁴. These procedures include price & reimbursement processes and the launch of product.

Pricing & reimbursement stage

The MA (or NME in US) is the essential step for the success and the commercialization of a new medicine. But it is not the last one for the prescribed drug before commercialization. The further main step is the negotiation around the price and the reimbursement of the new drug. Getting the approval does not mean getting a reimbursement. This negotiation takes place at the national level and governmental institutions may significantly influence drug's prices

This step is critical because it determines the potential access to the drug by patients (limitations of the size of population if the reimbursement is too low and/or the drug too expensive). It is also essential because the agreement about the evolution of new drug's price through its marketing exclusivity is also negotiated between company and national agency.

Three elements may influence this negotiation:

- The application document including various information (CTD, targeted population...)

- The recommendation given by the health authority which has assessed the previous file
- The forecasted assessed by the pharmaceutical company concerning the revenues and market share related to the new drug

Commercialization & Pharmacovigilance

After complying with all these stages, the drug is then launched and managed on the market. Two activities are taking place around it: the medical and marketing activities.

- Medical activities include two parts. The first focuses on further clinical studies undertaken to clarify the characteristics of the compound and try to increase the size of the population targeted by the drug. The second phase corresponds to the pharmacovigilance (or Phase IV). Starting from the clinical stage, this activity is pursued throughout the product life cycle of the drug. Its aim is to collect, monitor, assess and report information from physicians and patients about the adverse effects of medications and reporting them to competent authorities and healthcare professionals.
- Marketing activities. They gather all actions undertaken by marketers to succeed the launch of the drug, its recognition by health professionals and maintain its position on the market.

1.2. CURRENT ISSUES OF THE PHARMACEUTICAL MARKET

The pharmaceutical companies are under pressure from a various issues, including losses of revenue (due to patent expirations, increasingly constraints of reimbursement) and an increase of regulatory requirements.

The results of the pharmaceutical industry's profitability and its growth are the consequences of these issues as we can see with the graph below:

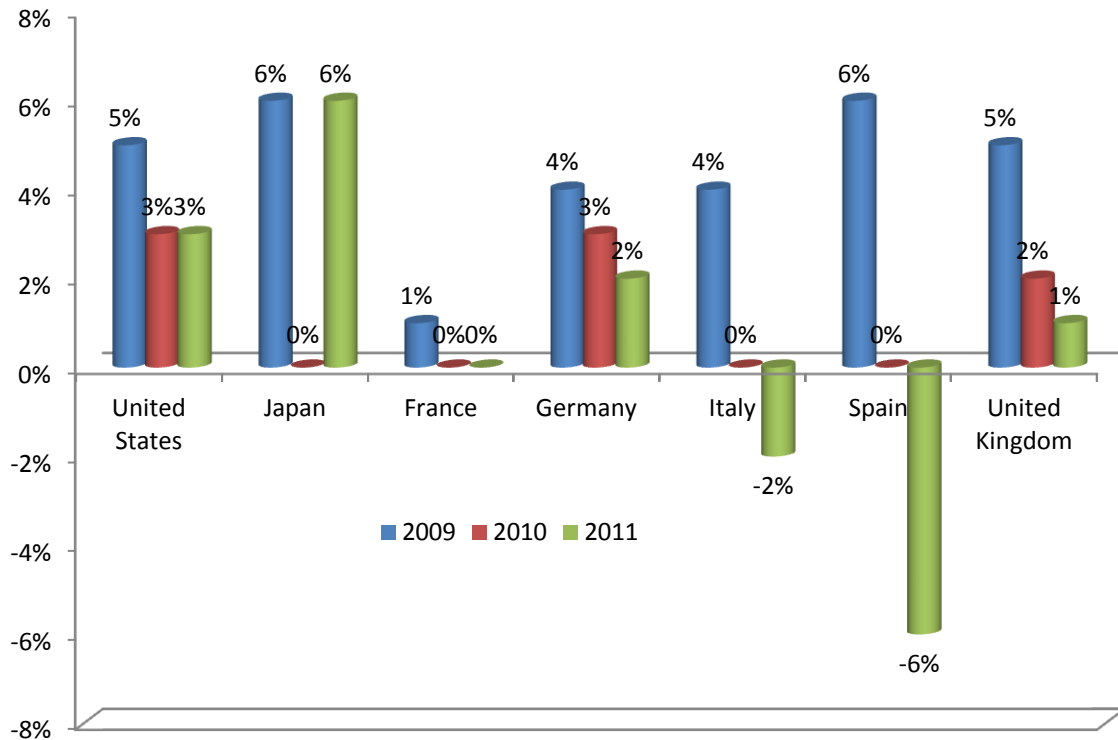


Figure 8 Evolution of the growth rate of revenues in the main pharmaceutical markets (LEEM 2012)

In US, the annual growth rate has decreased down to 3% in 2011 compared to 8% of growth between 2002 and 2006 (EFPIA 2012)

In Europe, the pharmaceutical industry is much more slowed:

- In Germany and in the UK, their annual growth is still positive (2% and 1% respectively)
- In France, the evolution of the market is completely stopped since 2010
- In Italy and Spain, the sales revenues decreased in 2011

The trend of the overall slowdown in the pharmaceutical market is confirmed by a low level of production in 2011:

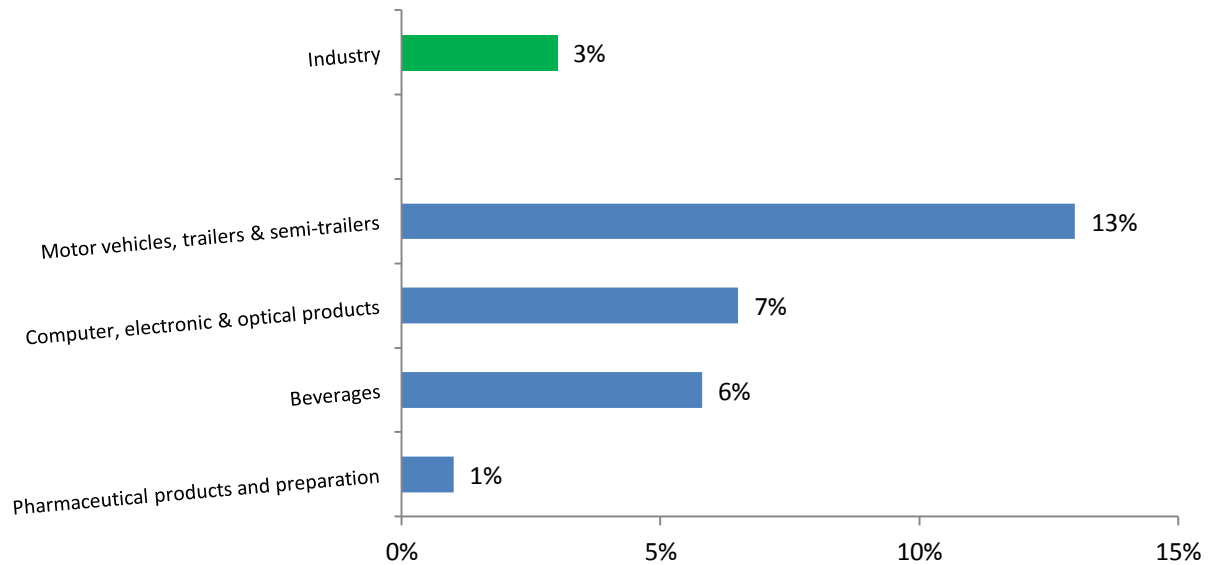


Figure 9 Annual growth rate for the index of industrial production (IPI), EU-27, 2011 (Eurostat data)

In the EU, the growth rate for the IPI in the pharmaceutical field reached only 1% compared to the growth for the IPI in the overall European industrial sector which is 3%¹⁵.

This lack of dynamism in the pharmaceutical field may be explained by various issues associated to the drug development described below:

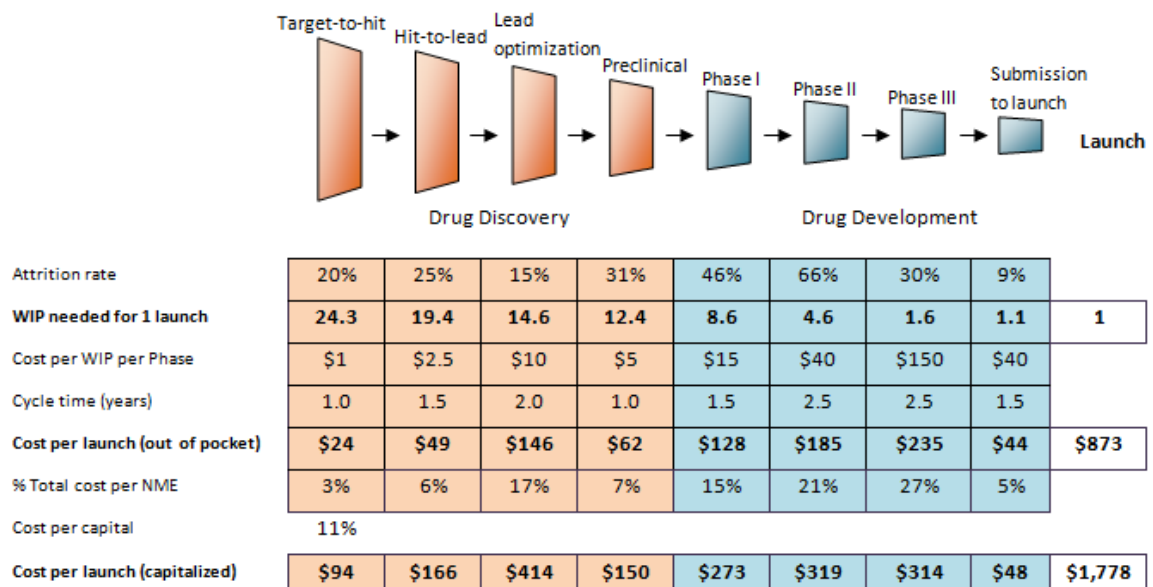


Figure 10 R&D model yielding costs to successfully discover and develop a single NME¹⁶

The model¹⁶ describes the different steps into the drug discovery and development, from the initial stage of target-to-hit to the final stage, launch.

It highlights some internal factors (R&D parameters) which have an impact on company's profitability:

- Cost
- Attrition rate
- Cycle time
- Clinical trials

These factors are intimately related to the substantial and sustainable R&D productivity¹⁶.

Other external parameters influence the profitability and sustainability of pharmaceutical market: payer pressure and generic & biosimilar erosion.

1.2.1. R&D PRODUCTIVITY

Since few years, various shareholders of the pharmaceutical market have noticed a slowdown of the new drug's production: the long-term average is merely one new remedy drug a year per company, despite R&D spending at a high of 18% of revenues¹⁶.

Among all the challenges faced by the pharmaceutical industry, improving R&D productivity may be one of the most important. Even if the company is able to manage and ideally reduce the impact of the factors which influence its profitability and its growth (patent expiration, payer pressure)... without manage and optimize the R&D productivity, the company may not be sustainable.

Definition of R&D productivity¹⁶

R&D productivity can be simply defined as the relationship between the value (medical and commercial) created by a new medicine (considered here to be an NME) and the investments required to generate that medicine. However, R&D productivity can be elaborated in two important dimensions: inputs leading to outputs, or R&D efficiency; and outputs leading to outcomes, or R&D effectiveness (figure below).

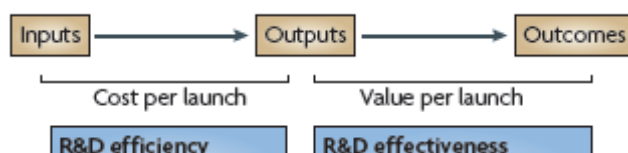


Figure 11 Dimensions of R&D Productivity¹⁶

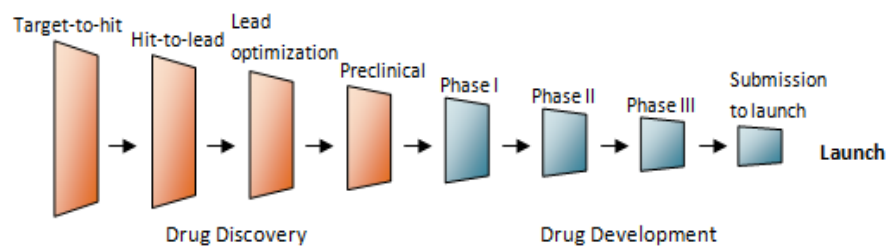
R&D efficiency represents the ability of an R&D system to translate inputs (for example, ideas, investments, effort) into defined outputs (as internal milestones), generally over a defined period of time. The question related to this dimension is “if commercialization (after getting the regulatory approval) of an NME is the desired output, how can this be achieved with greater efficiency (that is, at a lower cost)? “

R&D effectiveness can be defined as the ability of the R&D system to produce outputs with certain intended and desired qualities (for example, medical value to patients, physicians and payers, and substantial commercial value).

Thus, R&D productivity can be viewed as a combination of both the efficiency and effectiveness of the drug discovery and development process; the goal of a highly productive R&D system is to efficiently translate inputs into the most desired and valuable outputs.

So, the key questions are where, how and by how much can R&D productivity be improved?

Below is detailed an analysis of R&D productivity (previously described) which modeling the essential elements of contemporary drug discovery and development that account for the current cost of a new medicine.



Attrition rate	20%	25%	15%	31%	46%	66%	30%	9%	
WIP needed for 1 launch	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1	1
Cost per WIP per Phase	\$1	\$2.5	\$10	\$5	\$15	\$40	\$150	\$40	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	
Cost per launch (out of pocket)	\$24	\$49	\$146	\$62	\$128	\$185	\$235	\$44	\$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost per capital	11%								
Cost per launch (capitalized)	\$94	\$166	\$414	\$150	\$273	\$319	\$314	\$48	\$1,778

Figure 12 R&D model yielding costs to successfully discover and develop a single new molecular entity¹⁶

R&D parameters include:

- the attrition rate related to the each stage,
- number of candidates (work in process WIP) needed in each stage of development to succeed one product launch,
- the cost assigned at each step,
- the cycle time required to progress through each stage of development
- and the cost of capital (reflecting the returns required by shareholders to use their money during the lengthy R&D process)

These factors are intimately related to the substantial and sustainable R&D productivity.

Based on the assumptions for success rate, cycle time and cost, the model further calculates the 'out of pocket' cost per phase as well as the total cost to achieve one NME per year (US\$873 million).

By capitalizing the cost (cost out of pocket multiplied by the cost of capital), the account of drug development to launch successfully one medicine is \$1,178 million (this model does not integrate the costs related to exploratory discovery research, fees not directly linked to R&D activities and post launch expenses).

