Workshop 4.1.2
Interplay between patents and regulation

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Strategies in the medical field

Why does the medical field have to be considered as specific?

The following peculiarities have to be taken into account:

- It concerns **public health**, therefore drugs necessitate a strict administrative control of non-toxicity and efficiency.

ANSM (Agence Nationale de Sécurité du Médicament) in France & EMEA (European Medicines Agency) in Europe, like the FDA (Food & Drug Administration) in the USA, are responsible for delivering Marketing Authorisations (MA).

- Governments are keen to ensure easy access to all medicines at the lowest possible price.

Strategies in the medical field

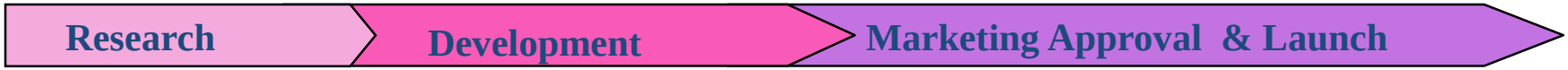
- Initially, National and European competition authorities have essentially focused on the question of parallel importations in the field of medicament.

- Progressively the Member States have been submitted to strong constraints as far as public health budget is concerned

- This led to the sector inquiry, carried out by the Commission between 2008 and 2009, involving 60 persons from the Commission in order to understand the practices of the pharmaceutical industry to slow down the entry into the market of generic products.

- In the framework of this inquiry, the European Commission discovered the strategy of patent protection and more particularly, the European Commission discovered that it was already possible to obtain a patent protection for a drug after the launch of its first marketing authorization on the market.

The general patenting scale during the life of a drug



Compound (genus)/first medical use

Compound (species)

Salts

Solid forms (solvates, polymorphs, particle size)

Formulation, Release Profile

Manufacturing process, intermediates

Additional indications (second medical use)

