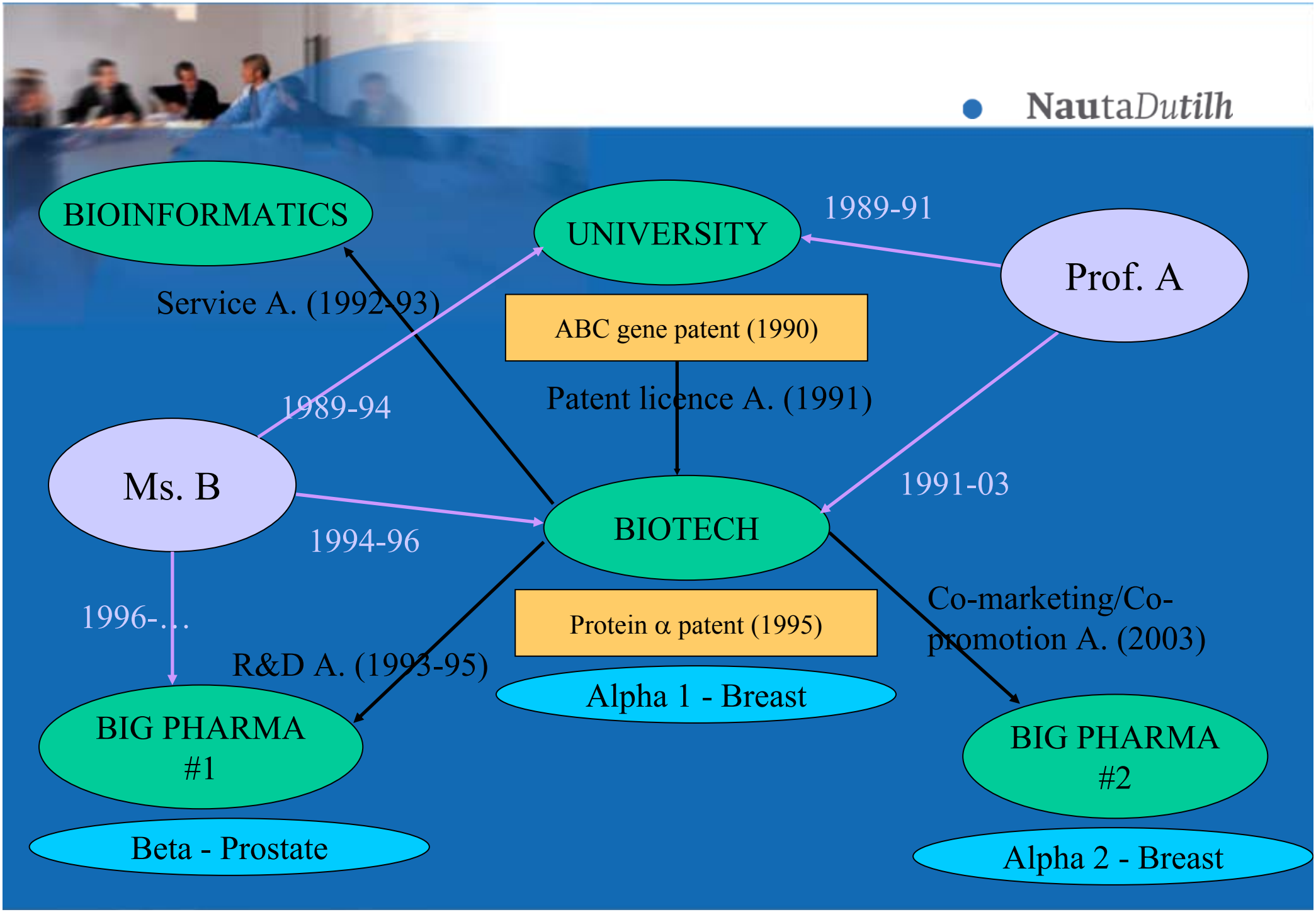
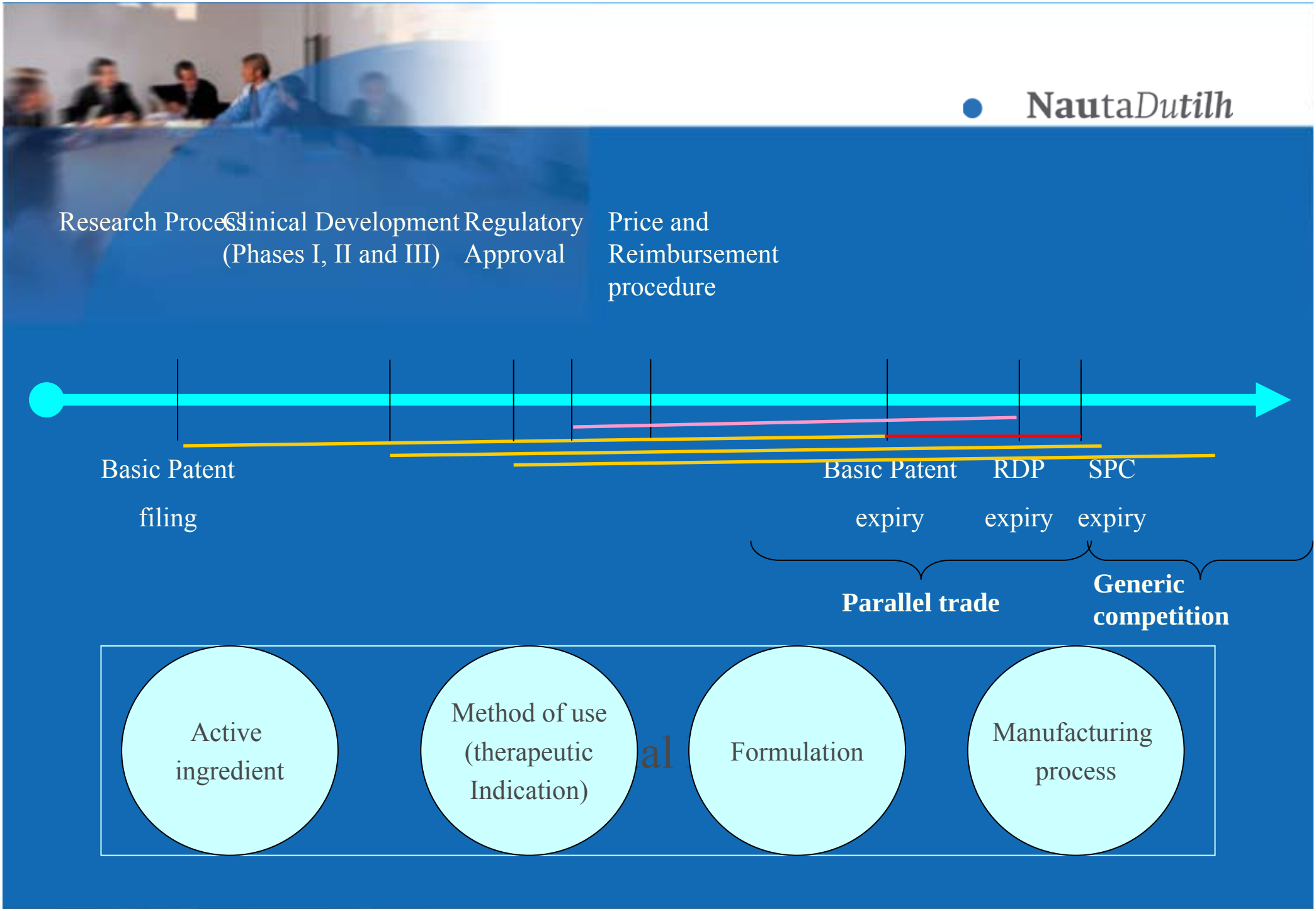
NautaDutilh

LIFE SCIENCES

LEGAL WORKSHOPS


NautaDutilh
BIOINFORMATICS
UNIVERSITY
1989-91
Prof. A
Service A. (1992-93)
ABC gene patent (1990)
Patent licence A. (1991)
1989-94
Ms. B
1991-03
BIOTECH
1994-96
1996-…
Protein α patent (1995)
Co-marketing/Co-promotion A. (2003)
R&D A. (1993-95)
Alpha 1 - Breast
BIG PHARMA #1
BIG PHARMA #2
Beta - Prostate
Alpha 2 - Breast


NautaDutilh
Research Process
Clinical Development (Phases I, II and III)
Regulatory Approval
Price and Reimbursement procedure
Basic Patent filing
Basic Patent expiry
RDP expiry
SPC expiry
Parallel trade
Generic competition
Active ingredient
Method of use (therapeutic Indication)
Formulation
Manufacturing process

NautaDutilh

Exclusivity Workshop

- Chair: William Bird (Bird Goën & Co)

- Fabienne Brison
- Olivier Lemaire
- Benoît Strowel

1989-1990

- Professor A is a well-known scientist working in the biogenetic department at a Belgian university ("UNIVERSITY"). Prof. A and his team, including his main assistant, Ms. B, have been working on new targets for cancer therapy. In the course of their research, Prof. A and his group identify a gene (the ABC gene) which, when modified to be over-expressed (by mutation in its promoter) causes breast cancer in mice. The ABC gene is also identified in humans.
- Prof. A considers filing a patent application with respect to the ABC gene.
- During that period, Prof. A also submits a paper for peer review with a leading scientific journal.