Cost issues

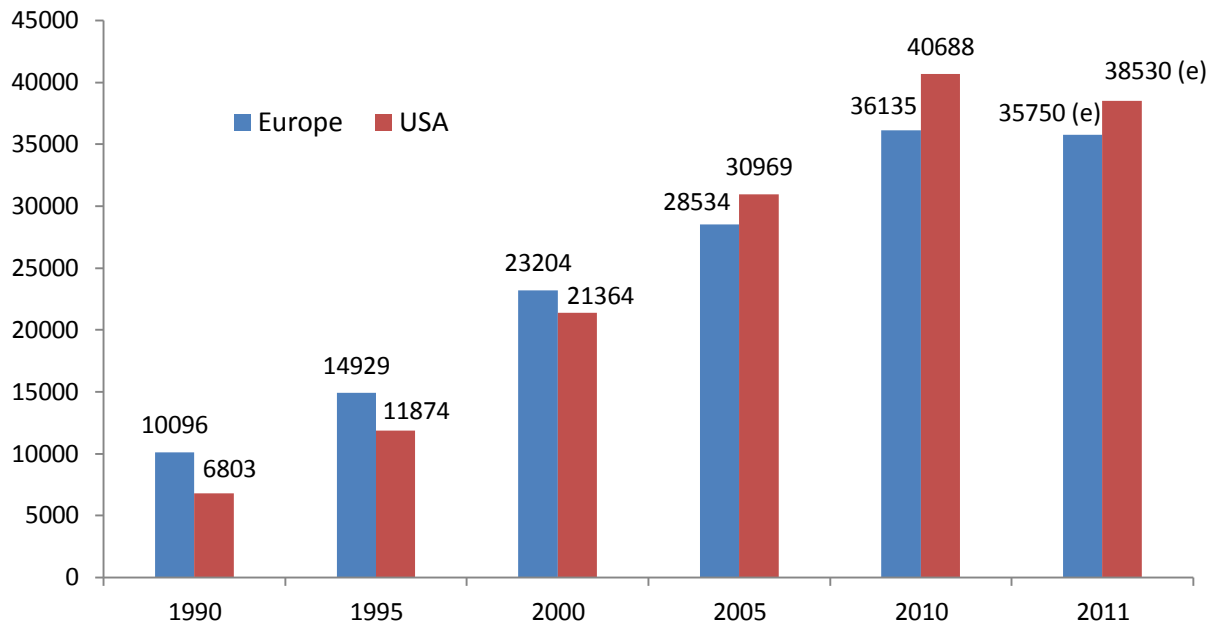


Figure 13 Pharmaceutical R&D Expenditure in Europe & USA (\$ million), 1990-2011 (source EFPIA)

(e): estimate

For twenty years, the pharmaceutical R&D expenditure has never stopped to reach in 2010 more than 74 \$ billion in countries which invest the most in the pharmaceutical R&D department (EFPIA 2012):

- in Europe, the financial investment has been multiplied by 3.6 between 1990 and 2010
- in the USA, the R&D budget was been multiplied by 6.

Since last year, the R&D expenses in USA and Europe is decreasing slightly. Between 2010 and 2011, the expenses decreased of:

- 5% in USA
- 1% in Europe

This decrease is likely related to the reduction of the overall pharmaceutical profits. Previously, the significant growth of expenditure was supported by the large sales revenues generated mainly by blockbusters. But with the loss of patent and marketing

protection of major blockbuster (without competitive replacement), the manufacturers have no longer enough budget to maintain the high level of financial investment to develop a new drug.

With the current model, how be able to produce successfully new drugs in the next years which could generate enough cash return for the industry’s survival?

Current cost of development:

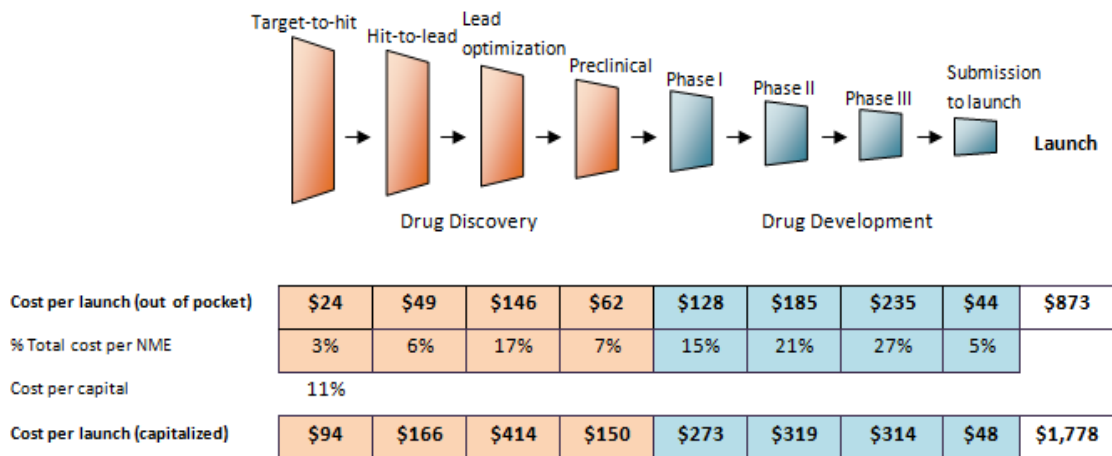


Figure 14 Cost required at each step of the drug development process

While it used to cost less than \$1 billion (\$842m) to launch a drug in 1999, the cost went as high as nearly \$2 billion (\$1,778m) in 2010.¹⁷

The large investment required for the successful development of only one drug influences the decision making about the nature and the characteristic of potential drug selected to be developed. Decision making will be based on criteria considered as reliable to get sufficient return on investment:

- Targeting a large population who would treat by the medicine
- Duration of therapy (chronic versus acute)
- Product with high level of complexity which could justify its high price

According to this, pharmaceutical companies would disregard some indications considered as less relevant for sufficient cash return.

Attrition rate

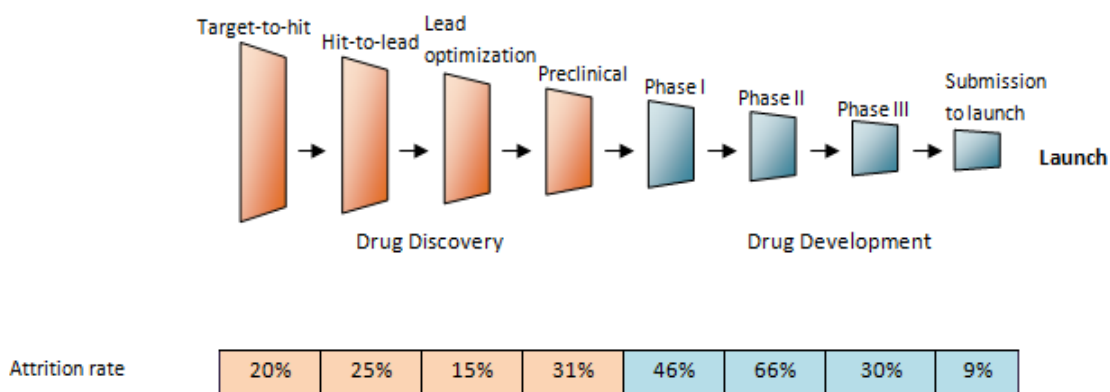


Figure 15 Attrition rate at each step of drug development

The major causes of attrition in the clinic were lack of efficacy (accounting for approximately 30% of failures) and safety (toxicology and clinical safety accounting for a further approximately 30%)¹⁶. The lack of efficacy might be contributing more significantly to therapeutic areas in which animal models of efficacy are notoriously not predictive, such as CNS and oncology, both of which have relatively higher failure rates in Phase II and III trials.

Cycle Time

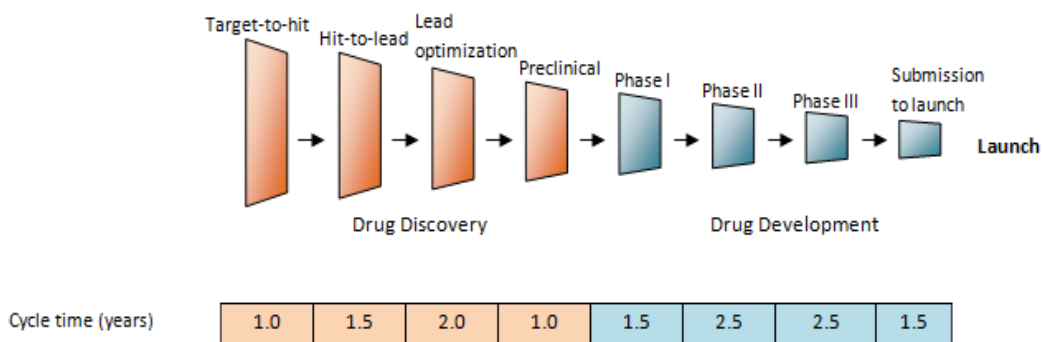


Figure 16 Average time span of every stage of drug development

The average time from synthesis of a self-originated NME to approval of a NDA has increased significantly, from an average 7.9 years in the 1960s to 12.8 years in the 1990s. Much of the increase is due to increases in clinical trial length (the time from filing of an **Investigational New Drug** (IND) application to NDA submission). This can be attributed to a variety of factors, including increased regulatory requirements, the need for more study subjects in clinical trials, an increasing difficulty of recruiting subjects for clinical trials, and the nature of the diseases being investigated. In addition, the average number of

procedures performed on patients has increased by 118% in Phase II and 51% in Phase III clinical trials¹⁸.

1.2.2. CLINICAL TRIALS CONSTRAINTS

As we can see with the model previously described, clinical trials are the critical steps of drug development, due to:

- Highest attrition rates
- Highest costs
- Highest cycle times

These parameters are inherently linked to the characteristics of the clinical trials themselves:

- Sample. To have significant statistical data and be considered reliable, the sample of population must be sufficiently important in term of size. But this will have an impact on the logistic aspect (and fees around it) and the duration of studies (time for inclusion...)
- Multicenter.
- Attrition rate
- Long term safety. With the last decades, the regulatory agencies (and physicians) are more and more concerned about safety profile of the administered drugs. The companies have to include significant long term safety data in their application file which has an impact on the cost and the cycle time of drug development.

1.2.3. APPROVAL

To be competitive, pharmaceutical companies have had to re-think the allocation of resources to:

- Invest sufficiently to maintain performance in term of technologies, knowledge, know-how
- Increase the timeframe of development
- Increase the R&D spending to produce and commercialize successfully one new drug

But, despite those significant efforts, the number of New Molecular Entities (which include NDA & BLA) approved by the competent agencies seems to reach a limit: for a decade, around 30 NME are approved every year in worldwide.

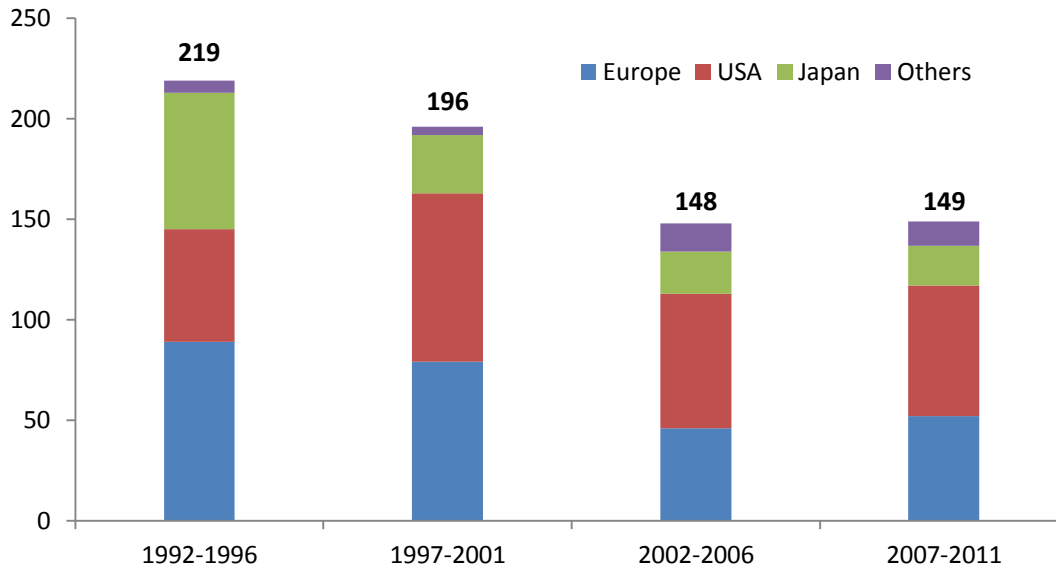


Figure 17 Number of New Chemical or Biological Entities, 1992-2011
- calculations according to nationality of mother company- (EFPIA 2012)

And the decrease seems to be confirmed when the NME approvals granted by the FDA's CDER:

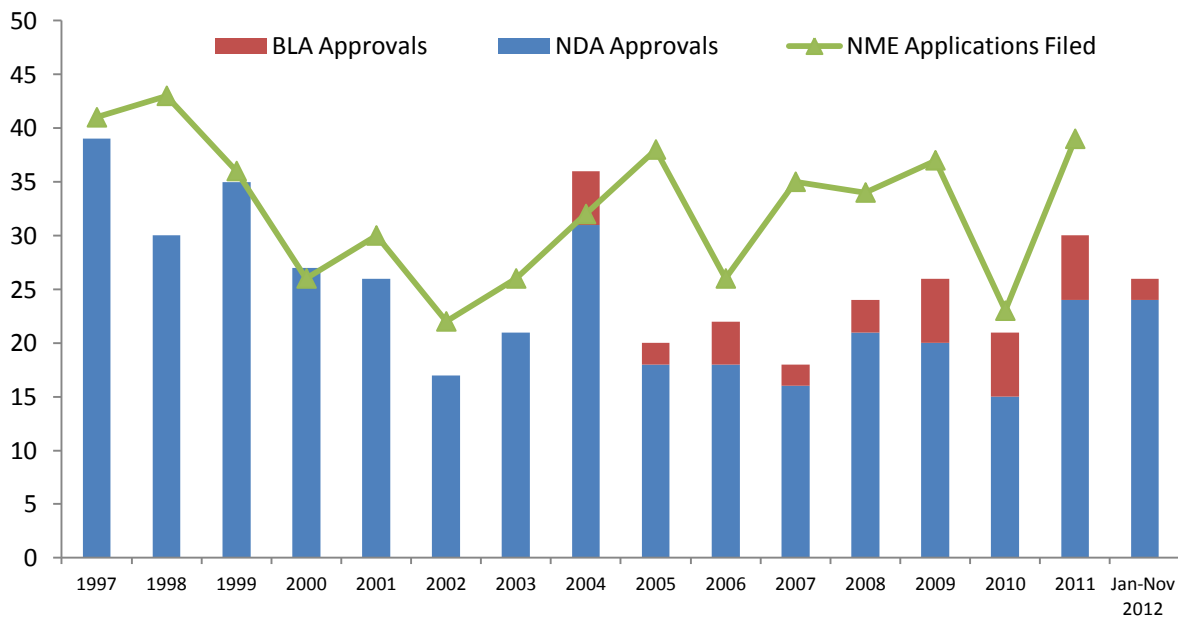


Figure 18 NME Applications Filed and Approved by FDA's Center for Drug Evaluation & Research (1997-2012)^{19, 20}

N.B: NMEs include both New Drug Applications (NDAs) and Biologics License Applications (BLAs).

For the past decade, CDER has approved an average of 23 NMEs per year. This includes applications for both New Drug Applications (NDAs) and Biologics License Applications (BLAs). This situation may be explained by the stable number of applications filed for NMEs⁷.

But this number should be weighted because the term “NME” gathers a large number of various “new drugs”. For example, it integrates the me-too drugs which are rarely a real innovation for taking care patients and their diseases.