Dosing regimen

Patient sub-populations

Biomarkers

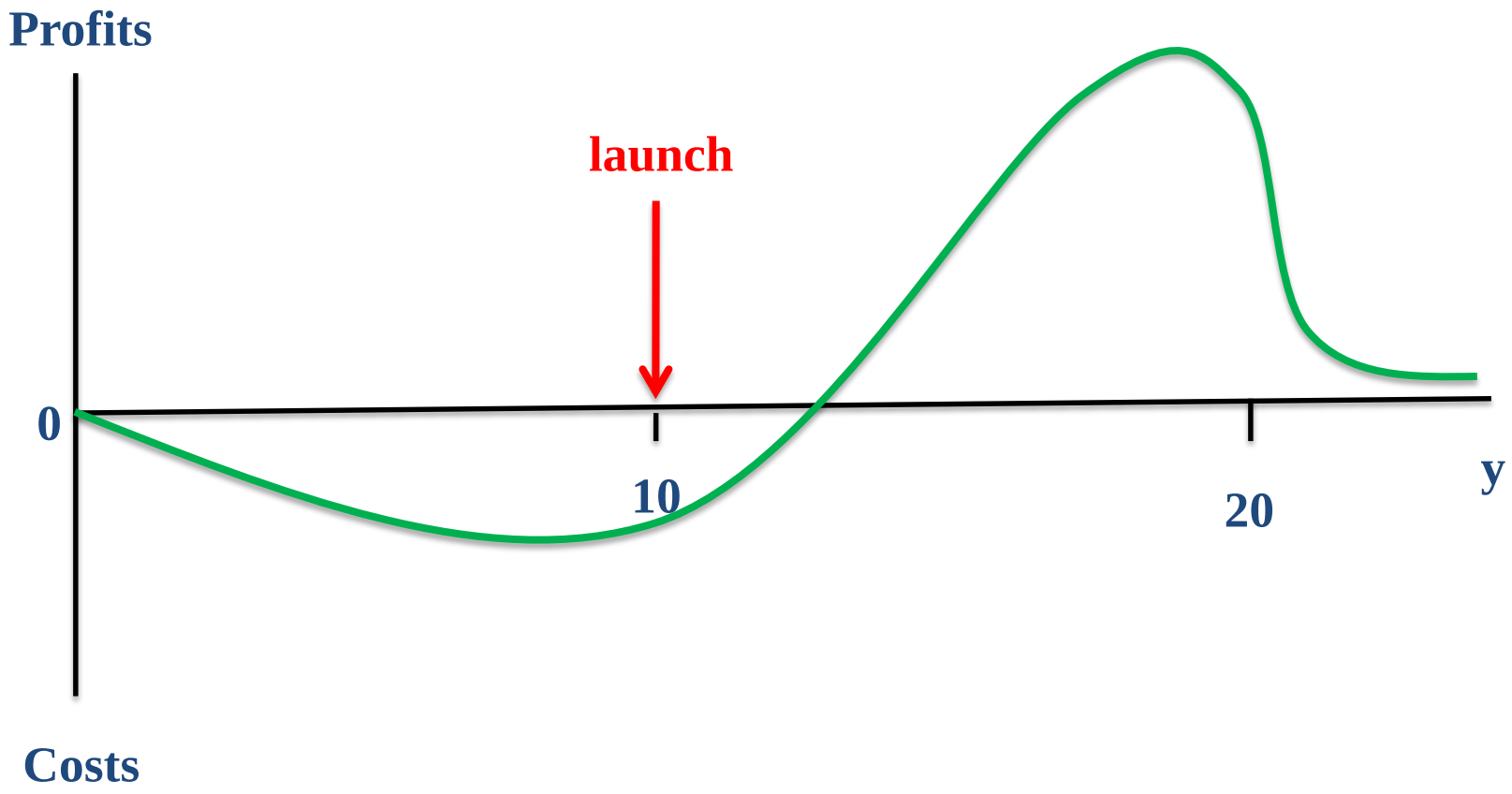
Combinations

Improved Formulations

Strategies in the medical field

- It is considered nowadays that about 14 years are necessary between the conception of a new active substance on drawing tables, and the distribution of the final drug in a pharmacy.
- The average cost for such a complete development is evaluated around 1 billion euros.
- **Strong protection is compulsory to expect return on investment and to sustain further researches**.

Life of a Successful Drug :
A very strong economic impact.



Strategies in the medical field

PROGRESSIVE ACCEPTANCE OF THE PATENTABILITY OF DRUGS

- Excluded before 1960 in France
- France: BSM (Brevet Spécial de Médicament) : January 1, 1960
- Germany: January 1, 1968
- Spain: October 8, 1992

- Trips Agreement 1994

- Portugal: June 1, 1995
- Turkey: January 1, 1999
- India: New TRIPS agreement in 2005 but strong resistance to grant protection for drugs.

- Canada: Protection duration was progressively extended to reach 20 years in 1991, products became patentable and the existing compulsory licensing regimen for pharmaceutical products was abandoned.

Public Health Authorities

European regulatory framework (Regulation (EC) n°726/2004 and Directive 2001/83/EC)

- Rules on data exclusivity and market protection
  - 8 years data exclusivity + 2 years market protection + 1 year market protection (new indication)
- Skilly labelling :
  - modified SmPC carving out a patented therapeutic indication

Public Health Authorities

National incentive measures for the development of generic drugs

- Prescribing and Supplying of drugs through the International Common Denomination (ICD), but…
- Cross-label risks in case of remaining patent rights

Public Health Authorities

PREGABALINE case in Europe (Pfizer)

Possibility for the generic product to carve out the patented 2nd medical use to avoid patent infringement.

1st patent	2nd patent	Generic applicant
EP 641 330 + SPC	EP 934 061	-
Expiration date 18/05/2013	Expiration date 16/07/2017	-
Product + medicine	2nd medical use Swiss claims (neuropathic pain)	-
Lyrica® **Global MA for** Generalized Anxious Troubles (GAT), epilepsy and neuropathic pain (NP)		**Sandoz Pregabaline** **1 MA limited to** GAT, epilepsy

Public Health Authorities

PREGABALINE case in Europe (Pfizer)

Sandoz sent out to the prescribers, doctors, physicians and pharmacists both inside and outside hospital services :

A warning of the patent infringement situation, clearly instructing that the generic product can only be prescribed and delivered for the two therapeutical indications mentionned in the SmPC and notice of the Sandoz Pregabaline in line with the carved out MA.

Public Health Authorities

PREGABALINE case in Europe (Pfizer)

French Court Order of October 26, 2015 (Paris Court)

Direct infringement NO

Product directly obtained by a process (Swiss claim)

No infringement because the notice, SmPC and carved-out MA exclude the protected indication for neuropathic pain, and « warning letters » discourage from prescribing a generic drug for the protected medical use.