NautaDutilh

Questions:

- What can be protected? The gene per se? The use of the gene for the treatment of cancer (or more specifically for breast cancer)? The use of the gene for diagnostic?
- Who is to be named inventor?
- What and when to publish research results?

Legal issues:

- Patentability of gene sequences
- Patentability of diagnostic methods (Enlarged Board of Appeal case law)
- Conditions for patentability (in particular novelty re publication of article + grace period in the US versus in EU)

Novelty

- Art. 54(2) European Patent Convention (EPC)

  (…) The state of the art shall comprise everything made available to the public (…)

Inventive step

- Art. 56 EPC

  (…) it is not obvious to a skilled person in the art (…)

Industrial applicability

- Art. 57 EPC

  (…) if it can be made or used in any kind of industry (…)

Exclusions of therapy and diagnostic methods

- Art. 52(4) EPC

  Methods of treatment of the human or animal body by surgery therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions (…)

‘Ordre public’ and morality

- Art. 53 EPC

  Inventions shall not be granted in respect of:

  (a) Inventions the publication or exploitation of which would be contrary to « ordre public » or morality (…)

NautaDutilh

Sufficiency (enablement)

- Art. 83 EPC

  The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

NautaDutilh

Biotechnological inventions

- Rule 23b EPC (e) 2

  (…) the sequence or partial sequence of a gene, may constitute a patentable invention

NautaDutilh

Claiming priority

- Art. 87 EPC

  (…) shall enjoy, for the purpose of filing a European patent application, in respect of the same invention, a right of priority

NautaDutilh

ABC gene patent application

- EP 123.456 covering the mutated ABC gene and the use of the mutated ABC gene for the diagnosis of cancer and for the development of medicinal products for the treatment of cancer, including proteins and antibodies capable of inhibiting the gene product of the mutated gene.
- Applicant: UNIVERSITY
- Filing date: 1 March 1990
- Inventor: Prof. A
- Designated countries: All EU (except Spain and Portugal) + Switzerland

NautaDutilh

Sufficiency (enablement)

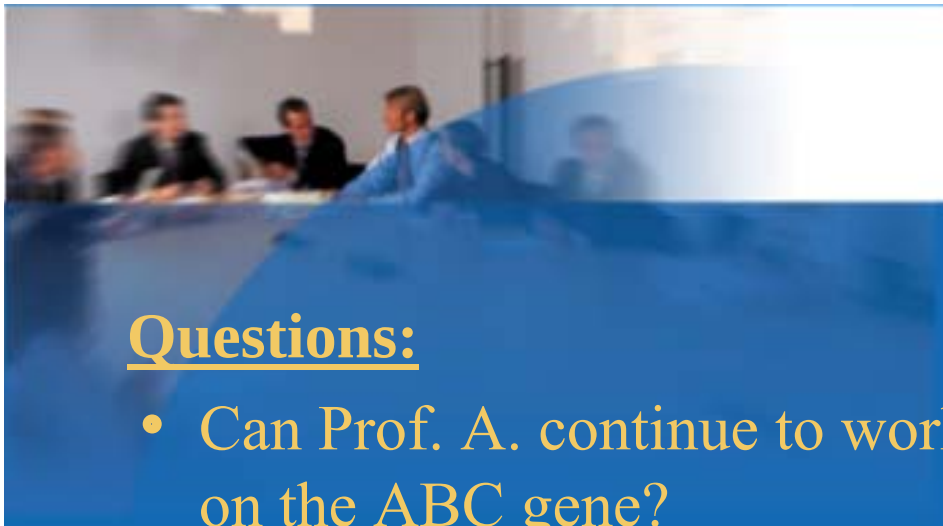
- Art. 83 EPC

  The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

NautaDutilh

1991

- Prof. A sets up a company (“BIOTECH”). He also continues to teach at UNIVERSITY.
- Seed capital is provided by Prof. A, UNIVERSITY and regional subsidies
- Prof. A continues to exchange information with former colleagues from UNIVERSITY



NautaDutilh

Questions:

- Can Prof. A. continue to work on the ABC gene?
- What is the status (ownership) of the information exchanged between Prof. A and his former colleagues from UNIVERSITY?

Legal issues:

- Licensing agreement on UNIVERSITY's patent application
- Confidentiality agreements and ownership of know-how/IP generated by the flow of information between UNIVERSITY and BIOTECH
- Flemish v. Walloon rules regarding ownership of university inventions

Criminal sanctions

- Art. 309 of Belgian Criminal Code:

  The person who communicates secrets belonging to the manufacture where he worked or is still working to others in a wilful or fraudulent way, shall be punished with imprisonment and a fine (…)

Employees

- Art. 17, 3°, a Employment Agreements Act of 3 July 1978

  The employee is obliged to (…) during and after the employment contract to abstain from divulging fabric secrets, trade secrets or secrets concerning personnel or confidential matters which he learns in the execution of his employment (…)

NautaDutilh

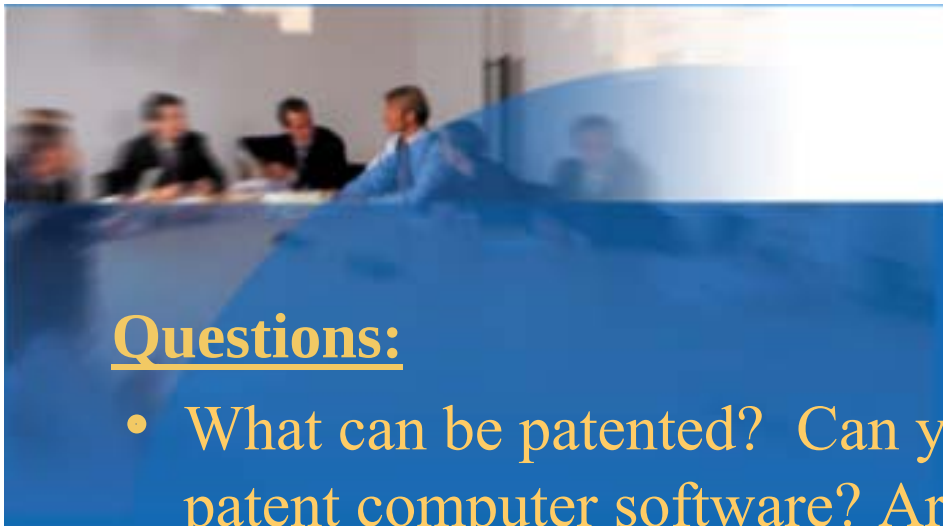
Patent License Agreement

- UNIVERSITY grants exclusive license rights to BIOTECH under its patent portfolio covering the ABC gene
- Geographic coverage : world

NautaDutilh

1992

- BIOTECH is contacted by a company specialized in bioinformatics (“BIOINFORMATICS”)
- BIOINFORMATICS developed mathematical and informatics models for combining data issued from gene libraries and proteomics research to identify possible drug candidates capable of binding to specific gene targets. BIOINFORMATICS also owns a patent on a screening method based on this bioinformatics tool.



NautaDutilh

Questions:

- What can be patented? Can you patent computer software? Are mathematical methods or algorithms patentable?
- Is there any alternative form of protection besides patent protection?

Legal issues:

- Patentability of in silico embodiments
- Mathematical methods
- Patentability of computer software
- Protection of the structure and/or the content of databases
- Protection of computer software via copyrights

NautaDutilh

Mathematical methods and software

- Art. 52(2) EPC

  The following shall not be regarded as inventions: (…)

  - mathematical methods

  - programs for computers

Database definition

- Art. 1(2) Directive 96/9 (Database Directive)

  'Database' shall mean a collection of independent works, data or other materials arranged in a systematic or methodical way and individually accessible by electronic or other means.

Database and copyrights

- Art. 3 Directive 96/9

  (1) Databases which, by reason of the selection or arrangement of their contents, constitute the author's own intellectual creation shall be protected as such by copyright.

  (2) The copyright protection of databases (…) shall not extend to their contents and shall be without prejudice to any rights subsisting in those contracts themselves.

Database and *sui generis* right

- Art. 7(1) Directive 96/9

  Member States shall provide for a right for the maker of a database which shows that there has been qualitatively and/or quantitatively a substantial investment in either the obtaining, verification or presentation of the contents to prevent extraction and/or re-utilization of the whole or of a substantial part, evaluated qualitatively and/or quantitatively, of the contents of that database.

Database and *sui generis* right (2)

- Art. 7(5) Directive 96/9

  The repeated and systematic extraction and/or re-utilization of insubstantial parts of the contents of the database implying acts which conflict with a normal exploitation of that database or which unreasonably prejudice the legitimate interests of the maker of the database shall not be permitted.