In 2012 (from January to November), 26 NMEs have been approved. But only 5 of them have gained a “Priority Review” status. This designation integrates drugs that appear to represent an advance in medical care over available therapy²⁰.

1.2.4. PAYERS PRESSURE

Over the past decade, serious concerns have appeared about the pharmaceutical industry’s integrity and transparency. During these years, this industry has faced accusation and preoccupation about drugs, in particular concerning their safety and efficacy. To illustrate this, the most recent event is Servier®’s case and the misuse of Mediator®. These troubles have altered the industry’s image and its reliability, resulting in increased regulatory pressure.

Furthermore, in addition to the pressure to reacquire the confidence of payers and patients, pharmaceutical companies have now to face economic issues.

For several years, governments have tried to find solutions to decrease health expenditures and limit budget healthcare deficits. Political pressure has increased during the recent economic and health crisis. This pressure focuses on:

- Limitations price and reimbursement
- Requirement of more safety data
- Promote further health cost savings

Because of these, a new drug may improve its probability of success to get approval if:

- It targets new therapeutic areas

- It induce significant cost and/or benefits over existing treatments

One of the strategies proposed by pharmaceutical industry is to change their drug portfolio from primary care driven blockbusters (painkillers, anxiolytics, hypolipemia drugs...) towards specialties such as oncology, immunology and inflammation, where the medical need is so high that prices are more easily accepted by regulators.

But it is a short-term solution due to the arrival of competition which will offer arguments to payer for limiting price of new medicines.

1.2.5. GENERICS AND BIOSIMILARS

With a growing need for countries to limit expenses, the generic penetration is as strong as ever (generic penetration including generic drugs and biosimilars)²¹:

- In Germany and the UK, the generics represents more than 60% of the global pharmaceutical market²²
- In France, the generics in the reimbursable drug market will exceed 24% of market share²³
- In the USA, the generic market approaches 70% of all prescriptions written¹⁶
- In China, generic drugs represent 63% of the pharmaceutical market²⁴.

Moreover, with the key patent expirations between 2010–2014 (i.e. Lipitor® or Zyprexa®), a diminishment of sales revenues estimated to \$113 billion would be noticed following the generic substitution. Indeed, for every dollar lost in declining product revenues due to patent expirations by 2012, it has been estimated that large-cap pharmaceutical companies will only be able to replace on average 26% with new product revenues¹⁶.

Generics

Through incentive policies (e.g. "Hatch-Waxman Act "or" Drug Price Competition and Patent Term Restoration Act" in 1984 which has authorized generic manufacturers to use the data of originator drugs), generics have become an inalienable component in the environment of the prescription medicines.

These are some parameters that characterize the generics market:

- Price of a generic may be around 60% less than that of the original brand just after the loss of patent protection. After one year, when several generic copies have been marketed, the average price may have decrease to less than 20% of the original²¹.
- Governments measures fostering the use of generics towards²⁸:
 - Generic manufacturers (pressure to introduce generics and fast generic approval)
 - Physicians which have recommendation to use active ingredient formularies and prescription ceilings
 - Pharmacists with substitution rights and financial incentives to increase generics' sales in their business.
 - Patients (increased copayment, generic campaign)
- Adequate Market Size. Because the main interest of generics is the reduction of costs inversely proportional to volume, the size of the market is an important consideration. For example, a common and chronic condition that requires long-term treatment implies a sustainable and large-scale demand for appropriate products.
- Categories of drugs. The generics target more often drugs that are prescribed mainly by family doctors than those prescribed by specialists. Two main factors may explain this selection:
 - Specialists are often the first prescribers of newly developed drugs. Thus, awareness of generics is relatively low among these physicians.
 - The cost of generics is low. Primary care doctors tend to be more aware of medicine costs than the specialist community. The pressure to monitor the health costs under control is more intense for primary healthcare.

For few years, a new type of generic product has been commercialized: the biosimilar drugs. But these new products differ significantly from classic generics in term of development (cost and timeframe) and regulatory requirements.

Biosimilar particularities

Biosimilars are copies of biologic drugs. They are also known as biogenerics and follow-on biologics. Unlike a conventional generic, which is an identical copy of the original molecule, a biosimilar is an approximation.

In the follow-on biologics market, the first drug has been approved only in 2006²¹. Even today, there are still only few categories of drugs in which biosimilars have been approved (EPO, G-CSF, hGH).

In 2011, the total biosimilar product sales will amount to \$250 million (half at least in the U.S.) which corresponds roughly to only on thousandth of the total generic market estimated to \$225 billion²¹. Beyond 2016, biosimilars of expensive biologics should be commercialized, which would significantly increase these estimates.

The low development of biosimilars can be explained by many challenges that generic companies have to deal with:

- Ability to develop a follow-on version. Because biologic drugs are more complex than the traditional chemical medicines, it requires more competencies. It is complex both to isolate and characterize the various components of the originator drug and to be able to reproduce one.
- Processing a biologic molecule. Because almost all generic companies came from the chemistry industry, they have to make significant investments to change their infrastructures to be able to receive a biosimilar product in their production line. But organizing successfully a production channel and manufacturing biologics require skills and know-how dramatically different from generic products.
- Regulatory hurdles for the introduction of biosimilar:
 - o Requirements to get biosimilar's approval are stronger than those for generic compound (addition of toxicology, non-clinical and clinical studies)
 - o In US, a very long period without of a well-defined statutory framework for obtaining regulatory approval until recently (in February 2012, publication of three guidance documents to assist industry in developing biosimilar products²⁶)

- In the EU, the procedures for the authorization of biosimilar are burdensome with a specially adapted guidance for each subtype of biological medicines.
- Significant investment for the development and manufacturing a biosimilar drug but also after regulatory approval:
 - Investment to pursue clinical studies. Even if a biological copy is approved as biosimilar of a reference product with multiple indications, its efficacy & safety must be justified (or demonstrated) separately for each of the submitted indications.
 - Because the weak awareness of biosimilar substitution compared to generics, manufacturers of follow-on biologics will need to carry out their own marketing campaigns, at least in the early years.
- Aggressive defensive strategies by originator companies to limit the entry of biosimilar into the market (for example, introduction of incrementally improved brand drugs).

To face to this competition, pharmaceutical companies can use some tactics

- Increase the timeframe of protection thanks to the strategic management of patents.
- Focus towards the development of new biologic drug due to the difficulty to produce them, and the lack of consensus of biosimilar products among regulatory authorities, physicians and payers²⁷.

Nevertheless, for the prescription medicines, these tactics merely delay the loss of their major revenue when the period of protection expires.

CHAPTER II – THE PRODUCT LIFE CYCLE MANAGEMENT, CONCEPT AND STRATEGIES

During the development and marketing of a new product, marketers must analyze the external and internal influences, positive and negative, in order to maximize the risk of success and make the most profit with the product and consumption of product.

One of the solutions to meet expected *Return on Investment* (ROI) is to manage these risks and opportunities through the life cycle of a compound or the Product Life Cycle.

2.1. PRODUCT LIFE CYCLE

No matter what type of industry, product lines and brands need to be managed over time. A useful tool for conceptualizing the changes that make take place during the time that a product is on the market is called the “*Product Life Cycle*” (PLC). It has been in use for many years to analyze the rise and fall of product demand. The typical model of a PLC starts with the development of a new product before its introduction to the market, followed by rapid growth. The product “enters” then in the maturity stage when sales growth reaches a plateau and finally decline when replacement products have been successfully introduced.

2.1.1. ORIGIN & DESCRIPTION

The PLC is studied and detailed in many studies for decades (Day 1981, Andersen 1984, Nelson 1992). In its simplest figure, the PLC explains the evolution of a product according to its sale over its life cycle.

It is usually acknowledged that the PLC describes product classes or product forms, though it has been suggested to apply this PLC theory to product brand.²⁸

The PLC underlines the idea that “companies have to face the fact that products need to be terminated and new products developed to replace them” (Drogamatzis, 2002).

Figure 19 illustrates the scope of product life cycle applications.

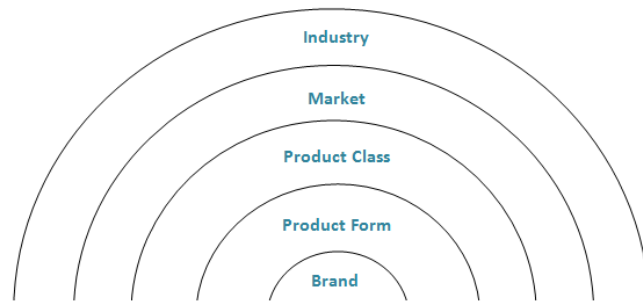


Figure 19 Scope of Product Life cycle Theory

PLC theory states that all types of product pass through similar stages identified as “Development or Introduction”, “Growth”, “Maturity” and “Decline”. The life cycle of an individual product is the combination of these stages. All of them are characterized by their duration, sales and profit level.

Figure 20 illustrates the typical product life cycle and its stages:

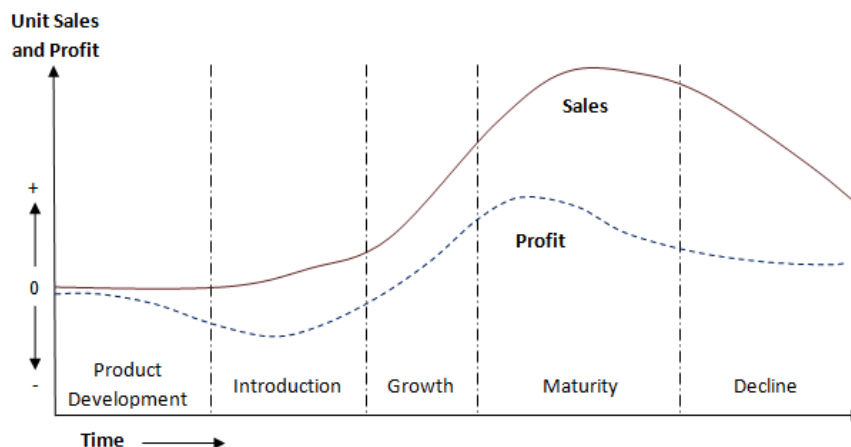


Figure 20 Typical Product Life Cycle

The PLC had its birth in marketing mix theory (Nelson 1992). The analysis made by specialists few decades ago suggests that a product’s life cycle is expected to be an evolutionary^{28,29}. This evolution is heavily influenced by changes in the product’s environment which is either internal (cost, manufacturing and distribution) or external (competitors, consumers and technology).

The following table describes the characteristics of every stage of a new product in a new market³³.

Development	Introduction	Growth	Mature	Decline
<ul style="list-style-type: none"> • Very high level of investment • Negative profitability period • Assessment and planning of marketing strategy • Optimization of product differentiation (technical and marketing differentiation) and positioning 	<ul style="list-style-type: none"> • High level of cost • slow sales volumes to start • no or little competition in the market segment targeted by the product • demand has to be “revealed” • “push” customers have to try the product • no money return at this stage • monitoring the speed of product adoption and may terminate them if disappointing 	<ul style="list-style-type: none"> • Costs reduced due to expansion • Faster sales and profit growth • Profitability begins to increase • Public awareness increases • Competition begins to increase with a few new players in establishing market • Price decreases (due to increase of competition) 	<ul style="list-style-type: none"> • Reduction of costs led by the increase of volumes and the implementation of process • sales volume peaks and market saturation is reached • increase in competitors entering the market • prices tend to drop due to the proliferation of competing products • maintain or increase market share by employing strategies: product improvements, advertising and sales promotional offers, dealer discount, price cutting, brand differentiation and feature diversification • restriction on profit margin particularly for follower brands • Industrial profits go down 	<ul style="list-style-type: none"> • Costs become counter-optimal • Sales volume decline • Prices, profitability diminish • Profit becomes more a challenge of production/ distribution efficiency than increased sales

Table 2 Stage Characteristics of a new product in a new market

2.1.2. THE TECHNOLOGICAL LIFE CYCLE

But the previous model may be too restrictive because it includes only the life cycle associated to the marketing actions: it highlights the resources, the efforts allocated during the PLC, from its elaboration until the decline phase.

In the **Technological Life Cycle** (TLC), differences are emphasized development and production technologies for industrial products. TLC is defined by stages characterized by the kind of technological resources required to create products²⁸. This model introduces the engineering efforts in the marketing model of PLC and highlights

Figure 21 illustrates these TLC stages:

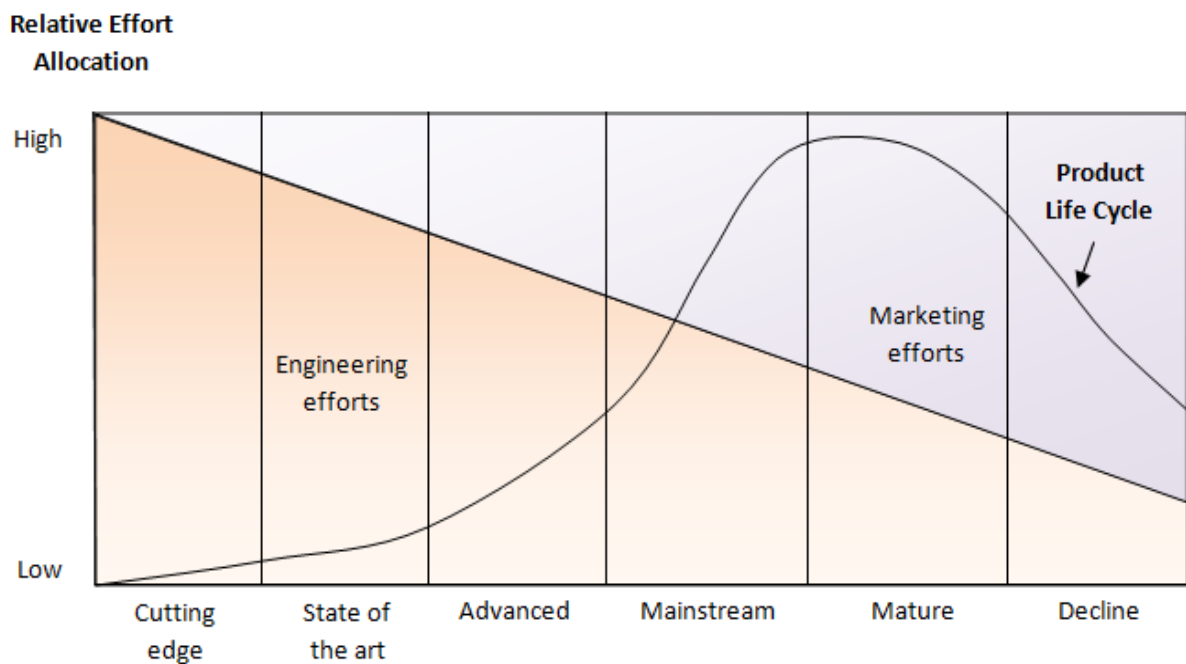


Figure 21 Typical Technological Life Cycle

- Cutting-edge technology generates new inventions that may become commercially viable.
- State-of-the-art technology is required to facilitate the transition of new inventions to production.

- The advanced stage of technology involves more producers and extensive marketing while mainstream technology describes production standardization by competitors.

High technology firms decide whether they have the production and marketing skills required to move a technological product through the TLC stages. If not, they have to determine at what stage it is advantageous to focus their particular resources. To perceive and apprehend these differences can enable companies to anticipate the technological evolution and react with appropriate strategies.