Public Health Authorities

PREGABALINE case in Europe (Pfizer)
French Court Order of October 26, 2015 (Paris Court)

Indirect infringement

• Providing and furnishing a non-authorized person with an essential means for carrying out the invention when the means is apt and intended for this carrying out,

Or

• An incent to infringe when the means is freely available on the market,

In the present situation none of the two hypothesis applied and indirect infringement was also denied. The French Court rejected the preliminary Injunction request

Public Health Authorities

PREGABALINE case in Europe (Pfizer)

Situation in other European countries

Germany : Indirect infringement recognized since discount contracts have been registered with Health Insurance companies and general tenders were concluded.

Spain and Italy : Regional or National Health Authorities sent out recommendations to all prescribers and pharmacists stating that :

- only the princeps product is authorized for neuropathic pain,

and

- the other generic medicines will not be reimbursed by the National Social Security Service for neuropathic pain.

Public Health Authorities

PREGABALINE case in Europe (Pfizer)

Situation in other European countries

Denmark : Preliminary injunction to deliver the generic product for neuropathic pain, delivered by the Court against pharmacists.

UK: High Court of Justice ordered National Health Services (NHS) to publish instructions for the doctors to prescribe brand product Lyrica® only and not the generic drug Pregabaline for treating neuropathic pain.

Competition law versus Patent law

Antitrust and Competition legal system in Europe

Applied by both the European Commission and the National Competition Authorities of each Member States

- Art. 101 TFEU
  - Prohibition of **restrictive agreements** : « …*are prohibited all agreements between undertakings and concerted practices which may affect trade between Member States (prevention, restriction or distortion of competition within the internal market)..*"
- Art. 102 TFEU
  - prohibition of an **abuse of dominant position** : « …a*buse of dominant position within the internal market or in a substantial part of it shall be prohibited as incompatible in so far as it may affect trade between Member States*…"

Competition law versus Patent Law

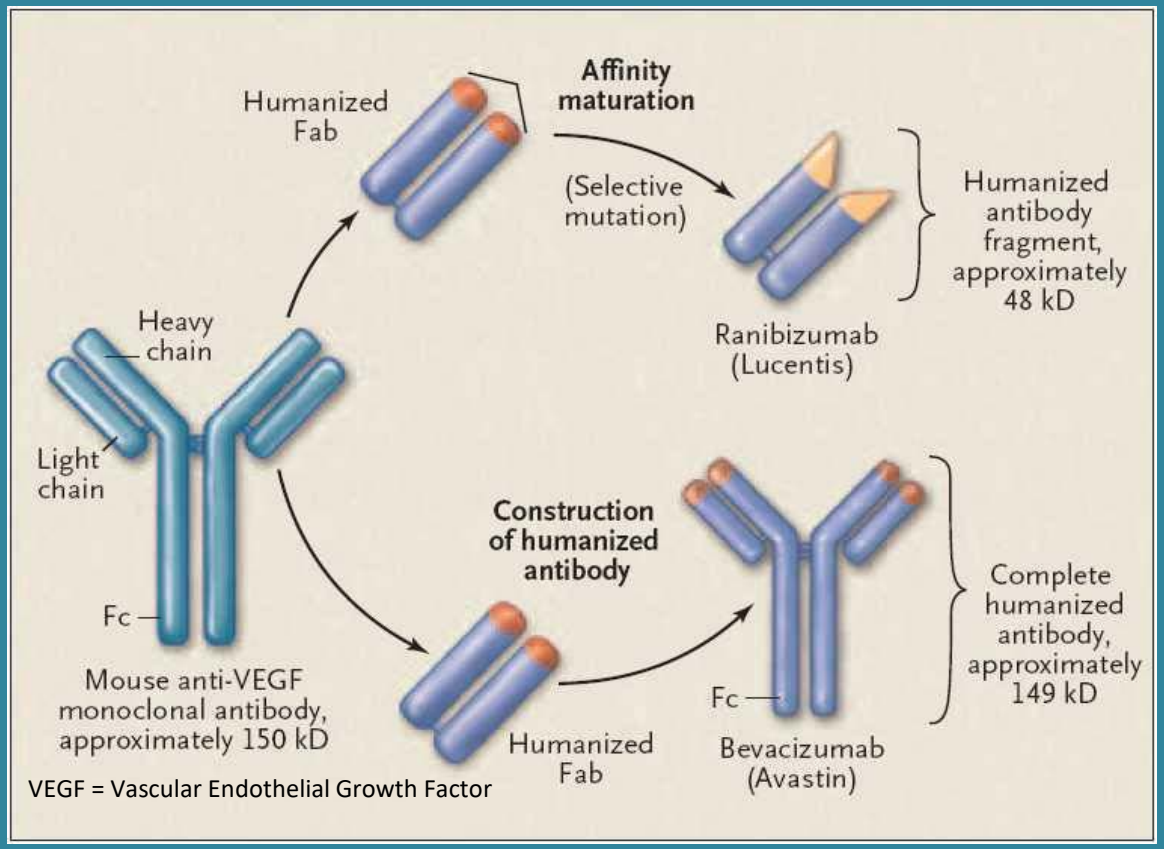
- **Art. 101 TFEU**

  – Lucentis –Avastin case in Europe :