Exception

- Art. 9(b) Directive 96/9

  Member States may stipulate that lawful users of a database which is made available to the public in whatever manner may, without the authorization of its maker, extract or re-utilize a substantial part of its contents:(…)

  In the case of extraction for the purposes of illustration for teaching or scientific research, as long as the source is indicated and to the extent justified by the non-commercial purpose to be achieved (…)

Duration

- Art. 10(1) Directive 96/9

  The right provided for in Article 7 shall run from the date of completion of the making of the database. It shall expire fifteen years from the first of January of the year following the date of completion.

Beneficiary

- Art. 11 Directive 96/9

  (1) The right provided for in Article 7 shall apply to database whose makers or rightholders are nationals of a Member State or who have their habitual residence in the territory of the Community.

(2) Paragraph 1 shall also apply to companies and firms formed in accordance with the law of a Member State and having their registered office, central administration or principal place of business within the Community; however, where such a company or firm has only its registered office in the territory of the Community, its operations must be genuinely linked on an ongoing basis with the economy of a Member State.

(3) Agreements extending the right provided for in Article 7 to databases made in third countries and falling outside the provisions of paragraphs 1 and 2 shall be concluded by the Council acting on a proposal from the Commission.

Software and copyright

- Art. 1 Directive 91/250 (Software Directive)

  (1) In accordance with the provisions of this Directive, Member States shall protect computer programs, by copyright, as literary works within the meaning of the Berne Convention for the Protection of Literary and Artistic Works. (…)

  (3) A computer program shall be protected if it is original in the sense that it is the author's own intellectual creation.

Scope of protection

- Art. 4 Directive 91/250

  Subject to the provisions of Articles 5 and 6, the exclusive rights of the rightholder within the meaning of Article 2, shall include the right to do or to authorize:

  (a) the permanent or temporary reproduction (…)

(b) the translation, adaptation, arrangement and any other alteration of a computer program and the reproduction of the results thereof (…)

(c) any form of distribution to the public, including the rental, of the original computer program or of copies thereof (…)

Software technical protection

- Art. 7(1)(c) Directive 91/250

  Without prejudice to the provisions of Articles 4, 5 and 6, Member States shall provide, in accordance with their national legislation, appropriate remedies against a person committing any of the acts listed in subparagraphs (a), (b) and (c) below: (…)

  (c) any act of putting into circulation, or the possession for commercial purposes of, any means the sole intended purpose of which is to facilitate the unauthorized removal or circumvention of any technical device which may have been applied to protect a computer program."

Database technical protection

- Art. 6 Information Society Directive 2001/29 (Information Society Directive)

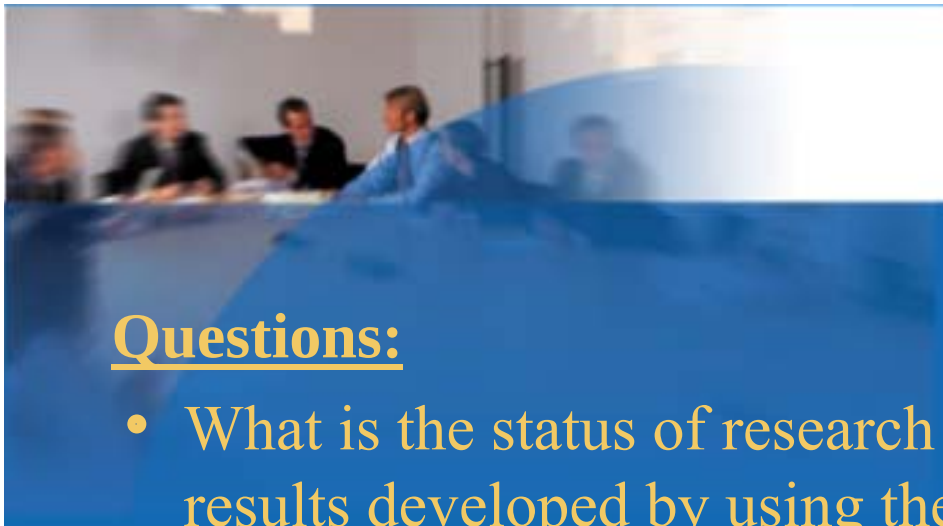
  (1) Member States shall provide adequate legal protection against the circumvention of any effective technological measures, which the person concerned carries out in the knowledge, or with reasonable grounds to know, that he or she is pursuing that objective. (…)

  (4) (…) When this Article is applied in the context of Directives (…) 96/9/EC, this paragraph shall apply *mutatis mutandis*.

NautaDutilh

1993-1995

- Contract between BIOINFORMATICS and BIOTECH whereby the latter will pay royalties on leads identified through BIOINFORMATICS' technology.
- BIOINFORMATICS identifies 3 families of drug candidates (proteins α, β, and γ) capable of binding to the ABC gene
- BIOTECH concludes an R&D Agreement with BIG PHARMA #1 for further research on the protein families identified by BIOINFORMATICS.



NautaDutilh

Questions:

- What is the status of research results developed by using the BIOINFORMATICS tools?

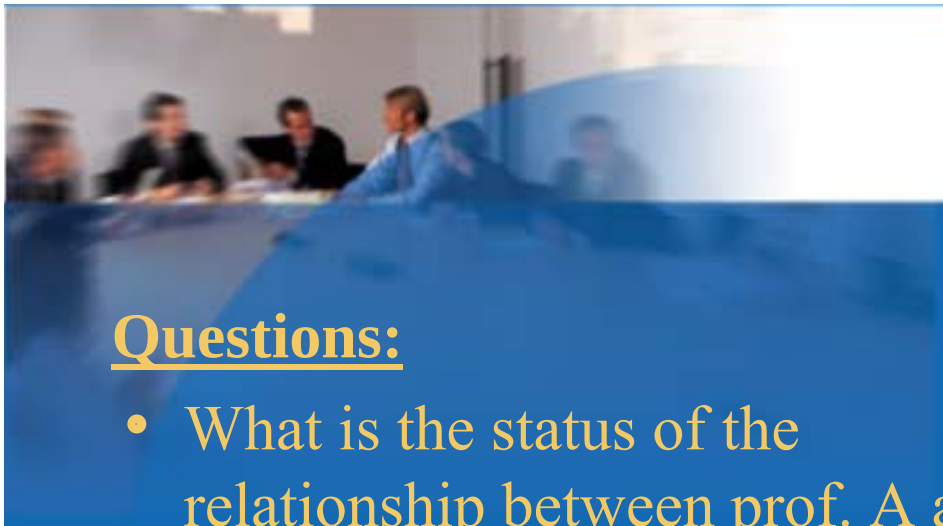
Legal issues:

- Ownership of results developed by BIOINFORMATICS.
- Reach-through claims on further developments made on the basis of the results obtained by using the BIOINFORMATICS method.

NautaDutilh

1994

- Ms. B's contract with UNIVERSITY is not renewed. She continues to assist Prof. A and BIOTECH as independent researcher. She participates actively in various key experiments with protein α.



NautaDutilh

Questions:

- What is the status of the relationship between prof. A and Ms. B (ownership of research results; confidentiality)?

Legal issues:

- Ownership of joint research with independent researchers.

NautaDutilh

1995

- BIG PHARMA #1 decides to put an end to the R&D Agreement.
- BIOTECH identifies protein α as suitable for inhibiting the over-expression of the ABC gene
- BIOTECH considers filing a patent application with respect to protein α

NautaDutilh

Questions:

- Issues of novelty/inventiveness with the ABC gene patent (claims relating to specific proteins capable of inhibiting the over-expression of the ABC gene)?

Legal issues:

- Claims to pharmaceuticals
- Second medical use claims

Exceptions to novelty

- Art. 54 (5) EPC

  (…) shall not exclude the patentability of a substance or composition comprised in the state of the art for use in a method referred to in Art. 52 paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

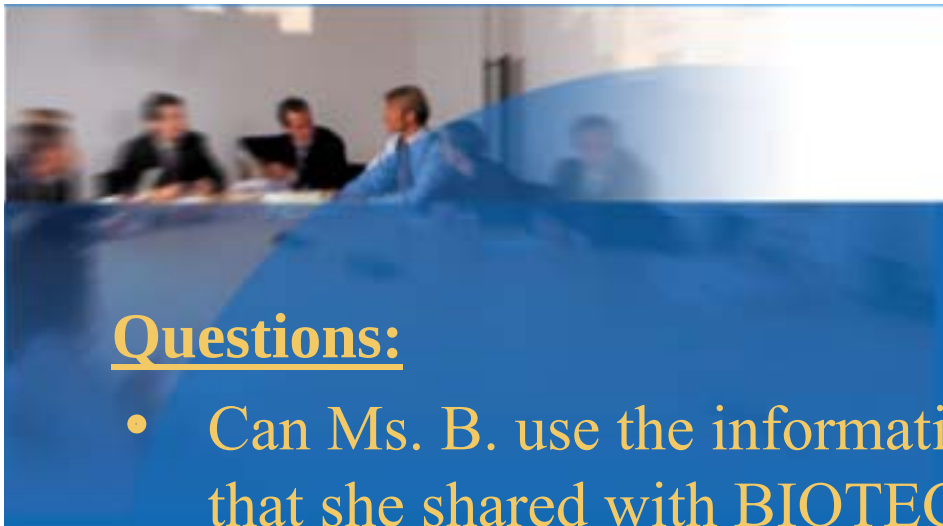
NautaDutilh

Protein α patent application

- EP 654.321 covering protein α as well as its use for the treatment of breast cancer
- Applicant: BIOTECH
- Filing date: 1 June 1995
- Inventor: Prof. A
- Designated countries: All EU + Switzerland + CZ

1996

- BIG PHARMA #1 files a patent application for the use of protein β for the treatment of prostate cancer
- Ms. B is hired by BIG PHARMA #1 as lead researcher for the further development of protein β



NautaDutilh

Questions:

- Can Ms. B. use the information that she shared with BIOTECH in her new job?
- Who owns the rights on the development made jointly between BIOTECH and Ms. B.?