The product life cycle: a more complex model

The product life cycle does not end with its withdrawal.

When the PLC has been analyzed by economists decades ago, the authors highlighted the five stages of the life cycle explained previously:

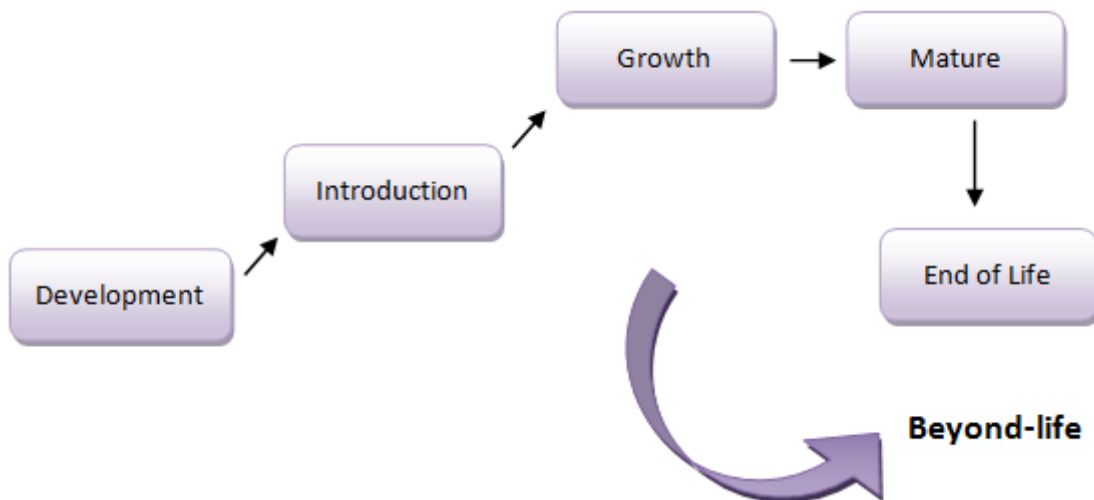


Figure 22 All phases of the product life cycle and beyond life cycle

But today the firms include the management of the beyond life of product in the modeling of its PLC when it is in development. They consider that the impact of the compound on the market does not stop at the end of the decline phase, when the last unit is sold. This integrates both tangible and intangible consequences.

- The tangible impact. It may include sustainable development³⁰, management of wastes from the manufacture of this product (recycling of the product

components, infrastructures and people involved in its production, distribution channels ...).

- The intangible impact. The firms now include into their business model the possible consequences of product on the population. For example, the case of thalidomide: molecule initially prescribed for pregnant women, the clinical consequences of his administration is still having an impact on generations descended to these women.

The product is managed in a portfolio.

In the previous part we have treated products as separate, distinct and independent entities. However brands or products are not often developed and commercialized in isolation. Many companies are multi-product, serving multiple markets and segments and commercialized in various geographical regions. These products are normally included within a product line³³ (group of brands/products closely related in term of functions and benefits they provide) and product mix (sum of the product line offered, it is the total set of products marketed in a company).

Some of these products will be strong, others weak. Some will require investment to finance their growth, others will generate more cash than they need.

Because the resources are limited, companies shall decide how to allocate them among the various needs of products so as to achieve the best performance for the company as a whole. In particularly within a product line, management decides which products to invest in or hold, or from which to withdraw support. The initiatives must be undertaken to manage balance between market segments, short and long-term or new and old products.

The process of managing groups of brand and product lines is called portfolio management.

Product Portfolio management

A product portfolio is all marketed products and all products currently in R&D that a company manages on a global scale. To be more specific, it includes all marketed product

lines, brands and all those compounds currently in R&D and in every national market in which the company is operational.

The portfolio management goals are gathered into three parts (Drogamatzis, 2002):

- Value maximization (market value, long-term profitability, ROI)
- Strategic fit (market segments, regions, competencies, resources...)
- Balance (long versus short-term, R&D versus marketing, long-term versus short-term market segments...)

The portfolio is in constant change because the parameters of value maximization, strategic fit, and balance may be influenced by environmental factors and incoming portfolio ideas.

Multiple variables appear during the overall Product Life Cycle: variables of R&D, production, efficiency...These variables have to be managed according to the strategic goals identified by the managers (sales/profit, return of investment, disinvestment, penetration, diversification, development...) and the position of their product on its life cycle (growth, maturity...)

2.1.3. THE PRODUCT LIFE CYCLE MANAGEMENT

In the industry, the Product Lifecycle Management is defined as a process of managing the entire lifecycle of a product from its conception, through design and manufacture, until the product's entry to the market and its life through it³⁵.

The Product Life Cycle Management integrates people, data, processes and business systems and provides a product information backbone for companies and their extended enterprise. The PLCM tools and systems assist organizations to face with the increasing complexity and engineering challenges of developing new products for the global markets.

In reality, two types of Product lifecycle management concepts should be distinguished:

1. The product life cycle management applied in the firm itself. It describes the engineering aspect of a product, from managing descriptions and properties of a product through its development and useful life.
2. The **product life cycle management** (or PLCM) refers in our case to the commercial management of life of a product in the market with respect to costs and sales measures.

2.1.4. THE PLCM IN MARKETING

Product life-cycle management (or PLCM) is the succession of strategies set up by business management as a product goes through its life-cycle. The condition in which a product is sold (advertising, competition) changes over time and must be managed as it moves through its succession of stages.

The goals of PLCM are to reduce time to market, improve product quality, reduce prototyping costs, identify potential sales opportunities and revenue contributions, and reduce environmental impacts at end-of-life³³.

PLCM makes the following three assumptions³³:

- Products have a limited life.
- Product sales pass through distinct stages, each posing different challenges, opportunities, and problems to the seller.
- Products require different marketing, financing, manufacturing, purchasing, and human resource strategies in each life cycle stage.

2.2. STRATEGIES OF THE PLCM

Research in marketing as well as in strategic management indicates that the “PLC is likely a fundamental variable affecting business strategy” (Day, 1981).

C. Hofer developed the most extensive theoretical profile of the PLC as it affects business strategy. Two propositions suggested by Hofer are of particular interest:

1. “the most fundamental variable in determining an appropriate business strategy is the stage of the product life cycle” (Hofer, 1975)
2. Major changes in business strategy are usually required during three stage of the life cycle: introduction, maturity, and decline.

C Anderson ³¹ describes the different strategies goals used to succeed and optimize the life cycle of the product at each stage:

- **Introduction stage:** tactics for the introduction stage emphasize a buyer focus, building on advertising, and increasing purchase frequency.
- **Growth stage:** in this stage, there is a focus toward strategic segmentation and building efficiencies in production and marketing. Performance of the product (as a response to its customer needs) is crucial, and product modification may be necessary. The investment and expenses associated with these strategies may be prejudicial to short term profits. Intense distribution is also emphasized.
- **Maturity stage:** high performance strategies for the maturity stage are more complex than for the previous two stages because of the larger number of research studies and variables. Basically, they center on improving efficiency in process, reducing overall costs in marketing and distribution, further differentiation of products, and further market segmentation.
- **Decline stage:** strategy depends on industry traits (e.g., the certainty with which demand will decline), whether some segments will have enduring demand, whether barriers impede exit of firms, and the nature of competition. The other variable, competitive strength includes average returns compared to competitors, relationship with customers, and vertical relationship. Depending on the mix of these factors, strategies ranged from an immediate exit to increasing investment in the declining business.

Whereas researchers have concluded that strategy plan should vary for each stage of the PLC, Andersen³¹ highlights an alternate possibility: the strategic variables may be the same for each stage of the PLC, but their management (or “direction”) would change based on the performance objective. For example, inventory levels would be raised when

increased market share is the objective, and they would be reduced if high ROI is the goal. According to the analysis of study³¹, research that confirmed the “different direction” hypothesis would be of great interest to strategic decision makers: it would limit the number of strategic variables that they would need to consider during strategy formulation.

To measure the impact of strategies on the life cycle, two strategic performance variables are usually used: ROI and market share (MS). Only one or both of them can be selected by the firm to analyze the performance of the product through its life cycle and influence the current and long term strategies.

Strategies measured and leaded by the MS³⁴

2 market criteria are taken in consideration (plus a third dimension to make a complete diagnosis):

1. Stage in the product life cycle (good indication of the trend in primary demand as well as the basic competitive patterns –numbers of competitors varies over time)
2. The position of a given firm in the market (small, dominant...)
3. Strategic goal alternatives of the firm (increase, maintain or reduce its competitive position)

By combining these three dimensions into a same table, the company can identify the resources necessary to succeed their strategy at an identified stage and the expected return for each of them.

Strategic Alternatives	Product Life Cycle: Market Share Position of the Firm																	
	Introduction						Maturity						Decline					
	Small		Average		Dominant		Small		Average		Dominant		Small		Average		Dominant	
Increase	I++	1	I++	0	I+++	-1	I++	-1	I+++	-2	I++++	-3	I+	-3	I++	-5	I++	-6
	E+++		E++		E++		E+		E+				E--		E--		E----	
Maintaining Position	I	0	I+	0	I++	0	I	0	I	3	I	4	I+	-2	I	1	I-	3
	E		E+		E++		E		E+++		E++++		E-		E+		E++	
Disinvest-ment	I	0	I-	1	I-	0	I-	2	I---	6	I	8	I-	1	I-	4	I-	5
	E		E		E		E		E+++		E++++		E		E++		E++	

I = Amount of investment required

E = Expected cash return

Numbers indicate the overall financial value for the cell (E-I)

Table 3 Diagnosis to optimize strategies through Product Life Cycle³⁴

Thanks to the previous analysis, organized in the above table, the study has highlighted the “ideal” strategic pathway to maximize the expected cash return.

Strategic Alternatives	Product Life Cycle: Market Share Position of the Firm								
	Introduction			Maturity			Decline		
	Small	Average	Dominant	Small	Average	Dominant	Small	Average	Dominant
Increase	1	0	-1	-1	-2	-3	-3	-5	-6
Maintaining Position	0	0	0	0	3	4	-2	1	3
Disinvestment	0	1	0	2	6	8	1	4	5

■ Indicate cells providing a good cash return
■ Indicate cells with a very poor profit level
 Numbers indicate the overall financial value for the cell
 → Arrows indicate the best marketing strategies as a function of the product life cycle

Table 4 optimized pathway through the product life cycle³⁴

This table is also useful in assessing the long-term viability of firm’s product line. A firm that has most of its products in the bottom left of the table is in a poor competitive position.

The time span of each lifecycle phase can be controlled, to a certain extent. This control is particularly vital of the maturity phase: this is the most important one to extend from a financial point of view because this is the period when the product is at its most profitable.

2.3. TACTICS APPLIED TO IMPROVE THE PLC

Many tactics are used to achieve strategic goals. They are set up at different times during the life cycle of product. They have two main objectives:

- Participate and improve drug’s differentiation.
- Increase and extend the S-curve (profits / sales) of the product life cycle

Because the product life cycle is closely linked to its differentiation, the actions to improve and maintain both of them are identical.

More generally, these tactics can be classified in few categories:

- New uses

- Further development of product
- Reduction of prices
- Brand's loyalty

Even if all of these tactics are usually set up during the mature stage, they can also be applied at whatever stage of the life cycle.

2.3.1. NEW USES

This tactic is applied to products already commercialized, usually during the mature phase of the product life cycle.

When the tactic "new uses" is a success, the consequences on the S-curves of unit sales and profit are bi-dimensional:

- It prolongs the period of mature stage and thus, extends the term of the end-of-life of the compound.
- It increases the volume of unit sales (and consequently the profit) by increasing enlarge the size of the population of customers potentially interested.

2.3.2. FURTHER DEVELOPMENT OF PRODUCT

While a product goes through its different marketed phases of its life cycle, some modifications about its conception are set up: improvement of quality, use, change of design... Thanks to this tactic, marketers expect to:

- Extend the patent protection
- Keep interest of customers (curiosity about novelty and innovation)
- Maintain or improve competitiveness thanks to technological advance

2.3.3. PRICE REDUCTION

After a certain period of time following marketing, the price of a product is usually reduced compared to its introduction price:

- Thanks to an optimizing of manufacturing process, the production costs are reduced
- Thanks to the premium price of the new compound during its first period of commercialization, the development costs have been “reimbursed”

With this price reduction, the product may maintain its attractiveness and face the competition. But there is specific tactics of price used by marketers: the promotional pricing (price reduction of a product or service to attract customers).

2.3.4. BRAND LOYALTY

The brand identity is the “promise” that a company makes to consumers. It should reflect benefits, performance, services and the value that the brand possesses³⁷.

The brand life cycle (BLC) is divided into four steps which might repeat endlessly:³⁸

- Development: creation of a brand
- Recognition: introduction of brand to increase visibility and finally gain recognition
- Loyalty: customers become loyal to a brand and not only one product (or product line)
- Sustainability/maintenance: pursue actions for brand awareness and brand loyalty

The BLC may have a significant influence on the PLC.

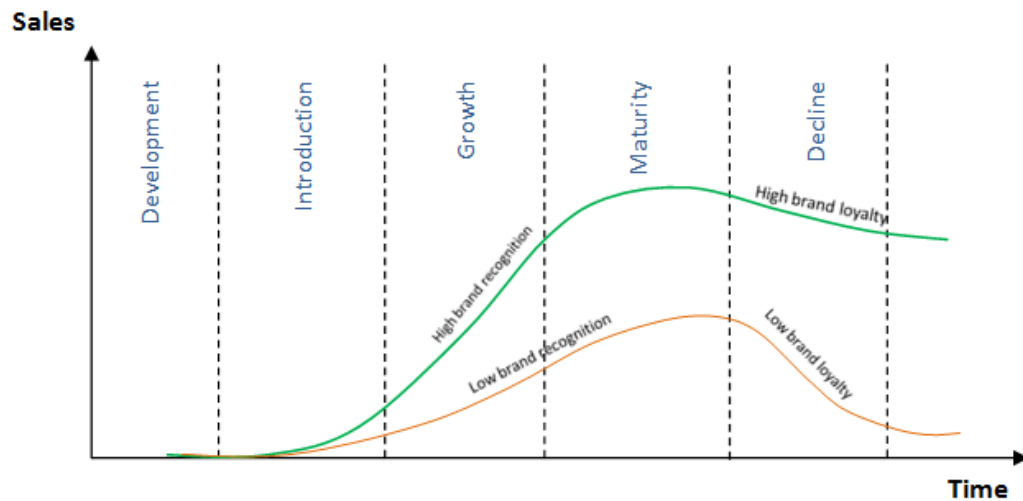


Figure 23 Brand Life Cycle

The impact of brand life cycle may be the most significant during introduction/growth stages and the decline phase:

- Brand recognition increases the product adoption
- Brand loyalty may slow the product decline

2.4. LIMITATIONS OF THE MODEL

Several criticisms³³ are associated to the use of the PLC concept:

- The difficulty to positioning a product on its life cycle and the unpredictability of the duration of each stage with accuracy.
- It may be wrong to consider that all products follow the classic S-curve of life cycle
- It could be the marketing management which influences the evolution of PLC and not the other way round. For example, a marketer may decide that a product is approaching its decline stage and so stop actively marketing actions which will inevitably trigger the decline of its sales (decline which might not have happened if the product was still considered in its maturity phase).