  Artificial differentiation between two similar drugs for the treatment of Age-related Macular Degeneration (AMD)/Cancer

Competition law versus Patent Law

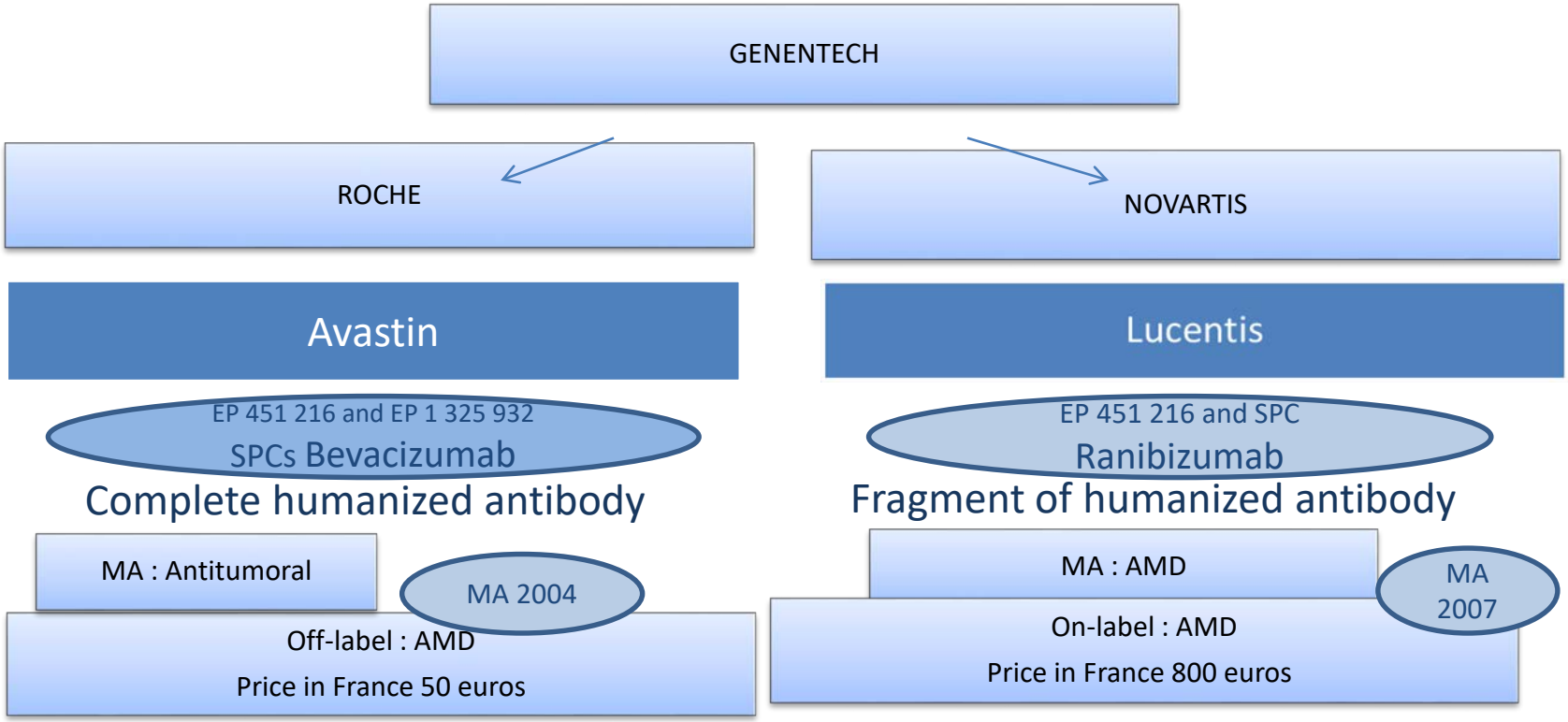
LUCENTIS / AVASTIN case



VEGF = Vascular Endothelial Growth Factor

Competition law versus Patent Law

Lucentis /Avastin case



Same therapeutic activities: Vascular Endothélial Growth Factor (VEGF) Inhibition
« interchangeable » Medicines but not « substitutable »,
differences : structures, administration route, dosage and side effects

Competition law versus Patent Law

The Italian Competition Authority fines ROCHE and Novartis on February 27, 2014.