Legal issues:

- Confidentiality and know-how
- Protection of trade and industrial secrets by employees
- Ownership of know-how by employees or independant researchers
- Survival of confidentiality clause after termination of contracts

NautaDutilh

1996-1998

- BIOTECH and BIG PHARMA #1 initiate pre-clinical testing and clinical trials with protein α and β respectively
- The ABC gene patent is issued by the EPO
- BIG PHARMA #1 files an opposition for alleged lack of novelty. It appears that Prof. A discussed the ABC gene during an international scientific conference in the US few days prior to filing the priority patent application

Novelty

- Art. 54(2) EPC

  (…) The state of the art shall comprise everything made available to the public (…)

NautaDutilh

Abuse of confidentiality

- Art. 55 EPC

  (…) a disclosure shall not be taken into consideration if it occurred no earlier than six months before the filing (…) and was due to, or in consequence of:
  (a) an evident abuse in relation to the applicant (…)

NautaDutilh

Questions:

- Can BIOTECH rely on the ABC gene patent to block clinical trials on protein β? Would this be different if the ABC gene patent was not yet issued?
- What are the possible legal grounds for opposition?
- What is the impact on BIOTECH if the ABC gene patent is invalidated by the EPO? And what if the ABC gene patent is upheld by the EPO?

Legal issues:

- Patent infringement and experimental use exemption
- Novelty and grace period (US versus Europe)
- Consequences of invalidity of ABC gene patent on BIOTECH and on BIG PHARMA #1
- Other forms of exclusivity;
- Strategic legal consideration in defending the opposition.

NautaDutilh

Clinical trials and patent infringement

- Art. 28 of Belgian Patent Act

  Acts done for experimental purposes on the subject-matter of the patented invention

On and/or with

- Art. 11 of draft law of 21 September 2004

  Acts done for scientific purposes on or with the subject-matter of the patented invention

NautaDutilh

Clinical trials and generic filings

- Art. 10(6) Directive 2001/83 as amended by Directive 2004/27/EC (as from October 2005)
  - "Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products"

NautaDutilh

1999-2003

- Phase II-III clinical trials are performed with protein α for the breast cancer indication
- The protein α patent is issued by the EPO
- It appears that protein α is also effective for the treatment of a rare form of cancer
- BIOTECH's board is pressing for obtaining a marketing authorization as soon as possible; compassionate use programs are envisaged

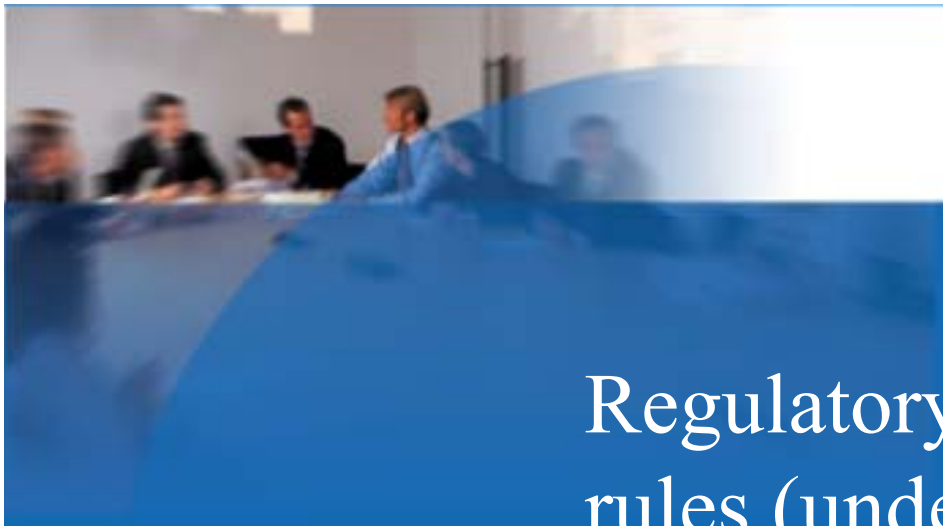
NautaDutilh

Questions:

- Are the results of preclinical and clinical trials of BIOTECH protected and for how long?
- Is a new (orphan) indication likely to increase exclusivity?
- Are there any downsides to initiating compassionate use programs in the Community prior to the first authorization?
- Can BIOTECH prevent a third party to obtain a parallel marketing authorization?

Legal issues:

- Regulatory data protection
- Orphan medicinal product exclusivity
- Bibliographic procedure and generic abridged authorizations
- Complementary nature of regulatory and patent rights?



Regulatory Data Protection – general rules (under current law)

- Art. 10(1)(a)(iii) Directive 2001/83

  1. In derogation of Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

  (a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

  (iii) that the medicinal product is essentially similar to a medicinal product which has been authorized within the Community, in accordance with Community provisions in force, for not less than [6/10] years and is marketed in the Member State for which the application is made. (…)

RDP for centralized products

- Art. 13(4) of Regulation 2309/93

  4. Medicinal products which have been authorized by the Community in accordance with the provisions of this Regulation shall benefit from the ten-year period of protection referred to in point 8 of the second paragraph of Article 4 of Directive 65/65/EEC.

NautaDutilh

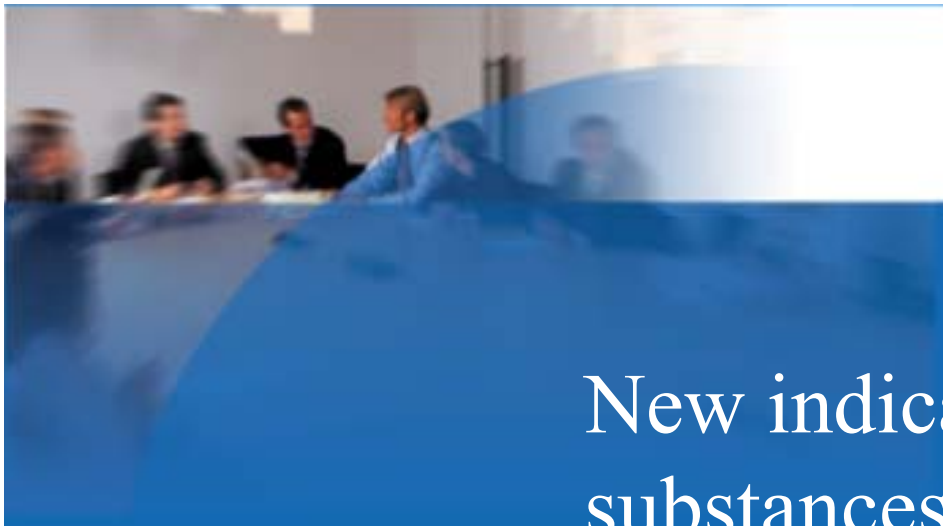
RDP rules under future legislation

- Art. 10(1) Directive 2001/83 as amended by Directive 2004/27

  1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.



New indications for well-established substances

- Art. 10(5) of Directive 2001/83 as amended

  5. In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

NautaDutilh

OTC switch

- Art. 74a of Directive 2001/83 as amended

  Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

RDP for centralized products

- Art. 14(11) of Regulation 726/2004 (as from November 2005)

  Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection (…)

(…) and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

Biosimilars (as from 20 November 2005)

- Art. 10(4) Directive 2001/83 as amended

  4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided

Orphan Marketing Exclusivity

- Art. 8 Regulation 141/2000

  (1) (…) without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

(3) By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

NautaDutilh

2003

- Marketing authorization applications are filed in Switzerland in early January
- MAA's are filed in the EU, US and Japan in 2Q03
- Due to additional data requirements, the EMEA procedure is suspended
- A marketing authorization is issued in Switzerland on 1 October 2003

NautaDutilh

Questions:

- What is the relationship between the marketing authorization and the exclusivity status of the medicinal product?
- What is the duration of an SPC?
- Can a Swiss authorization reduce IP protection in the EU?

Legal issues:

- SPC and Swiss/Liechtenstein issue
- Influence on RDP periods

Supplementary Protection Certificate

- Art. 13(1) Regulation 1768/92

  1. The certificate shall take effect at the end of the lawful term of the basic patent for a period equal to the period which elapsed between the date on which the application for a basic patent was lodged and the date of the first authorization to place the product on the market in the Community reduced by a period of five years.