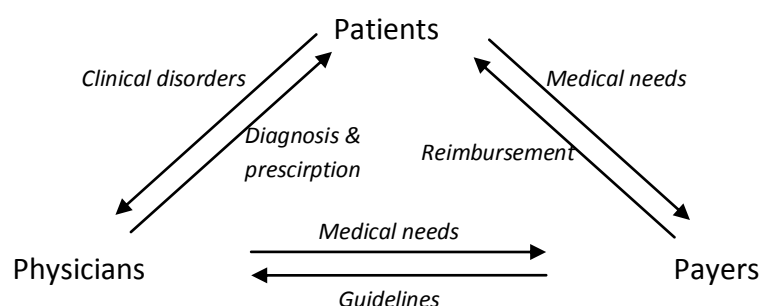
Because of these limitations, strict adherence to PLC can lead a company to misleading objectives and strategy prescriptions.

CHAPTER III – THE PLCM CONCEPT APPLIED IN THE PHARMACEUTICAL AREA: SIMILARITY AND SPECIFICITIES

3.1. A DRUG, A PARTICULAR PRODUCT

3.1.1. A NON TYPICAL RELATIONSHIP : DRUG VERSUS PATIENTS

Drug may be considered as an atypical product because consumers and buyers are different. Patients are the population targeted by the product: they are the consumers of drugs but, usually, they do not choose them and do not pay them (particularly for the prescribed drugs). The “consumer” is constituted of three parts: the physicians which are decision makers, national healthcare structures which are the buyer and finally the patients which are the consumers. Each part influences the 2 others:



When a drug is developed and marketed, the pharmaceutical company should consider each part to bring successfully the new drug to the market.

3.1.2. A DRUG, A MONITORED PRODUCT

A new medicine cannot be “freely” created and marketed. Monitoring and regulatory requirements are set up at the beginning of drug development (particularly during clinical phases) and pursued through the commercialization:

- Required authorization to undertake non-clinical and clinical studies
- Required accreditation for factory producing of active ingredients and medicines,

- Price and reimbursement negotiation with competent national authorities
- Pharmaceutical monopoly
- Monitored advertising:
 - o Limited (and even prohibited in some cases) for patients and customers.
 - o Controlled when it addresses to healthcare professionals
- ...

These particularities of the pharmaceutical industry do not have an influence on the model of drug life cycle. Nevertheless they may have a significant impact on the strategic tactics to perform and maintain the S-curve of life cycle.

3.2. THE LIFE CYCLE OF A NEW BRAND DRUG

In this work, a new drug corresponds to a new product that has never been marketed and is now approved by the competent health agency to be administered to patients and customers. Its development and commercialization steps follow the same model of the Product Life Cycle: Development, Introduction, Growth, Maturity and Decline.

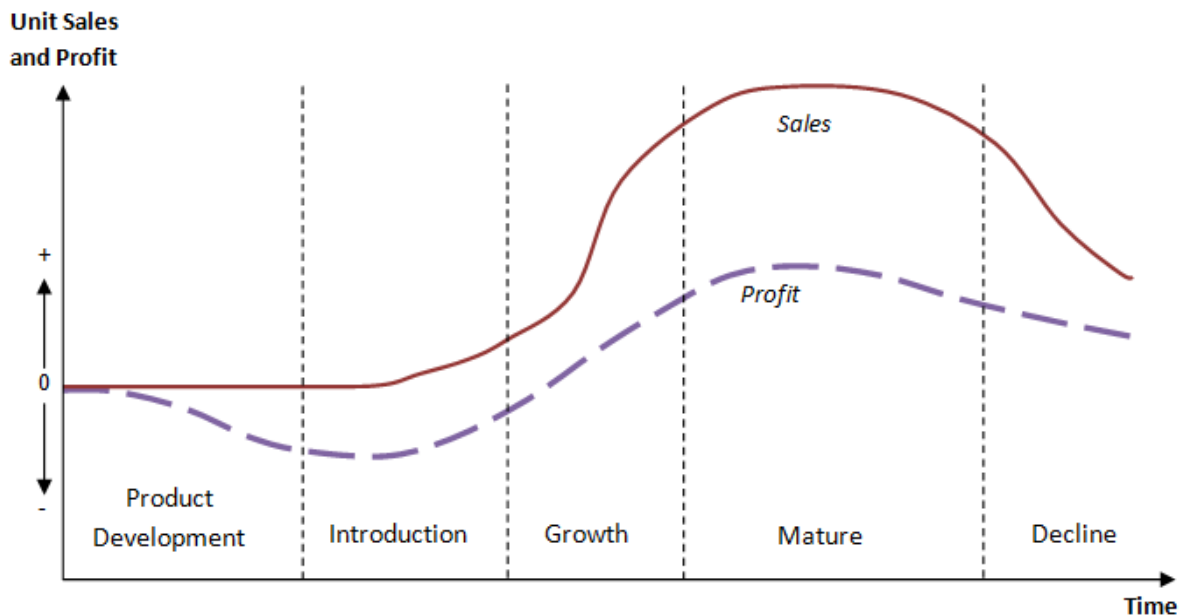


Figure 24 Sales & Profit through Product's Life Cycle Stages

Development

This is a long and risky period of resource-intensive activities and no product sales, thus a prolonged negative profitability period.

During this stage, the marketing actions start to be thought and placed: it is the premarketing. In general, premarketing is initiated at least two years before the drug launch²⁵, or at the beginning of Phase III of clinical research. The activities needed for premarketing require significant human, material and financial resources.

Reasoning	Methodology	Strategy	Key Activities	Internal Activities
Faster market penetration	Create a demand	Positioning	Market research	Forecasting
Higher market shares	Develop a user pool	Targeting	Clinical trials	Manufacturing
High long-term profits	Build company image	Profiling	Congresses	Logistics
	Build awareness	Promotion	Publications	Product management
		Formulation	Develop Ols	Medical marketing
		Packaging	Advisory Board	Sales forces
		Pricing	Develop global campaign	Regulatory support
		Comarketing	Branding	PR
		budgeting	Training	
			Public relations	
			Advertorials mailings	

Table 5 the Case for Premarketing²⁵

Introduction Phase

The manufacturer tries to gain product acceptance from the prescribers or patients. The overall marketing strategy at this stage is to attract the key opinion leaders (KOLs) of the therapeutic area targeted by the new drug. These KOLs are essential to communicate the product's characteristics and its benefits to the other specialists. This tactic is based on the pyramid of influence cascade.

The product is offered only in a limited number of dosage strengths and formulations, while the prices are often high and stable.

During this phase the industry's marketers' main information need is market data that helps them to define the product's optimal targeting, positioning and profiling.

The main goal of marketers during this stage is to increase consumer awareness. In order to reach this objective, the following activities can be implemented: ²⁵

- Offer clinical trial experience
- Include physicians and patients in long-term treatments
- Develop opinion leaders
- Develop media spokespersons (such as successful patient testimonials);
- Sampling or couponing,
- Risk reduction
- Adapt promotion and marketing channels

Growth Phase

In the growth (or expansion) phase, product sales revenues are moderate but rapidly growing and its profitability is increasing, while more competitors are entering the stage. The marketer's main objectives are to expand the distribution breadth and product line by offering new product benefits and forms. Furthermore, the increasing competitive industry is driving product prices down. As far as the product promotion is concerned, the messages tend to be more persuasive and sometimes comparative to competition's (where comparative pharmaceutical advertising is permitted). The sales force is expanding, reaching more and more patients, often shifting its priority from the medical specialists at the beginning to the large number of family physicians or general practitioners.

At the peak of the growth phase, some marketing scholars have proposed the existence of a separate phase called the turbulence phase²⁵. This period is when product sales plateau and signifies the imminent entrance into the maturity phase. Some of the characteristics of the turbulence phase are:

- The slowing of the sales growth,
- Fewer competitors than before, and
- A stabilizing distribution base.

Maturity Phase

At some point in a product's life cycle every product reaches maturity. As it was described previously, this phase is characterized by a stabilized sales performance, with low costs and high profits. At this stage, marketers are occupied with maintaining the product's advantages, often fighting competitive new product launches with new features and benefits usually thanks to several additional clinical studies. A full product line is now available, offering a wide spectrum of product dosages, administration route possibilities, and formulations. Both price and distribution are stable at this step.

Decline Phase

Eventually, the product enters its decline phase, with decreasing sales, rising fixed costs, and an eroding profitability. Now, pharmaceutical marketers are faced with the dilemma of further "harvesting" the product²⁵. It corresponds to a dilemma between prolonging its sales as long as possible or terminating the product and introducing replacement. The product's advertising becomes a reminder and sales force time and effort are reduced.

For the prescription medicines successfully implemented in the therapeutic arsenal, the entry into the decline phase is usually triggered by the marketing of generics (or biosimilars) following the end of market exclusivity of the originator drugs

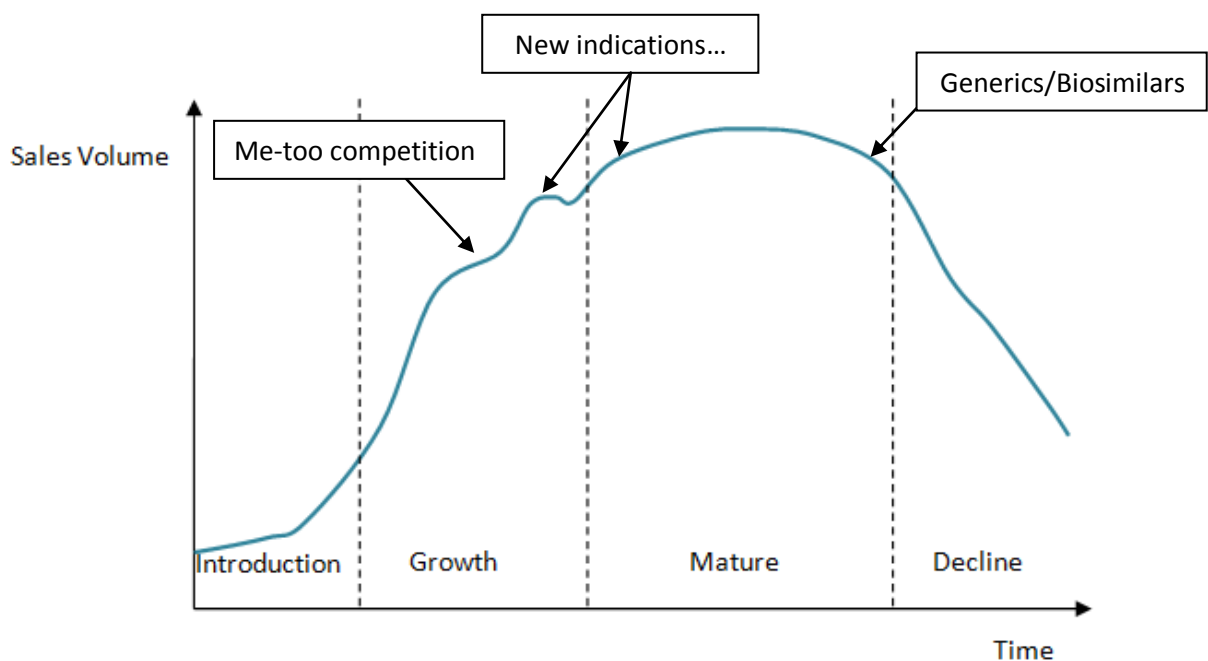


Figure 25 Elements which influence prescribed drug's life cycle

During all stages of prescribed brand drugs, companies used various tactics to improve and sustain its life cycle, as new indications:

- New indications
- New dosages/new formulation
- Switch **Over-The-Counter** (OTC)...

But they have to deal with external elements which have also a negative impact on the growth and sustainability of product's sales and market share:

- The me-too drugs
- The generics and biosimilars

The limitations of the new drug's expansion

❖ Me-too competition

The "me-too" drugs (or follow-on drugs) are described as new chemical entities which have similar characteristics compared to already commercialized patented drugs about chemical structure and mode of action. They aimed to treat the same disorders as existing medicines. Usually, to get approval, they have to provide minor, although possible important advances (therapeutic, frequency of administration...)

This competition can appear at any stage of life cycle and early triggers the end of life of a product.

❖ Entry of generic and biosimilar drugs

The consequences of the entry of generics and biosimilars are not the same according to the category of medicines: it concerns mainly the prescriptions drugs.

For them, generics (and biosimilars) are systematic competitors and usually they initiate the entry of the originator medicine into its decline phase.

3.3. PLCM TACTICS USED TO IMPROVE LIFE CYCLE OF NEW BRAND MEDICINES

Very often a successful life cycle needs to be prolonged either in order to maintain a significant revenue for the organization or because the existing product pipeline does not guarantee a promising blockbuster in the near future²⁵.

To be as efficient as possible, all tactics used in the PLCM, they have to be thought and initiated as soon as possible in the life cycle (ideally, assessed in premarketing and started at the end of clinical development or, at the latest, at the beginning of the launch phase). The earlier these tactics are set up, the more the maximum of the return on investment will be.

The tactics used in the industrial field may be also applied in the pharmaceutical sector:

- New indications
- Continual improvement of product
- Evolution of price
- Brand's loyalty

Nevertheless, in this sector, some of them have less influence on the sales performance. Moreover, there are tactics specific of the pharmaceutical market.

- Switch to ***Over-The-Counter drugs*** (OTC drugs)
- Therapy combination

3.3.1. NEW INDICATIONS

By getting the authorization to prescribe the new brand drug in other indications, the marketers are expects several benefits:

- In term of cash. Thanks to this tactic, the number of patients should be raised and thus potentially increasing the sales volume and profits.
- In term of reliability. Thanks to the clinical studies to get the new application, the marketing can provide more clinical data (efficacy and safety data) to comfort decision makers for prescription of this drug.

They are two possible orientations in the characteristics of the additional indications as to the first indication. These orientations can be combined into a unique new indication:

- The indication is in the same therapeutic area as the pivotal study. The main interest of this strategic orientation is to spend resources, granted to the development of study and introduction of the new indication in the market, more efficiently. The substantial investments in clinical development are still needed, but in this case, the investments necessary for marketing actions are greatly reduced since the protagonists and means involved in the training and promotion of the product are the same as the first indication (same Key Opinion Leaders -KOLs, same sales reports...).

The new therapeutic indication is sufficiently distinct from the primary indication and has a medical benefit to incorporate the therapeutic arsenal. According to the European Directive (Directive 2001/83/EC), its application has to be assessed by the competent authority which determines whether this new indication brings a significant clinical benefit in comparison with existing therapies. If health authorities consider this distinction significant, it may cause an extension of the protection period. This extension can reach one year. The advantage of this approach is not simply to increase period of product exclusivity on the market (this period extension usually corresponds to approximately only one tenth of the total duration of the marketing protection) but mainly to maximize period during which the profits are more substantial.

To illustrate this tactic, Plavix® case will be studied (case more detailed in the following part of this work). In the US, Plavix® sales reached a peak of 4\$B/year. Thanks to the completion of pediatric study, the product obtained an extension of exclusivity period of only 6 months. As a result, a benefit of \$ 2 billion had been made.