- ROCHE € 90,6 Millions
- NOVARTIS € 92 Millions

- Decisions confirmed in Appeal (the Appeal Court seized the CJUE)
- Further action to claim damages by the Italian government (request of 1,6 billion €)
- Final agreement kept secret

Competition law versus Patent Law

In France

- March 19, 2015, the French Commission benefits/risks of the French National Health Authority (ANSM) gave a favorable opinion for a Recommendation of Temporary Use (RTU);

- June 24, 2015, ANSM issued an authorization of RTU for Avastatin in the treatment of Age-related Macular Degeneration without the Roche's consent .

- Roche appeal before the French Counsel of State :
  - September 21, 2015, refused after a short proceedings audience
  - Case on the grounds pending before the Counsel.

Competition law versus Patent Law

- Abuse of dominant position : **Art. 102 TFEU**
  - LOSEC case (Astra Zeneca)
    - Abuse of dominant position for :
      - Misleading information to National Patent Offices to obtain a SPC and impact on the duration of SPC : wrong 1st Marketing Authorization dated 1987 (France) and not 1988;
      - Withdrawal of the Marketing Authorization (for the capsules) and launch of tablets.
    - Fine: 60 Million (European Commission 2005)
    - Reduce fine : € 52,5 Million (CJUE case C-457/10 P)

Competition law versus Patent Law

- Abuse of dominant position : Art. 102 TFEU
  - XALATAN case (Pfizer)
    - Misuse of divisional patents, SPCs, warning letters, multiplication of law suits against generic manufacturers
    - Fine : € 10,6 Million

Control by the European Commission of Amicable Agreements between innovative and generic pharmaceutical manufacturers

Art. 101 TFEU

- Problem if :
  - Restriction of entry into the market of generics
  AND
  - Transfer of value

- Systematic annual survey of pharmaceutical patent settlements including pay-for-delay agreements published by the European Commission

(http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/)

Control by the European Commission of Amicable Agreements between innovative and generic pharmaceutical manufacturers

Art. 101 TFEU

- Example : PERINDOPRIL case (SERVIER)

Waiver of patent infringement and entering into law suits, payment of royalties.

Laboratory name	Fines (Million euros)
Servier	330
Lupin	40
Matrix Laboratories	17,1
Teva	15,5
Unichem and Niche	13,9
Krka	10