NautaDutilh

2006

- A centralized marketing authorization is issued to BIOTECH by the Commission for protein α
- A centralized marketing is issued to BIG PHARMA #2 one week later
- An SPC application is filed in all the EU Member States

NautaDutilh

Questions:

- What does the regulatory department need to do when a marketing authorization is obtained in a given Member State?
- Is there a difference between a centralized and a mutual recognition marketing authorization?
- Is the scope of protection of an SPC equal to the scope of the basic patent?

Legal issues:

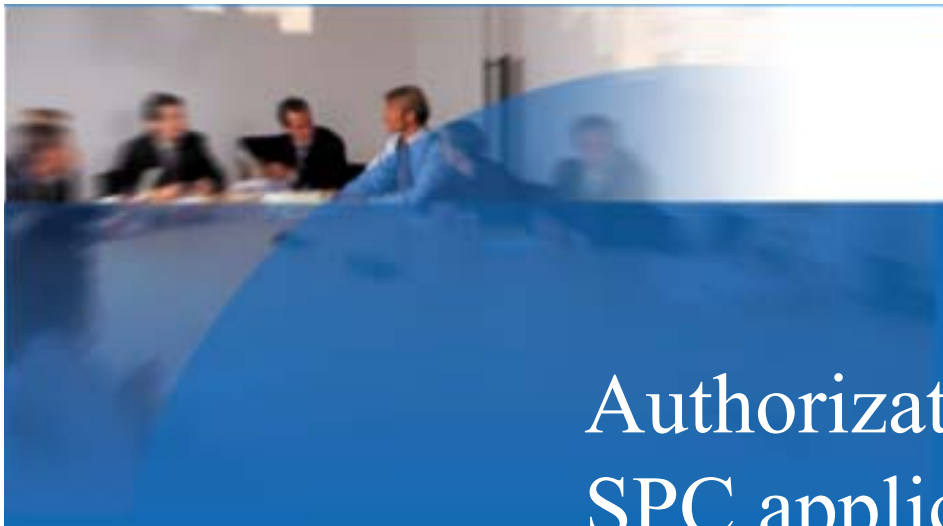
- 6-months period for filing SPC application
- Centralized products and new Member States
- Definition of "product" under SPC Regulation
- Starting point of RDP
- Duration of RDP

NautaDutilh

Supplementary Protection Certificate

- Article 7(1) Regulation 1768/92

  The application for a certificate shall be lodged within six months of the date on which the authorization referred to in Article 3 (b) to place the product on the market as a medicinal product was granted.



Authorization in the country where SPC application is filed

- Art. 3 (b) Regulation 1768/92

  A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:
  (b) a valid authorization to place the product on the market as a medicinal product has been granted in accordance with Directive 65/65/EEC or Directive 81/851/EEC, as appropriate;

Definition of Product

- Art. 1(b) Regulation 1768/92

  'product' means the active ingredient or combination of active ingredients of a medicinal product;

NautaDutilh

Contracts Workshop

- Chair: Bernard Majoie (Blue Medical)

- Thomas Chellingsworth
- Philippe Péters
- Patrice Vanderbeeken

NautaDutilh

1989-1990

- The ABC gene invention is being developed at UNIVERSITY
- A patent application is filed and scientific articles are submitted to editors for peer review

NautaDutilh

Questions:

- Who owns the IP rights on the invention?
- Who owns the rights on the article?
- How to protect confidential information?

legal issues:

- Ownership of inventions made by:
  - Employees
  - Universities
  - Third parties
- Ownership of copyright
- Confidentiality agreements researchers/editor/peer reviewers

Ownership of inventions

- Art. 8 Patent Act of 28 March 1984

  The right to a patent shall belong to the inventor or his successor in title.

  If two or more persons have made an invention independently of each other, the right to the patent shall belong to the person whose patent application has the earliest date of filing.

  For the purpose of proceedings before the Office, the application shall be deemed to be entitled to exercise the right of the patent.

Moral right of inventor

- Art. 12 Patent Act of 28 March 1984

  The inventor shall have the right to be named as such in the patent; he may also oppose such naming.

University inventions

- Art. 169*ter* §1 Flemish Decree of 12 June 1991 with regard to Universities

  Property rights in discoveries made in the course of their research by university faculty members and researchers affiliated with the Scientific Research Fund as well as by the holders of research grants from the Vlaams Instituut voor de Bevordering van het Wetenschappelijk-Technologisch Onderzoek in de Industrie or a Flemish university shall belong exclusively to the university. (…)

NautaDutilh

(…) In this same vein, the university acquires all property rights pertaining to discoveries made by other persons engaged in research at the university insofar as such an assignment of rights is confirmed in writing with the interested parties. The term "discoveries" shall be construed to mean: inventions capable of being patented, cultures, designs and models, topographies and semiconductors, and computer programs and databases that can be put to commercial use with a view to an industrial or agricultural application.

Moral rights of authors

- Art 1(2) Copyright Act of 30 June 1994

  The author of a literary work shall enjoy an inalienable moral right in his work. (…)

Assignment of copyrights

- Art. 3(1) Copyright Law of 30 June 1994

  (…) All contracts affecting the author shall require written form.

  Contractual provisions relating to copyright and to its modes of exploitation shall be interpreted restrictively. (…)

  The author's remuneration, the scope and duration of the assignment shall be set out explicitly for each mode of exploitation. (…)

Employee's works

- Art. 3 Copyright Law of 30 June 1994

  (3) Where the works are created by an author under employment contract or a service relationship, the economic rights may be assigned to the employer on condition that assignment of such rights is explicitly laid down and that the creation of the work falls within the scope of the contract or service relationship. (…)

In such cases, the fourth (…) subparagraph of paragraph 1 (...) shall not apply.

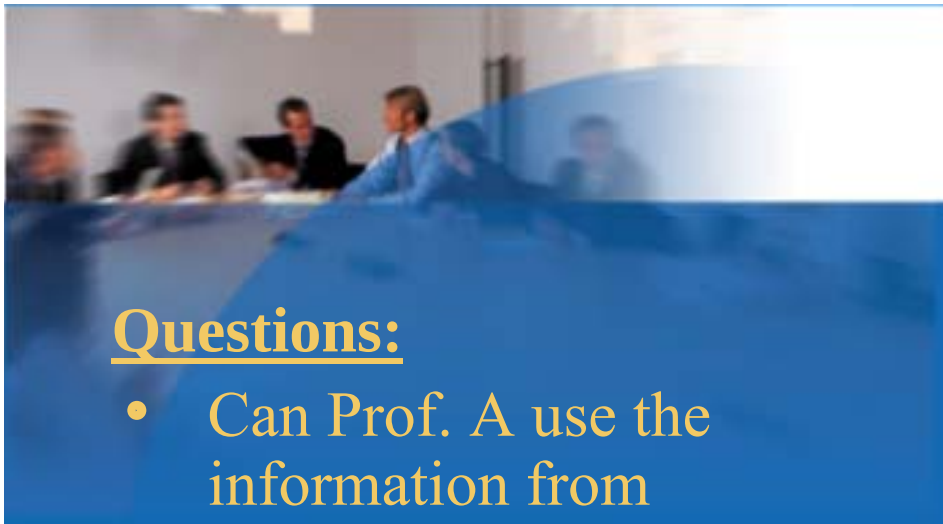
The clause affording the copyright assignee the right to exploit a work in a form that is unknown at the date of contract or of the appointment to the service relationship shall be explicit and shall lay down participation in the profits obtained from such exploitation.

The scope and conditions of transfer may be laid down in collective agreements.

NautaDutilh

1991

- BIOTECH is set up to develop novel biologic compounds capable of inhibiting the over-expression of the ABC gene, which is held to be responsible for causing breast cancer
- Prof. A continues to exchange information with his former research team at UNIVERSITY



NautaDutilh

Questions:

- Can Prof. A use the information from UNIVERSITY? What are the risks of "loose" relationships between UNIVERSITY and spin-off?
- Who owns IP rights?
- How to deal with transfer of IP rights (including know-how)?

Legal issues:

- Confidentiality agreement between BIOTECH and UNIVERSITY
- Ownership and joint inventions
- Important elements of Patent and Know-how License Agreement
- Technology Transfer Block Exemption Regulation

Prohibited agreements

- Art. 81(1) EC Treaty

  1. The following shall be prohibited as incompatible with the common market: all agreements between undertakings, decisions by associations of undertakings and concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the common market. (…)

Exemptions

- Art. 81(3) EC Treaty

  The provisions of paragraph 1 may, however, be declared inapplicable in the case of:

  - any agreement or category of agreements between undertakings;
  - any decision or category of decisions by associations of undertakings;
  - any concerted practice or category of concerted practices.