Pediatric form

The majority of the pediatric indication is never investigated by the pharmaceutical industries as first indication for various reasons: safety/tolerability, financial and ethical constraints. But health agencies have established some incentives to encourage pharmaceutical industry to invest into a clinical study of pediatric form of the drug.

The resulting benefits correspond to an extension of the period of marketing protection up to one year (whatever the results of the study showed or not significant efficacy to treat children with the drug).

This tactic may have a positive impact in terms of benefits for the pharmaceutical company and its product. But this tactic poses also a risk for the sustainability of the product and may lead to a premature end of its life cycle. During the clinical studies necessary to get new indications, they may highlight some side effects and clinical risks for the patient which did not have been revealed during the pivotal study. In addition to stop the development of this new indication, these outcomes will then impact the benefit/risk balance of the drug in its main indication, and may also induces a reevaluation of the authorization by the health authorities.

3.3.2. CONTINUAL TECHNICAL IMPROVEMENT OF PRODUCT

The technical improvement of drug is set up steadily throughout its life cycle. It includes three types of improvements:

- New dosages. By multiplying the number of dosages available for one drug, it diversifies the response to the request. It facilitates the physician's introduction of the medicine into the patients' therapeutic protocol (patients often affected by several medical troubles and treated by various medications).
- New formulation. During the commercial life cycle of drug, improvements may be made in the formulation of the compound to meet the diversified demand. These improvements usually focus on increasing the frequency of taking medicine, a demand often requested by chronic diseases patients (once daily for tablets, once to twice per month for injectable products ...). The other

main improvement of the formulation of a product already on the market (well established) is to diversify the way to administer drug and thus to make it available to various population (children, old population, physically limited patients...)

- New device. In the « old » market where many competitors are present (like diabetes market), the differentiation is not only based on the characteristics of the compound (clinical and technical characteristics). It is also based on the device used to administer the product (ease of taking up, ease of use...)

The “continual technical improvement” tactic is involved in the product differentiation to face the competition. But it also has an impact on the perception of physicians (the decisions makers) who consider they have a product "more manageable" with a wider offer for the patient concerning the dynamic of drug management.

The other interest of this continual improvement is to extend patent protection.

3.3.3. EVOLUTION OF PRICE

Unlike other sectors of the industry, the establishment of prices and their management in the pharmaceutical market is framed in most countries under pharmaceutical regulatory (North America, Europe, Japan, China ...). The price is negotiated with national health agencies, just after getting market approval. Moreover, the evolution of this price during its period of commercialization is also agreed.

For some countries, like the United States or Germany, the price of the originator drug will increase steadily throughout the period of commercialization.

But for the majority of dominant pharmaceutical markets (Europe, except Germany, Japan and China), the drug's price will tend to decrease, in a variable way according to the country and products according to a calendar, thresholds of sales volumes...). These variations will depend on agreements concluded with national health authorities in the negotiation of pricing and reimbursement of new prescription drugs.

This price evolution is not affected by the external factors which influence the market. But, if the change of drug price is usually in each country, why the licensee of the brand

drug would not decide to align its price with that of generic products just before their market introduction and thus be able to face competition?

This approach has been attempted several years ago with an antibiotic: Clamoxyl® (containing amoxicillin and produced by GlaxoSmithKline©). Following its significant loss of market share and revenues due to the generic entry, the licensee has tried to cope with competition by aligning its prices with those of generics. However, this attempt failed.

Indeed, by aligning its product to that produced by the generic industry, it would challenge them during negotiation with distributors and pharmacies. But a compound from generics is never traded alone: the negotiation covers a large range of generic. The negotiation between pharmaceutical company and its buyers involves one product rather than the negotiation with generics cover dozens and dozens of specialties. Generic industry has a greater bargaining power. A much more significant discount can be done with generic company compared with pharmaceutical company. Pharmacists and distributors prefer thus selling the generic rather than the originator drug to get the best return.

Pharmaceutical industries (which produce brand medicines) cannot challenge with generic companies because they will always have a few number of “deprotected” specialties (in comparison to the large number of specialties produced and sold by the generics).

To summarize the tactic of the evolution of prescribed drug's price does not really affect the evolution of the product life cycle in the pharmaceutical market, unlike other markets (food, high technology...). The price change of prescription medicines is granted before the commercialization of new compound and paired with the agreement on the pricing and reimbursement. It is not relevant in the decision of the physician for selecting the most appropriate medication for the patient.

3.3.4. BRAND LOYALTY

As for the price change, the tactic associated with the brand are less "intense" compared the intensity for other types of product (mobile phone, cosmetic ...).

As described above, the brand's loyalty is based on two aspects:

- The brand related with the product itself. For brand drugs, loyalty is not built mainly through advertising tools and sales force to target people commonly used in other industrial sectors. In the pharmaceutical market, the presentation and recognition of the benefits of a new drug takes place between the industry and prescribers; and not only between the manufacturer and the consumer (the patient). Because regulations limit the scope of marketing and sales forces and the "public" targeted by these actors matches an initiated and professional audience, the brand 'loyalty is often intrinsically linked to the characteristics of the drug (efficacy, safety, form, first in class...). This notoriety and loyalty are progressive and grow gradually as clinical data are added to the initial product monograph (long-term safety, further indications ...).
- Another type of brand's loyalty is usually created and maintained by marketers. It is the loyalty associated with the company itself. It is found in different types of industries, the most varied of each other: food such as Nestle© and DANONE©, high tech like Apple© ...). But this characteristic is not found in the pharmaceutical sector. Physicians, pharmacists and other health professionals know the name of the molecule (International Nonproprietary Name -INN). They also know the brand name drug related to it, but they do not integrate into their professional practice the name of the company related to a specific drug.

There is therefore a form of brand loyalty for the originator medicine related to the familiarity that the physicians and/or the patients have in their daily practice and to the feedback of information about the drug's properties. Marketing people have to set up a tactic to build awareness quickly and effectively when new product is launched on the market. But this recognition will be secured only through the time and thanks to the observations of the drug's effects on the long term and on a large-scale population.

3.3.5. SWITCH TO OVER-THE-COUNTER DRUG

The switch to Over-The-Counter (OTC) consists to integrate a drug previously delivered thanks to a prescription to the list of OTC drugs (drugs in free access, without prescription). The switch permits marketers to integrate a new part of the pharmaceutical market; and thus increasing significantly the number of patients potentially targeted by this compound. Furthermore, the entry into the OTC market offers a greater “freedom of movement” for marketing:

- Freedom regarding the price of the medicinal product not anymore subject to prescription (and thus tactics associated to price such as price reduction at the discretion of the manufacturer, promotional offers ...)
- Freedom regarding advertising materials that are less constrained by national health authorities for OTC drugs compared to listed medicines. To name differences, there are:
 - o advertising to patients: while it is prohibited for all prescription, advertising is permitted for OTC.
 - o advertising control by competent authorities: regulation associated with advertising campaigns is also different depending on the type of drug (listed or OTC). Whereas it is *a priori* control for prescription medicines, the control is *a posteriori* for OTC drugs.

However, the “switch to OTC” tactic is not systematically applied for all listed drugs because they have to meet positively a number of preliminary criteria:

- The formulation. The OTC medicines will have systematically a formulation which eases their use by consumers (topical, tablets ...)
- A sufficient safety profile (no need of biological survey, sufficient variation of daily dosage without adverse clinical consequences)
- The indications targeted by OTC can only concern minor clinical disorders with short-term period and which can be managed by the patient himself.

3.3.6. FIXED-COMBINATION MEDICINAL PRODUCTS

Fixed-combination consists to an association of the active ingredient of the originator with another molecule. They are used either to facilitate the administration of several drugs or to benefit from the added effects of the two medicinal products given together³⁹.

Potential advantages of fixed combinations include one of the following:

- an improvement of the benefit/risk assessment,
- a simplification of therapy which improves patient compliance.

Fixed-combination products are usually marketed in the late period of market exclusivity of the originator compound.

In summary, strategic tactics of prescription drugs can be implemented into the PLC as following:

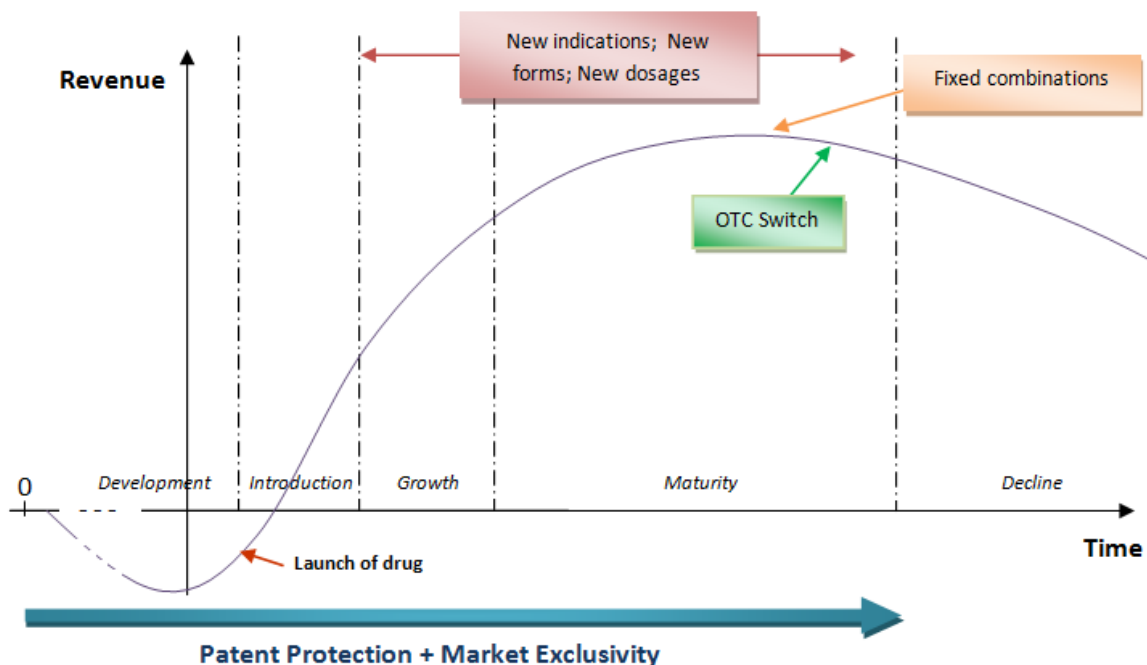


Figure 26 Life Cycle of Innovator Product¹¹

CHAPTER IV- THEORY VERSUS REALITY: COMPARISON AND DISCUSSION

4.1 PRODUCT LIFE CYCLE MANAGEMENT IN PRACTICE

For this part, we will see the practice of PLCM in only one multinational company, Sanofi©. The following information below have been collected from interviews of two senior marketing managers and from my own experience as a marketing trainee.

In the company, the lifecycle management of one brand drug is divided into two main parts:

- The **Life Cycle Management** (LCM) which corresponds to the development and the management of further indications potentially added to the pivotal indication.
- The **Life Cycle Prolongation** (LCP) which includes the other tactics used to improve and maintain the product life cycle.

The PLC and its strategic tactics implemented by marketers may be gathered into two types of marketing: pre- and post-marketing.

4.1.1. IN PRE-MARKETING

In the pharmaceutical sector, the LCM is often thought before launching any clinical trial because the possibilities of LCM indications may support or not the development of a drug candidate (they add value to the product).

But the decision to invest into LCM clinical trials is usually made after the first positive outcomes of the phase III of pivotal indication but the “moment” may change according to therapeutic area, characteristic of the LCM study (if it is closed or not to the first indication). Sometimes, the LCM trial is undertaken just after the end of Proof of Concept (Phase I/II).

Ideally, the other tactics used by marketing (gathered into the subtype LCP) should be decided and started during premarketing step. But, in reality, they are set up in post-approval. This delay on the overall marketing schedule is linked to the current policy of

cost-effectiveness: the decision-makers wait to assess the sustainability of drug on the market before considering investing more cash than necessary to get the first approval.

Variables to measure performance of a PLCM in pre-marketing

These variables can be applied at all types of strategic tactics used by marketing. Before the launch, these are only forecast tools:

- Sales assessment
- Financial tools (i.e. Net Present Value -NPV)
- Key Opinion Leaders' expertise
- "Intention to prescribe". This tool is used in market research and analyzes the product awareness, the knowledge and the appreciation of specialists about the drug. The interest is also to measure the adherence of physicians about the drug candidate and then measure its evolution every predefined period (3 to 6 months).

4.1.2. IN POST-MARKETING

After getting the approval and commercializing the new brand drug, marketers in charge of the product may rework the PLCM tactics already implemented. Thanks to the first feedbacks of the large-scale use of compound, the marketing may be able to refine or complete the overall LCM tactics (opportunities or brakes linked to new clinical effects revealed by the scaling up of number of patients).

Usually, the LCP tactics may be implemented in post-authorization and are focused on:

- Formulation, dosage, device, presentation
- Compliance (tactic used according to characteristic of a product) thanks to patient assistant programs, awareness programs for physicians...
- Combination therapy. It was the trends a few years ago (encouraged by health authorities) but today combination therapy has no more added value.

Variables to measure performance of a PLCM in post-marketing

The tools used in pre-marketing are still applicable in post-marketing. But other variables are added to the previous ones. These are variables which measure drug sales (total or by indication):

- Financial value,
- Market share,
- Number of units sold, number of patients, number of prescriptions

Marketers may compare these results to forecasts.

4.2 SANOFI'S CASES

4.2.1. CASE OF A BIOLOGIC MEDICINE CURRENTLY BEING DEVELOPED

In this case, it is a *monoclonal antibody* (mAb) for which Phase II has been validated. If it is successfully brought to the market, it would be the second product of its biochemical class. Initially, this drug should be indicated for the long-term treatment of patients affected by rheumatoid arthritis.

From this stage of clinical development a premarketing planning is implemented. Marketers are beginning to work on differentiation, positioning and promotion of the drug candidate according to:

- The technical and clinical characteristics of the product and its device
- The expectations relative to the pivotal study
- The population potentially targeted by the future medicine.

In addition to the strategic marketing planning associated with the pivotal indication, other strategic tactics start to be decided and set up: the development of further indications.

As a first step, the previous clinical and non clinical phases have been analyzed. The collected data are also completed by relevant results from scientific studies.

According to the outcomes of the analysis, the decision was taken to focus on the other rheumatologic disorders triggered by an inflammatory mechanism (as ankylosing spondylitis, polymyalgia rheumatic, juvenile idiopathic arthritis...) and determine the medical needs for each of them.

The main interest to focus the rheumatologic area is a cost-effectiveness advantage. To commercialize further indications (LCM indications) it is required to complete a Phase III clinical study with positive results (in term of efficacy and safety), which means significant investment. But as it has been explained before, by keeping the same therapeutic area as the one of the pivotal study, costs saving can be made: no more investment is necessary for the sales force and the actions of drug awareness because all indications involve the same actors (same sales reports, same physicians...).

Nevertheless medical needs enough relevant for the mAb would not be identified, because of:

- The high number of competitor already commercialized on the rheumatologic market (in 2012, there are 8 biologic products). Moreover, most of them have currently multiple indications which give them a significant advantage in term of awareness and reliability to use them off-label if necessary.
- The few number of inflammatory rheumatologic indications for which there would be no significant medical need and for which there would be a sufficient ROI.