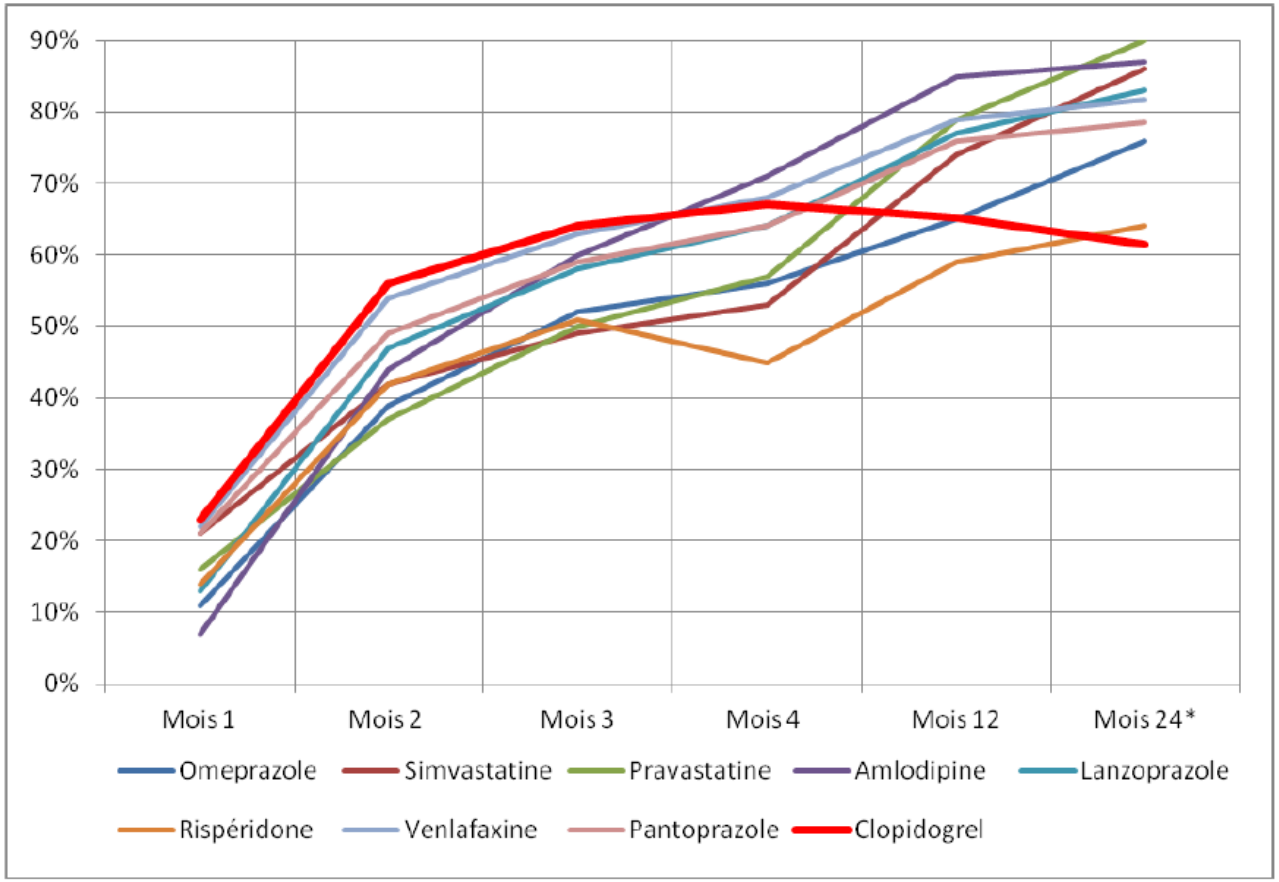
Information/Denigration

- PLAVIX case (SANOFI) Art. 102 TFEU

  - denigration of a generic product under a different salt form.
  - Abuse of dominant position in the framework of a global strategy of defamation comprising an incentive for the doctors to specify on their prescription the mention “non-substitutable”.
  - Incent of pharmacists to substitute in favor of their own generic subsidiary (Winthrop) through reward programs.
  - Fine : € 40.6 Million

Information/Denigration

- PLAVIX case (SANOFI) Art. 102 TFEU



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Decision n° 13-D-11

Information/Denigration

- PLAVIX case (SANOFI) Art. 102 TFEU

Molécule	Date de générification	Mois 1	Mois 2	Mois 3	Mois 4	Mois 12	Mois 24*
Omeprazole	Avril 2004	11 %	39 %	52 %	56 %	65 %	76 %
Simvastatine	Mai 2005	21 %	42 %	49 %	53 %	74 %	86 %
Pravastatine	Juillet 2006	16 %	37 %	50 %	57 %	79 %	90 %
Amlodipine	Août 2007	7 %	44 %	60 %	71 %	85 %	87 %
Lanzoprazole	Déc. 2007	13 %	47 %	58 %	64 %	77 %	83 %
Rispéridone	Déc. 2007	14 %	42 %	51 %	45 %	59 %	64 %
Venlafaxine	Déc. 2008	22 %	54 %	63 %	68 %	79 %	82 %
Pantoprazole	Mai 2009	21 %	49 %	59 %	64 %	76 %	79 %
Clopidogrel	Octobre 2009	23 %	56 %	64 %	67 %	65 %	62 %

http://www.autoritedelaconcurrence.fr/user/standard.php?id_rub=483&id_article=2091
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Information/Denigration

- SUBUTEX case (Schering-Plough)
  Art. 102 TFEU

  – Global selective strategy of pharmacist loyalty program via differentiated commercial offers.

  – Fine : € 15.3 Million

Decrease of medicine price after generic launch

- For the generic product : automatic reduction of **60 %** below the original brand price at the moment of its market entry, and 18 months later further decrease by **7%**

- For the original product : consecutive reduction imposed by CEPS (Economical Committee of Health products) :

  - **reduction 20%** at the moment of generic market entry and
  - reduction **12,5%** 18 months later

- Influence of a pending infringement law suit on the price of the original product

Conclusion

CJUE in its judgement C-457/10P (Astrazeneca) expressed that only were acceptable :

- "…practices coming within the scope of competition on the merits, which is such as to benefit consumers.."

Thank you for your attention