- which contributes to improving the production or distribution of goods or to promoting technical or economic progress, while allowing consumers a fair share of the resulting benefit, and which does not:

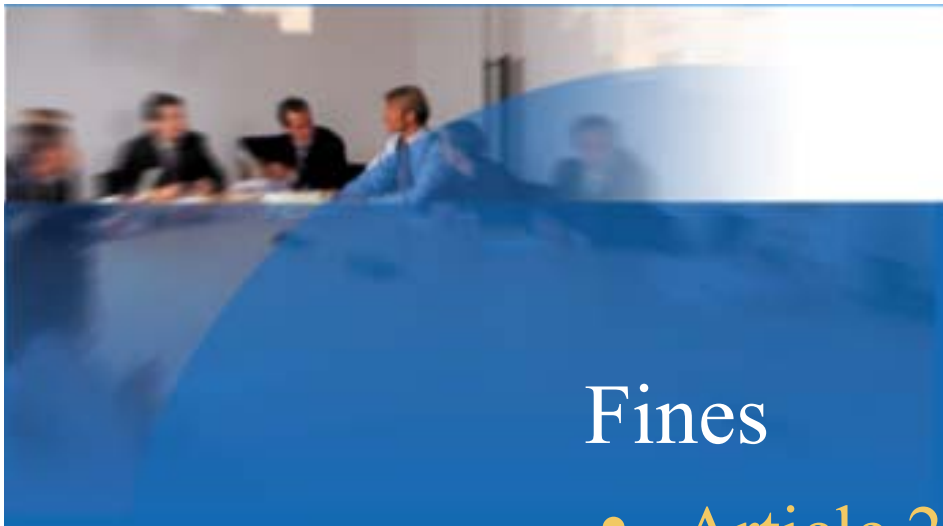
  (a) impose on the undertakings concerned restrictions which are not indispensable to the attainment of these objectives;

  (b) afford such undertakings the possibility of eliminating competition in respect of a substantial part of the products in question.

Sanctions

- Article 81(2) EC

  Any agreements or decisions prohibited pursuant to this Article shall be automatically void.



Fines

- Article 23(2) Regulation 1/2003

  The Commission may by decision impose fines on undertakings and associations of undertakings where, either intentionally or negligently:

  (a) they infringe Article 81 or Article 82 of the Treaty (…)

  For each undertaking and association of undertakings participating in the infringement, the fine shall not exceed 10 % of its total turnover in the preceding business year.

Technology Transfer Block Exemption

- Art. 2 Commission Regulation 772/2004

  Pursuant to Article 81(3) of the Treaty and subject to the provisions of this Regulation, it is hereby declared that Article 81(1) of the Treaty shall not apply to technology transfer agreements entered into between two undertakings permitting the production of contract products.

Competing undertakings

- Art. 2(1) Commission Regulation 772/2004

  1. Where the undertakings party to the agreement are competing undertakings, the exemption provided for in Article 2 shall apply on condition that the combined market share of the parties does not exceed 20 % on the affected relevant technology and product market.

Non competing undertakings

- Art. 2(2) Commission Regulation 772/2004

  2. Where the undertakings party to the agreement are not competing undertakings, the exemption provided for in Article 2 shall apply on condition that the market share of each of the parties does not exceed 30 % on the affected relevant technology and product market.

Hardcore and Excluded Restrictions

- Art. 4(1)(d) and 5(2) Commission Regulation 772/2004

  The restriction of the licensee's ability to exploit its own technology or the restriction of the ability of any of the parties to the agreement to carry out research and development, unless such latter restriction is indispensable to prevent the disclosure of the licensed know-how to third parties.

Hardcore and Excluded Restrictions (2)

- Art. 5(1)(c) Commission Regulation 772/2004

  Any direct or indirect obligation on the licensee not to challenge the validity of intellectual property rights which the licensor holds in the common market, without prejudice to the possibility of providing for termination of the technology transfer agreement in the event that the licensee challenges the validity of one or more of the licensed intellectual property rights.

Outside the safe harbour

- Para 130 Comm. Guidelines on the application of Article 81 of the EC Treaty to technology transfer agreements

  There is no presumption of illegality of agreements that fall outside the scope of the block exemption provided that they do not contain hardcore restrictions of competition. In particular, there is no presumption that Article 81(1) applies merely because the market share thresholds are exceeded. Individual assessment based on the principles described in these guidelines is required.

NautaDutilh

Exclusive licensing between competitors

- Para 164 Comm. Guidelines

  Non-reciprocal exclusive licensing between competitors is block exempted up to the market share threshold of 20 %. Above the market share threshold it is necessary to analyse what are the likely anti-competitive effects of such exclusive licensing.

Exclusive licensing between non-competitors

- Para 165 Comm. Guidelines

  Exclusive licensing between non-competitors — to the extent that it is caught by Article 81(1) (64) — is likely to fulfil the conditions of Article 81(3).

NautaDutilh

1992

- BIOINFORMATICS approaches BIOTECH for a collaboration regarding further research on the ABC gene
- 3 families of leads (proteins α, β and γ) are identified by BIOINFORMATICS

NautaDutilh

Questions:

- Are there any confidentiality issues?
- Are results generated by BIOINFORMATICS protectable?
- Who is the owner of the leads identified with BIOINFORMATCIS' technology?

Legal issues:

- Confidentiality agreement
- Protection of technology v. protection of results
- (Co-)ownership

Co-ownership of patents (1)

- Art. 43 of Patent Act of 28 March 1984

  §1.Unless agreed otherwise, co-ownership of a patent application or of a patent shall be governed by the provisions of this Article.

  §2. Each co-owner shall have the right personally to exploit the invention.

  No co-owner may burden a patent application or a patent with a right, grant a license to exploit or institute infringement proceedings without the agreement of the other co-owner or, failing agreement, the authorization of a court.

The indivisible shares shall be deemed equal.

If a co-owner wishes to assign his share, the other co-owner shall have a right of pre-emption for a period of three months from the notification of the intended assignment.

Either party may request the presiding judge to appoint an expert in accordance with the rules of judgments in chambers in order to determine the terms of assignment. The expert's conclusions shall bind the parties save when, within a month of their notification, one of the parties, announces that he renounces the assignment; in which case that party shall bear the cost thereof.

- §3. Section I and IV of Chapter VI of the First Title of Book III of the Civil Code shall not apply to co-ownership of a patent application or a patent.
- §4. A co-owner of a patent application or of a patent may notify the other co-owners that he relinquishes his share in their favour. Once such relinquishment has been entered in the Register, such co-owner shall be relieved of all obligations in respect of the other co-owners; the latter shall divide the relinquished share among them in proportion to their rights in the joint property, except when otherwise agreed.

Co-ownership of patents (2)

- Art. 577(2) of Civil Code

  §1. In the absence of agreements and specific provisions, the ownership of property that belongs jointly to several persons or entities shall be determined as follows:

  §3. Each co-owner shall be allocated a portion of the property's rights and liabilities corresponding to his or her share.

§5. A co-owner can use and enjoy the property held in common in accordance with its intended use insofar as such use is compatible with the rights of the other co-owners.

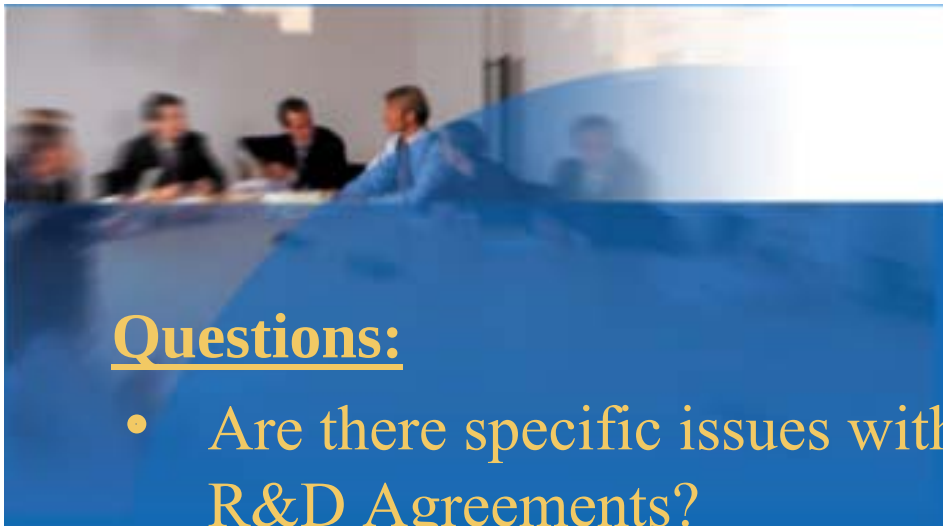
Co-owners are entitled to take steps whose sole purpose is to protect their rights and to engage in acts of provisional administration for the property.

§7. Each co-owner shall contribute to preservation and maintenance expenses as well as to administrative fees, taxes and other costs associated with the property held in common.

NautaDutilh

1993-1995

- 1993: BIOTECH and BIG PHARMA #1 decide to join efforts for further research on the protein families identified through the collaboration with BIOINFORMATICS
- 1995: The R&D Agreement with BIG PHARMA #1 comes to an end
- 1995: BIOTECH files protein α patent application and decides to continue further preclinical development



Questions:

- Are there specific issues with R&D Agreements?
- Is there any risk of undermining competition?