If this situation appears, the marketers would decide to enlarge the therapeutic areas targeted by their drug candidate: they could focus on disorders for which the inflammatory mechanism is close to rheumatologic.

4.2.2. CASE OF A PRESCRIPTION DRUG ALREADY COMMERCIALIZED :PLAVIX®'S CASE

Plavix®, a chemical compound commercialized by BMS© and Sanofi© is indicated for cardio-vascular disorders:

- Acute coronary syndrome (primary prevention of cardio-vascular complications)

- Secondary prevention of recent myocardial infarction, stroke or established peripheral arterial disease (PAD)

It got its first approval in the US in 1997 and in 1998 for the EU. Plavix® is considered as a blockbuster with its US revenues reaching \$4 billion per year at its peak of sales.

Plavix® marketing is a textbook case with a unique history which cannot be replicated anymore in the future. It is interesting because of the management of its life cycle.

This management was atypical for several reasons:

- The size and heterogeneity of population included in the pivotal study (CAPRIE). It gathered more than 19,000 patients with various pathologic profiles (MI, ischemic stroke and PDA). Nowadays, the pharmaceutical companies would not undertake anymore a clinical with the same sample due to cost-effectiveness reasons and reduction of risk of failure (due to adverse effects, lack of efficacy...).
- A dozen of LCM studies realized through Plavix® life cycle (CURE, CHARISMA, CLARITY, ACTIVE-A...). But, these trials did not intend really to extend drug prescription over its pivotal indication. In fact, during the first years of Plavix® commercialization, specialists and general practitioners were muddled about the appropriate use of the drug. Because the heterogeneity of the first clinical trial, it was difficult for them to isolate and identify the patient profile for which the product would be effective. The LCM studies have permitted to precise clearly the right type of patients in addition to confirm the safety and tolerability profile of the compound.
- An atypical evolution of its curve of sales revenues through its period of commercialization. In spite of the entry of the generic of Plavix® in Europe, the curve is still pursuing its increase. But this “success” is not related to the characteristic of product neither the usual strategic tactics used for Plavix®. The evolution is explained by the sequence of

marketing approvals and the loss of market exclusivities around the Globe:

- in 1998 for North America and Europe
- in 2006 for China and Japan
- in 2009, entry of its generic drug in Europe
- in 2012, entry of generic in US

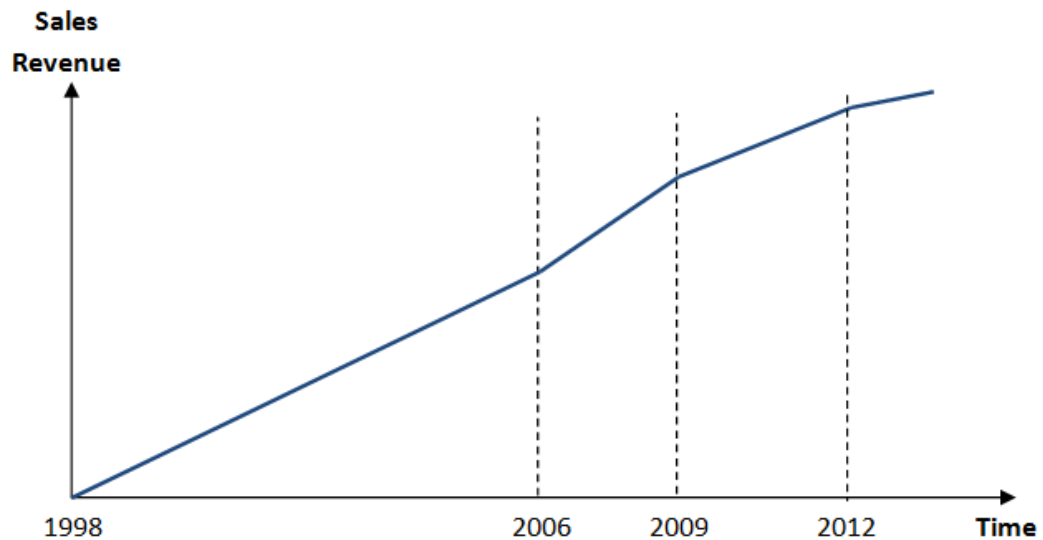


Figure 27 Evolution of sales revenues of Plavix® worldwide

The impact of the loss of patent and data protection followed by the entry of generics in Europe has been diluted through time (patents used in China and Japan different from those in US and in Europe). The Asiatic sales have supplanted the unavoidable collapse in sales related to the commercialization of generics in Europe. Nevertheless, due to the change into the market dynamics and the upcoming integration of China into leading market, this tactic will not be reused anymore.

4.3 AN ASIDE, THE BIOSIMILARS' COMPETITIVENESS

Even if biologic drugs have been present on the pharmaceutical market for decades, biosimilars are still a novelty for every one (R&D, marketing, payers, physicians...).

A lot of these people raise the question about the real competitiveness of these biosimilars, specially compared to that of generics. Because of the strong barriers named and described previously in Chapter I, some of them have reservations regarding the sustainability of this category of medicines.

Nevertheless, other professionals have doubts regarding the relevance of these arguments:

- The most important generic companies have sufficient resources to invest into the development and the production of a biologic compound and to acquire the competences and the know-how if necessary.
- These companies often belong to big pharma which usually manufacture and commercialize an existing biologic medicine. They have thus the infrastructures required to produce a biosimilar.

Moreover, for some of these professionals convinced by the sustainability of biosimilars, having strong barriers to market entry may become an advantage: they would limit the competition of a given product. Indeed, the generic companies will not be able to produce a biosimilar for each biologic brand drug due to the significant investments required (in term of money, people, place and time). Finally, generic manufacturers will be thus in competition with 3 or 4 biosimilars for a specific product instead of the dozen of competitors in the generic situation.

Regarding constraints related to regulatory of biosimilars, some of marketers believe that the health authorities will tend to relax them in the next years to encourage the biosimilar development and thus cut health care costs. The price difference between brand biologic and biosimilar is certainly lower than that of chemical compounds in term of ratio (30 to 40% of expected reduction for biosimilars versus 80 to 90% for generics). But this gap is weighted when this difference is assessed according to the absolute value. Indeed, the biologic brand drugs are significantly expensive. A low reduction of price in percentage is easily attractive for payers.

4.4 A UNIQUE MODEL OF PLC FOR ANY MEDECINE?

When we analyze in detail the life cycle of a large number of medicines, we are able to note that the evolution of this cycle and its S-curve is closely linked to internal and external characteristics of product (formulation, therapeutic area, competition, regulatory...). But, these various products have sufficient commonalities in term of strategies and associated tactics for scientific literature to establish a global model about the drug life cycle and its management (from its development to the end-of-life).

Yet significant differences linked to these same characteristics may justify a doubt about the relevance to apply a unique PLC model for the all drugs already or not marketed:

- Internal characteristics.
 - Type of medicine product. As it has been mentioned in Chapter I of this thesis, the national and international regulatory have ranked under one banner “medicines” various categories of products (chemical and biological) and therapeutic processes (biotherapy). Each of these subtypes has requirement regarding their development (financial investment, timeframe, clinical constraints, infrastructures...) and regulatory to which they are subject.
 - Therapeutic area. It may correspond to the category selected by pharmaceutical company as pediatric indication or orphan designation. For each of categories, a specific regulatory is applied (about development, clinical trials, market exclusivity...). Furthermore, concerning the rare diseases, the marketing tactics associated to this category may differ of these associated to “more classic” disorders (e.g. the significant involvement of patient organizations).
- External characteristics.
 - Competition. It is the competition related to copy medicines which may differ significantly. While the generic market has been present for many years in mind and practice of various shareholders of medical community (physicians, pharmacists, health authorities, pharmaceutical industry...), the biosimilar market is still emergence stage (in term of regulatory,

feedbacks...). This fracture has an impact on the intensity of each of them regarding their competitiveness.

- Type of market. They may be numerous: prescriptions drugs, OTC compounds, generics, biosimilars, homeopathy...According to the category to which the medicinal product belongs, it can influence significantly the evolution of the S-curve and the duration of its life cycle. To illustrate this variation, we can simply compare the market of prescription medicines versus generics market: while the duration of life cycle for the first type is most often limited by the period of patent protection and market exclusivity, the second is only limited by the interest and the benefits of one generic compared to its competitors and the other generic classes.

We may also raise the question about the sustainability of the current PLC model and its management through the development and the marketing of a new drug. As it may be noticed, the “step-by-step” model (the success of one is required to launch the following one) would reach its limits: a substantive investment for a development consistently longer, associated to a reduced productivity.

These development issues have an impact on the marketing tactics applied during the commercialization of a drug:

- They may decrease the period of market exclusivity. Because of this reduction may not have enough “time” to set up all tactics considered to increase sales revenues. This lack of time has thus consequences on the maximization of the ROI of product.
- Due to cost of one clinical trial, the current trend is not to invest in other potential LCM indications before the “stability” of the new drug on the market has been proven. But in return, this may limit the possibilities to increase the ROI by increasing the size of population.

CONCLUSION

Actuellement, pour la plupart des médicaments commercialisés, leur cycle de vie ressemble souvent à un modèle largement décrit dans de nombreuses publications et ce depuis plusieurs décennies et composé d'une succession d'étapes. Ce cycle commence avec une longue phase de développement (une phase séquentielle constituée elle-même de nombreuses étapes, la validation de chaque étape nécessaire à la poursuite du développement). Après l'obtention de l'Autorisation de Mise sur le Marché, le nouveau médicament entre alors en phase de lancement, période durant laquelle les actions marketing sont nombreuses et intenses afin de faire intégrer le nouveau composé dans le « pipeline » des médicaments couramment utilisés par les médecins. Elle est suivie d'une phase de croissance qui doit être idéalement la plus courte possible pour rentabiliser au maximum le retour sur investissement de l'entreprise pour ce produit et ainsi rentrer rapidement en phase de maturité. En théorie, les industriels managent ce cycle de vie afin que cette période soit la plus longue de la période de commercialisation pour que les profits soient les plus conséquents avant l'entrée en phase de déclin, généralement liée à l'arrivée des génériques et bio-similaires sur le marché. Mais en pratique, cette phase de maturité est limitée, voire quasi inexistante lorsqu'on décrit le cycle de vie de certains types de médicaments déjà commercialisés :

- Limitée. Parce que le temps de développement est de plus en plus long, la protection des brevets de même que la protection des données des médicaments ne suffisent plus pour permettre à l'industriel de mettre en place tous les moyens et les tactiques marketing pour maximiser la rentabilité du produit.
- Voire « inexistante ». Si on s'appuie sur la définition et les caractéristiques de cette phase de maturité (maintient d'un plateau des volumes de ventes, réduction des coûts...), il apparaît que cette phase ne puisse plus être systématiquement atteinte pour certains médicaments du fait d'un temps trop limité entre le début des phases de lancement et de déclin. Cette période trop courte empêche l'industriel de mettre en place ses actions marketing suffisamment tôt pour atteindre le maximum des ventes.

Mais ce modèle de cycle de vie et le management associé semblent aujourd'hui dépassés car incapables de s'adapter aux changements et aux enjeux auxquels doivent se confronter les industries pharmaceutiques :

- Le cycle de vie classique d'un produit pharmaceutique décrit dans la littérature n'est aujourd'hui plus forcément adapté à tous les types de médicaments autorisés par les autorités de santé.
- Malgré une augmentation croissante et significative des ressources investies dans la R&D et de l'optimisation de l'allocation et du management de ces mêmes ressources à tous les stades du cycle de vie du médicament, la période de développement n'a jamais été aussi longue et le nombre de médicaments nouvellement autorisés et significativement innovants est toujours aussi bas et semble stagner depuis quelques années.

Avec le changement de la perception des professionnels et des autorités de santé quant au management et la prise en charge des patients et de leurs pathologies (médecine personnalisée, optimiser le management des coûts/bénéfices...), il semble inéluctable que le modèle de management du développement et de commercialisation soit également amené à changer pour permettre à l'entreprise d'être toujours performante nécessaire pour se maintenir sur le marché pharmaceutique hautement compétitif.

Certains industriels ont atteint les limites du cycle de vie du médicament actuellement décrit et réfléchissent dès à présent sur la réorganisation de ce modèle, des premières étapes de développement jusqu'aux différentes phases de son cycle commercial et au-delà (en prenant compte en compte « l'après déclin »).

Une Start-up s'est actuellement orientée vers cette réflexion d'un nouveau type de management du cycle du médicament : l'entreprise Sobios®. Partenaire de Dassault Systèmes, cette société est spécialisée dans le développement de logiciels de simulation proposant des solutions de gestion du cycle de vie du produit de santé, de son développement en passant par sa commercialisation et jusqu'à son retrait du marché.


VU ET PERMIS D'IMPRIMER

Grenoble, le 26/11/2012

LE DOYEN

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ANNEXES

Interview P. S.

Dans le cas de Sanofi, le concept « Life Cycle Management » se focalise exclusivement sur l'analyse et la mise en place des indications additionnelles à l'indication principale. Les autres stratégies utilisées pour optimiser le life cycle/protéger le princeps des génériques (formulation, dosage...) sont inclus dans le concept LCP (Life Cycle Prolongation).

Pour le résumé écrit de l'interview, ces concepts seront regroupés sous la dénomination « PLCM » (Product Lifecycle Management)

Premarketing

Existe-t-il des variables pour mesurer la performance du PLCM ?

- Il s'agit plus d'outils prévisionnels :
- Prévisions des ventes
- Outils/calculs financiers (NPV par exemple)
- Expertises des KOL

« intention to prescribe » (market research) => soumission du TPP du médicament candidat auprès des médecins; étude plus complète = "conjoint" qui fait varier les paramètres cliniques du produit.

Ces outils vont permettre d'évaluer le risque associé à chacune des stratégies du PLCM (1st indication, LCM)

A quel moment du développement le PLCM est-il mis en place ?

2 cas de figure :

- 1st indication et LCM. Lorsqu'arrivé à l'étape de Proof of Concept (POC, déterminé durant les études de Phase II), une analyse est faite pour recentrer et préciser la population ciblée par la 1st indication (déterminé en fonction des unmet needs...pour optimiser la vitesse et le % de succès d'obtention de l'AMM)
- LCP : les stratégies associées sont mises en place en post-authorization ; idéalement, le LCP devrait commencer en pre-market mais, actuellement, il est mis en place après le lancement, décision liée à la politique de « cost-effectiveness » (avant d'envisager d'investir d'avantage d'argent qu'il n'est nécessaire pour l'obtention de l'AMM, les décisionnaires préfèrent voir si le produit a de l'avenir sur le marché.

Un des intérêts du LCM post-market : possibilité d'étendre la market exclusivity à +1 an si la population ciblée est suffisamment différente de celle ciblée en 1^{ère} indication.

Remarque : possibilité aussi de poser une protection sur une des nouvelles indications si l'effet est décrit pour la 1^{ère} fois.

Quels sont les facteurs influençant le PLCM en pré-marketing

- Financiers (investissements....)
- Médicaux

- Facteurs externes : « competitive intelligence » & structure du marché

Post-lancement

Stratégies du PLCM en post-market

LCM, envisagé au cours du développement clinique, à partir de la population sélectionnée pour les études. Il est ensuite affiné/compléter dans la phase post-lancement avec l'identification de nouvelles opportunités liées aux effets découverts grâce au changement d'échelle du nombre de patients sous thérapie.

Intérêt du LCM : étendre market exclusivity (+1 an) voire étendre patent protection si l'effet décrit pour la première fois.

Quelles sont les variables de performance utilisées en post-authorization ?

Sales monitoring : par indication et par segment du LCM+ 1st indication comparé aux forecasts

« Sales » (ventes) : cela comprend à la fois la valeur pécuniaire mais aussi le nombre d'unités, nombre de patients, nombre de prescriptions.

Quels sont les facteurs influençant le PLCM en post-marketing ?

- Identiques à ceux retrouvés en pre-marketing :
- Financiers (investissements....)
- Médicaux
- Facteurs externes : « competitive intelligence » & structure du marché

Dans votre pratique, quelles sont les outils déjà employés pour le PLCM d'un princeps (pré et post authorization) ?

- New indications/LCM
- Formulation, dosage (one a day), présentation
- Combination therapy : pour obtenir l'agrément, il était nécessaire de prouver que 2 composés associés étaient plus efficace que pris séparément ; bien qu'utilisé dans le passé, cette stratégie est beaucoup moins utilisée à présente à cause des exigences des autorités compétentes mais aussi de la perte de la capacité de discrimination des EI entre les 2 composés (« à quel produit est-il dû ?) => difficile pour le « Risk Management » post-lancement.
- Compliance (fonction des caractéristiques du produit)/ PAP/ programmes destinés aux médecins (guidelines)
- Patent protection (galénique, device...)

LCM : il peut étendre la population ciblée par le produit ou au contraire le restreindre (pour raisons médicales, problème de safety/ découverte d'EI lors d'études LCM qui limite son utilisation à la population initialement ciblée) => calculer l'impact de l'échec d'une indication LCM dans le calcul financier

Planification du PLCM

Il n'existe pas de modèle pré-établi (à la fois sur le fond et sur la séquence des événements), trop de paramètres internes et externes qui influencent le modèle.

Le LCM est lui séquentiel (pas forcément idéal pour être le plus efficient ; lié à la politique de cost-effectiveness)

Exemple : Plavix ; 1st indication : pour une petite tranche de la population => devenu un blockbuster en rajoutant une indication après l'autre

Exemple qui ne pourra plus se faire à présent, à cause

- Du coût de développement conséquent pour déclencher un LCM
- De la diminution de la patent life

Aparté sur les biosimilaires

Les autorités poussent à l'utilisation (exemple de la FDA et du cas Lovenox)

Il reste l'idée que la pression des génériqueurs sera moins forte avec les biotech à cause de :

- produit de haute technologie : compétence spécifique
- infrastructure et logistique très différent de celles du manufacture chimique
- investissement important (avec de lourdes études clinique) et gap entre princeps et biosimilaire plus réduit que celui des génériques

Mais dans les faits :

- s'ils n'ont pas le savoir-faire, ils « l'importeront »
- capacité industrielle : à présent, la pluparts des principales firmes de génériques appartiennent à des big pharma qui eux ont la capacité et les structures pour produire des biotech
- Seule différence entre generic et biosimilaires : seuil de la taille du marché qui incitera ou non l'entrée des biosimilaires (marge suffisamment intéressante pour s'implanter), seuil plus élevé pour les biosimilaires.

Barrière aux biosimilaires par les autorités uniquement si il y a un risque qu'on leur reproche d'avoir risqué la santé des gens au profit de l'économie.

Interview –E. N.

Pre-marketing

1) A quel moment du développement le LCM et le pré-marketing sont lancés ?

- Pré-marketing = toute activité qui va aider à différencier et promouvoir le produit en amont du lancement ; il commence généralement durant la phase III (avant les résultats de l'étude) et est renforcée entre la fin de l'étude pivot et le lancement du médicament sur le marché.
- LCM réfléchi avant même de lancer les études cliniques : les possibilités du LCM vont supporter la décision ou non de développer un produit (les LCM potentiels donnent de la valeur au produit)
Les opportunités potentielles du LCM sont identifiés très tôt au cours du développement clinique : en phase I/II. La décision d'initier ou non une étude complémentaire (étude LCM) est généralement prise après les résultats positifs d'une 1^{ère} étude de phase III =indication principale (additionnés à une confiance quant à la viabilité de l'étude pivot) mais le « moment » peut varier en fonction de l'aire thérapeutique, des caractéristiques de l'étude LCM (si proche ou non de l'indication de l'étude pivot).

2) Quelles sont les variables utilisées pour mesurer la performance/ « l'efficacité » des tactiques LCM mises en place ?

Il s'agit d'indicateurs quantitatifs et qualitatifs :

- Analyse de la notoriété du produit spontanée ou assistée, appréciation du produit, connaissance du produit et de ses caractéristiques (études de marché, questionnaires)
Il s'agit de tester l'adhésion ou non vis-à-vis du médicament candidat et voir son évolution dans le temps (tous les 3/6 mois) avec objectifs à la clé (x % d'adhésion).

Ces indicateurs ne sont pas spécifiques du LCM bien entendu

3) Quels sont les facteurs qui influencent le PLCM d'un médicament (indication pivot + LCM) en pré-marketing ?

Les résultats d'une étude clinique ont un impact sur la viabilité d'une autre indication (notamment en ce qui concerne les EI ; ex- Multaq).

Après que la décision de lancer l'étude ait été prise :

- ⇒ Une fois décidée, l'étude est rarement arrêtée (exception EI graves ou analyse intermédiaire démontrant l'inutilité du produit). Finir une étude (quelque soit son résultat, positif ou négatif) est toujours un plus en terme d'acquisition de connaissances scientifiques concernant le produit et la pathologie donnée.

Avant la décision, 2 aspects sont à prendre en compte : intérêt médical/ intérêt économique

- Intérêt médical se divise en 2 parties :
 - Besoin médical ?
 - Faisabilité ? (Est-il possible de faire la démonstration au travers d'une étude clinique ?
Absence de paramètres fiables permettant de démontrer l'efficacité d'un produit ex-

Faisabilité logistique d'un protocole d'étude clinique : besoin identifié mais les patients ciblés sont localisés dans des pays émergents où il n'y a pas de centre de recherche ; besoin mais pour lequel il est nécessaire de screener un nombre « infini » de patients pour en trouver un éligible à l'étude,).

- Intérêt économique
 - o Quel est le marché ? (nombre de patients, incidence, % de patients diagnostiqués, % de patients suivis par un médecin –sous-diagnostiqués, mal orientés...-
 - o Market Access (accès au marché) ; risque de refus d'enregistrement ou de remboursement par les autorités de santé nationales (potentiellement trop cher, pas suffisamment de bénéficiaires → prix/remboursement) ; barrières à l'inclusion dans les protocoles hospitaliers (organes de décision locaux)

Post lancement

- 1) Quelles sont les variables de performance/ « d'efficacité » des stratégies mises en place durant le cycle de vie du médicament ?

Indicateurs utilisés en pré-marketing + autres critères quantitatifs tels que les chiffres de ventes, les parts de marché recueillies au niveau national et/ou au niveau régional (UGA = Unité Géographique d'Analyse ; en France 600/700 UGA ≈ taille d'une circonscription)

- 2) Quels sont les éléments qui influencent le PLCM (LCM et indication pivot) ?

2 « systèmes » complémentaires

Remarque : le LCM ne prolonge pas vraiment la période de protection des données (en moyenne protection durant la commercialisation d'environ une dizaine d'années) ; En Europe prolongation de la période d'exclusivité au maximum d'un an si l'indication LCM est considérée comme vraiment différente de la 1^{ère} (pas de prolongation aux US sauf dans le cas des études pédiatriques) .

Exemple : Plavix -60% des ventes aux US & 4 \$B /an ; aux USA, Plavix a obtenu une extension d'exclusivité de 6 mois suite à la réalisation d'une étude pédiatrique (même si le résultat est négatif) => 2 \$B en plus

- 3) Quelles sont les autres outils qui permettent de maintenir/de prolonger le PLCM ?

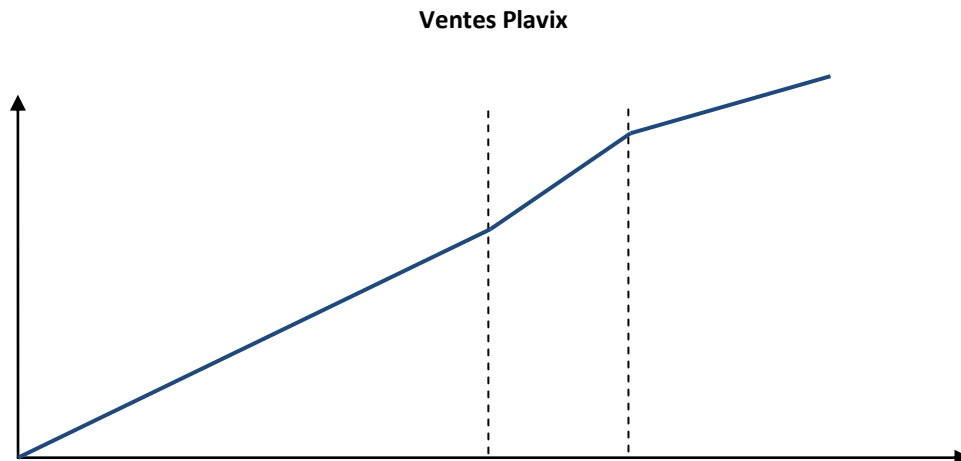
Autres outils qui entretiennent le PLCM (hors LCM) : développement des formes galéniques et des dispositifs de haute technicité à valeur ajoutée (dispositif de haute technicité : utilisés pour les produits du diabète) => le but étant d'étendre l'usage du produit dans le temps.

Autre tactique = association thérapeutique ; tendance il y a quelques années (favorisée par les autorités de santé) n'a plus aujourd'hui de valeur ajoutée (l'efficacité de l'association n'est jamais meilleure que la prise séparée ; pas de possibilité d'adaptation de dosage, d'heure de prise).

- ⇒ Elle apparaît vers la fin du cycle, de manière quasi concomitante à l'entrée des génériques. Son prix est donc comparé à celui des génériques plus qu'à celui des princeps

Cas Plavix

- ❖ Mis sur le marché à des dates différentes entre les pays développés et les pays émergents :
 - En 1998 pour les US/Canada/Europe
 - En 2006 pour Chine & Japon
 - En 2009, Plavix générique en Europe
 - En 2012 Gx aux US



⇒ L'impact de l'entrée des génériques dilués dans le temps (en Chine & au Japon – brevets différents /US&EU – les ventes ont pu supplanter l'effondrement liés aux génériques en EU)

- ❖ Le LCM (nouvelles indications) du Plavix n'a pas étendu le nombre de patient en comparaison de celui de l'étude pivot (AVC, SCA et AOMI -artériopathie oblitérante membres inférieurs) qui était très large (étendue qu'on ne retrouverait plus pour les actuelles études pivot) => positionnement pas assez clair ;

Le LCM (une dizaine d'études), en plus de clarifier (de préciser) le positionnement du composé, a systématiquement confirmé les résultats de l'étude pivot, surtout en terme de tolérance

N.B : le risque du LCM est de d'obtenir des résultats contradictoires de ceux de l'étude initiale

De plus en plus les autorités de santé demandent 2 études pivot dans la même population de patients pour confirmer les résultats

Prix des médicaments

Décidé avant le lancement du produit durant la phase de négociation du remboursement avec les autorités, le prix d'un médicament n'est pas fixe :

- En Allemagne et aux US, le prix peut être augmenté au cours du temps
- Europe/Chine/Japon, le prix ne fera que baisser au cours du temps (accords prix/volumes passés avec les autorités de santé et négociés avant le lancement)

Pourquoi alors ne pas réduire le prix du princeps pour qu'à la fin de la période d'exclusivité, son prix soit comparable à celui du générique ?

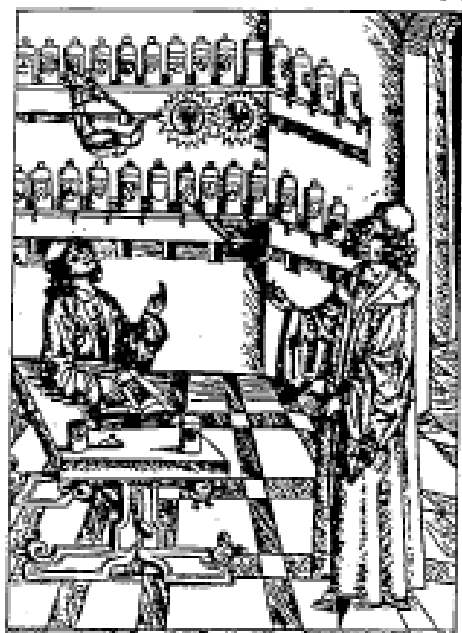
Tactique déjà employée mais échec (ex Clamoxyl) car alors que la compagnie vend un produit, le génériqueur vend toute une gamme. Il a donc un pouvoir de négociation plus important (rabais sur la gamme et non sur un produit => plus intéressant pour les distributeurs et officines)

Biosimilaires

- 30/40% moins cher pour les biosimilaires (vs 80/90% moins cher avec les génériques)

Considérés comme inéluctables car :

- même si la barrière à l'entrée est beaucoup plus forte comparée à celle des génériques (coût initial fort), au final, cela peut être un avantage pour les compagnies réussissant à franchir cette barrière => moins de concurrence entre biosimilaires vs génériques (2/3 biosimilaires vs 10 génériques)
- tendance à l'assouplissement des contraintes pour autoriser les biosimilaires.



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



LE PRODUCT LIFE CYCLE MANAGEMENT APPLIQUE AU MARCHÉ PHARMACEUTIQUE

TOMAS Lucie

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

Résumé :

Depuis plusieurs années, les entreprises pharmaceutiques ont dû faire face à des obligations de plus en plus fortes, à la fois sur le plan économique, réglementaire et éthique. Ces contraintes ont à présent un impact visible sur le processus du développement qui n'a de cesse de se rallonger malgré un investissement croissant des ressources. Elles influencent également le dynamisme du marché.

Afin d'optimiser les bénéfices financiers des médicaments princeps mis sur le marché, les entreprises pharmaceutiques utilisent un concept largement répandu dans le milieu industriel : le « Product Life Cycle Management » (PLCM). Adapté aux spécificités et aux limites du domaine pharmaceutique, le PLCM élabore, planifie et manage les stratégies et les actions qui en découlent, dans le but évident de maximiser le retour sur investissement.

Pourtant, malgré les ressources conséquentes allouées au développement et l'optimisation du management du composé durant toute son existence, le modèle actuel du cycle de vie du médicament semble avoir atteint ses limites. On observe en effet depuis 2011 un des plus forts ralentissements de la croissance du marché pharmaceutique comparée à celles de ces dernières décennies.

Ce constat pourrait amener les industriels à mettre en place dans le management de leur produit un modèle rénové voire totalement réinventé et, ainsi, trouver une solution concrète afin de faire sortir le marché pharmaceutique de son marasme.

Mots-clés : marché pharmaceutique, enjeux économiques et réglementaires, cycle de vie, product life cycle management, tactiques stratégiques.

Soutenue à la Faculté de Pharmacie de Grenoble le 10 décembre 2012 devant le jury composé de :

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