Legal issues:

- R&D Agreement
- Research and Development Block Exemption Regulation

R&D Block Exemption

- Art. 1 Commission Regulation 2659/2000

  Article 81(1) shall not apply to agreements entered into between two or more undertakings (hereinafter referred to as "the parties") which relate to the conditions under which those undertakings pursue:

(a) joint research and development of products or processes and joint exploitation of the results of that research and development;

(b) joint exploitation of the results of research and development of products or processes jointly carried out pursuant to a prior agreement between the same parties;

(c) joint research and development of products or processes excluding joint exploitation of the results.

Access to joint research

- Art. 3(2) Commission Regulation 2659/2000

  All the parties must have access to the results of the joint research and development for the purposes of further research or exploitation.

  (…)

Non competing undertakings

- Art. 4(1) Commission Regulation 2659/2000

  1. Where the participating undertakings are not competing undertakings, the exemption (…) shall apply for the duration of the research and development. Where the results are jointly exploited, the exemption shall continue to apply for seven years from the time the contract products are first put on the market within the common market.

Competing undertakings

- Art. 4(2) Commission Regulation 2659/2000

  2. Where two or more of the participating undertakings are competing undertakings, the exemption provided (…) shall apply for the period referred to in paragraph 1 only if, at the time the research and development agreement is entered into, the combined market share of the participating undertakings does not exceed 25 % of the relevant market for the products capable of being improved or replaced by the contract products.

Products marketed after 7 years

- Art. 4(3) Commission Regulation 2659/2000

  3. After the end of the period referred to in paragraph 1, the exemption shall continue to apply as long as the combined market share of the participating undertakings does not exceed 25 % of the relevant market for the contract products.

Hardcore restrictions

- Art. 5(1) Commission Regulation 2659/2000

  a) the restriction of the freedom of the participating undertakings to carry out research and development independently or in cooperation with third parties in a field unconnected with that to which the research and development relates or, after its completion, in the field to which it relates or in a connected field; (…)

b) the prohibition to challenge after completion of the research and development the validity of intellectual property rights which the parties hold in the common market and which are relevant to the research and development or, after the expiry of the research and development agreement, the validity of intellectual property rights which the parties hold in the common market and which protect the results of the research and development, without prejudice to the possibility to provide for termination of the research and development agreement in the event of one of the parties challenging the validity of such intellectual property rights; (…)

c) the limitation of output or sales;

d) the fixing of prices when selling the contract product to third parties;

e) the restriction of the customers that the participating undertakings may serve, after the end of seven years from the time the contract products are first put on the market within the common market;

f) the prohibition to make passive sales of the contract products in territories reserved for other parties;

g) the prohibition to put the contract products on the market or to pursue an active sales policy for them in territories within the common market that are reserved for other parties after the end of seven years from the time the contract products are first put on the market within the common market;

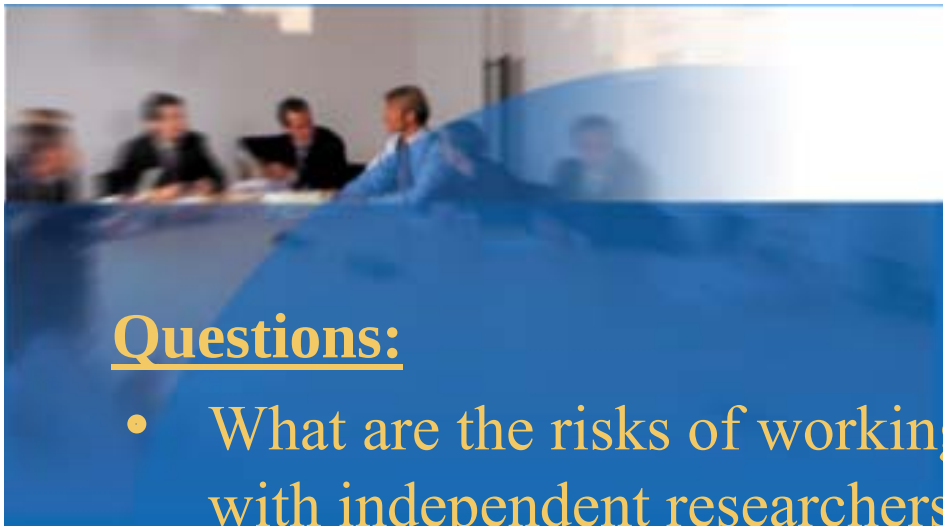
h) the requirement not to grant licences to third parties to manufacture the contract products or to apply the contract processes where the exploitation by at least one of the parties of the results of the joint research and development is not provided for or does not take place;

i) the requirement to refuse to meet demand from users or resellers in their respective territories who would market the contract products in other territories within the common market. (…)

NautaDutilh

1994

- Ms. B's contract at UNIVERSITY is not renewed. She continues to work with Prof. A and BIOTECH as independent researcher and participates actively to the elaboration and performance of key experiments on protein α



NautaDutilh

Questions:

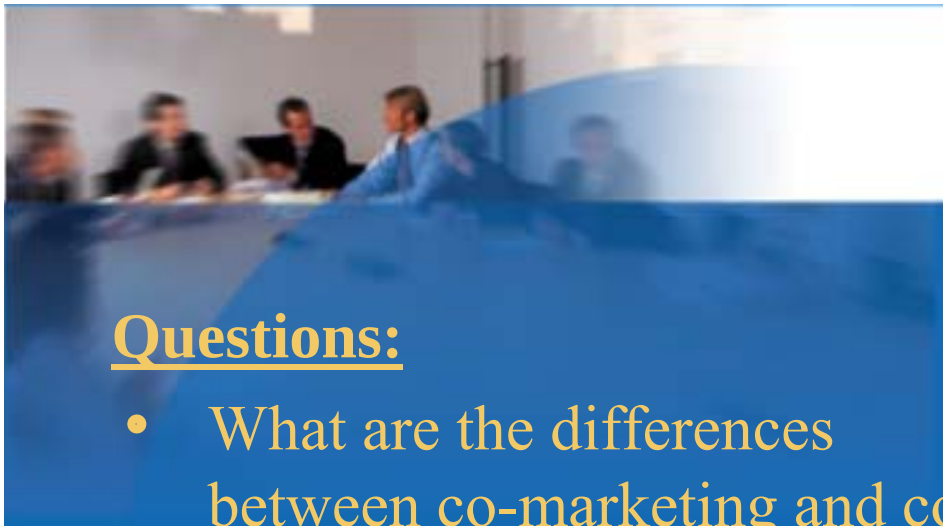
- What are the risks of working with independent researchers?

Legal issues:

- Ownership of IP on joint collaboration
- Confidentiality/know-how

1996-2003

- Further development (preclinical testing and clinical trials) is made by BIOTECH on protein α
- A marketing authorization is eventually filed in EU, US, Japan and Switzerland
- BIOTECH envisages a co-marketing/co-promotion agreement with BIG PHARMA #2



NautaDutilh

Questions:

- What are the differences between co-marketing and co-promotion agreements?
- Are there specific competition law issues?

Legal issues:

- Co-marketing Agreement
- Co-promotion Agreement
- Cartel

NautaDutilh

REGULATORY WORKSHOP

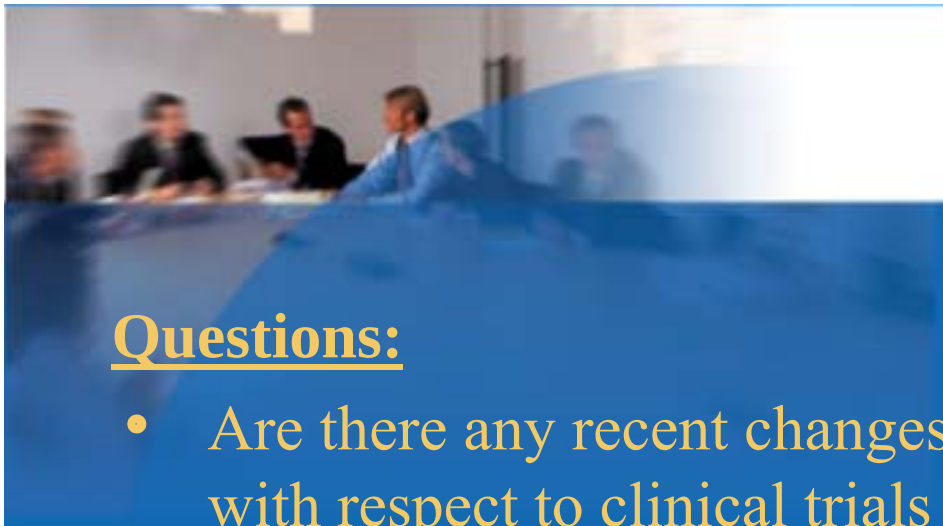
- Chair: Annie Hubert (Amgen)

- Massimo Gonnella
- Olivier Lemaire
- Maarten Meulenbelt

NautaDutilh

1989-1997

- Protein α is identified as being a suitable active ingredient for a medicinal product inhibiting the over-expression of the ABC gene for the treatment of breast cancer.
  Preclinical tests in animals carry positive results.
  BIOTECH envisages phase I clinical trials in healthy volunteers



NautaDutilh

Questions:

- Are there any recent changes with respect to clinical trials in Europe or Belgium?
- Who is held to be a sponsor?
- Who is liable in case of problems during a clinical trial? Can the sponsor limit its liability?
- Can the sponsor use patient personal data freely?

Legal issues:

- New Belgian law on experimentation
- Liability of sponsors
- Data Privacy Act

Scope of new Act on experiments

- Art. 2, 11° Act of 7 May 2004 on experiments on human beings

  11°″experiment″ : any trial, study or investigation on human beings in view of developing biological or medical knowledge.

Sponsor

- Art. 2, 21° Act of 7 May 2004 on experiments on human beings

  21° 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of an experiment.

Liability and Insurance

- Art. 29 §1 Act of 7 May 2004 on experiments on human beings

  The sponsor is, even faultless, liable for the damage which the subject and or his rightful claimants sustained and which shows either a direct or an indirect connection with the trials, every contractual provision aiming at limiting this liability is considered null.

Mandatory insurance

- Art. 29 §2 Act of 7 May 2004 on experiments on human beings

  Before commencing the experiment, the sponsor shall enter into an insurance contract which covers this liability, and the liability of every individual intervening in the trial, irrespective of the nature of the affiliation between the intervening individual, the sponsor and the subject.

Limitation of liability

- Art. 29 §3, 2nd al., Act of 7 May 2004 on experiments on human beings

  With the exception of the cases established by the King, the insurer can oppose no nullity, no defence or no dissolution which result from the law or the insurance contract, to the subject or to this rightful claimants.

NautaDutilh

Scope of Data Privacy Act

- Article 3bis Act of 8 December 1992 on Privacy Protection

  The Belgian Law applies to the processing of personal data carried out in the context of the effective and actual activities of permanent establishment of the controller on Belgian territory.

Controller

- Article 1 §4 Act of 8 December 1992

  Any natural or legal person, the factual association or public authority that alone or jointly with others determines the purpose and means of the processing of personal data.

Processor

- Article 1 §5 Act of 8 December 1992

  Any natural person, legal person, factual association or public authority that processes personal data on behalf of the controller, except for the persons who under the direct authority of the controller or the processor, are authorised to process the data.

Data subject

- Article 1 §1 Act of 8 December 1992

  Any identified or identifiable natural person (which can be identified through an identification number or one or more specific elements which are characteristic of his physical, physiological, psychological, economical, cultural or social identity).

Personal data

- Article 1 §1 Act of 8 December 1992

  Any information relating to an identified or identifiable natural person.

Processing

- Article 1 §2 Act of 8 December 1992

  An operation or set of operations that is performed upon personal data, whether or not by automatic means, such as collection, recording, organisation, storage, adaptation, alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment, combination, as well as blocking, erasure or destruction of personal data.

Recipient

- Article 1 §7 Act of 8 December 1992

  Any natural person, legal person, factual association or public authority to which data are disclosed, whether a third party or not.

General prohibition to process personal health data

- Article 7 §1 Act of 8 December 1992

  The processing of personal data related to the health, is forbidden.

Exceptions for health data

- Article 7 §2 of Act of 8 December 1992
  - Written consent of the data subject
  - Necessary for the purpose of carrying out the specific obligations and rights of the controller in the field of employment law, social security, public interest
  - Necessary to protect the vital interests of the data subject

- Necessary for the prevention of a concrete danger or the suppression of a specific criminal offence
- Necessary for the purposes of preventive medicine or medical diagnosis, the provision of care or treatment to the data subject or to one of his relatives, or the management of health care services operating in the interest of the data subject, and if those data are processed under the supervision of a health professional
- Necessary for scientific research

NautaDutilh

1999

- During development, BIOTECH discovers that proteins α and β are also active for the treatment of a rare form of cancer affecting less than 5 per 10,000 inhabitants across Europe

NautaDutilh

Questions:

- Is it possible to obtain a separate MA for the orphan medical indication?
- What are the important considerations when choosing the marketing authorization procedure?
- Can both protein α and β obtain orphan medicinal product status?

Legal issues:

- Marketing authorization procedures
- Orphan medicinal product market exclusivity and off-label use
- Similarity and clinical superiority

Orphan Marketing Exclusivity

- Art. 8(1) Regulation 141/2000

  … without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Similarity and clinical superiority

- Art. 8(3) Regulation 141/2000

  By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

  c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

NautaDutilh

1997-2003

- Phase I, II and III trials are completed in a number of countries
- BIOTECH's board is pressing for obtaining a marketing authorization as soon as possible; compassionate use programs are envisaged

NautaDutilh

Questions:

- What are the rules for compassionate programs for centralized products?
- Can the product be provided against payment?
- Can a company "advertise" compassionate use or named patient programs?

Legal issues:

- Compassionate use
- Special needs

General rule

- Art. 6(1) Directive 2001/83

  1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

Compassionate use for centralized products

- Art. 83 Regulation 726/2004 (as from November 2005)

  1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.

2. For the purposes of this Article, ‘compassionate use’ shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life threatening, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.

Special needs

- Art. 5 Directive 2001/83

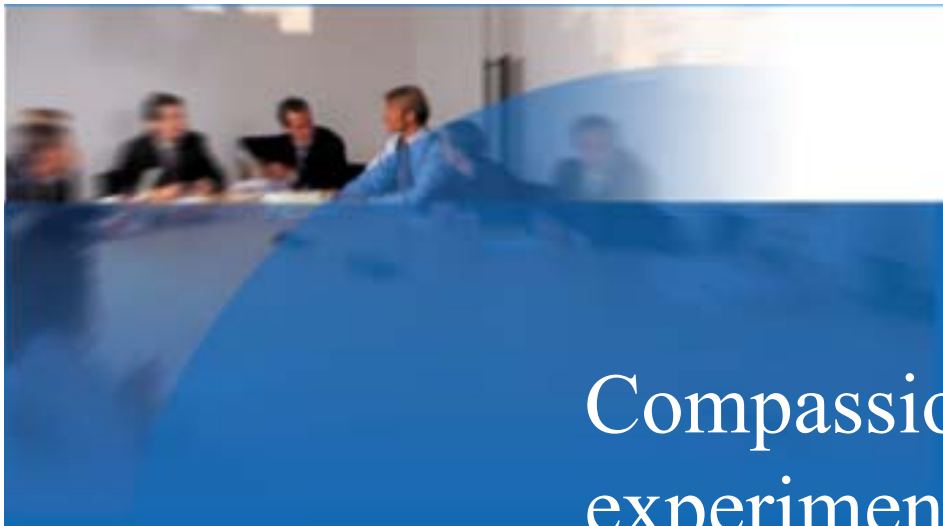
  A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health care professional and for use by his individual patients on his direct personal responsibility.

NautaDutilh

Imports of non authorised products in Belgium

- Art. 6bis §3 Act 1964 on medicinal products

  § 3. In order to fulfil a medical prescription, a non-approved medicinal product can be imported by the pharmacist. The conditions and modalities relating to the import of such medicinal product, as well as possible restriction, shall be laid down by the King.



Compassionate use and Act on experiments

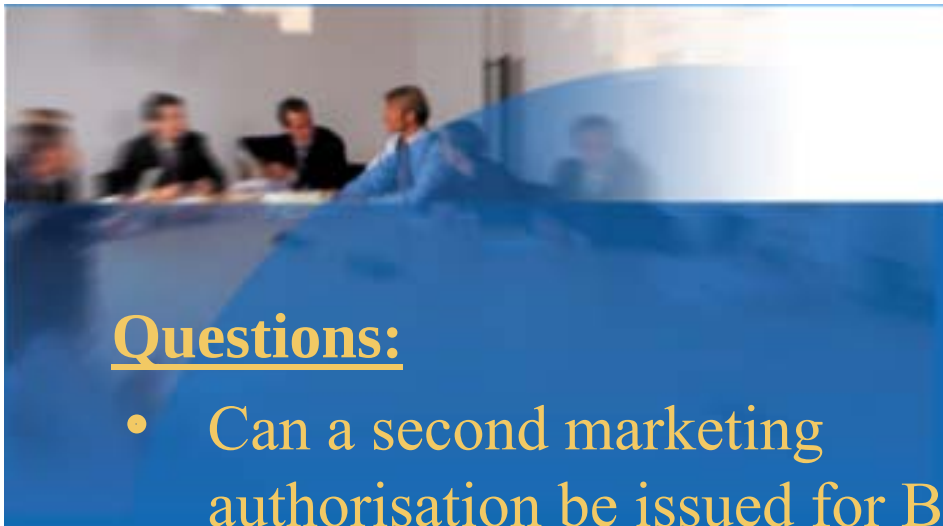
- Art. 3 Act of 7 May 2004 on experiments on human beings

  The present law applies to the conduct of experiments on human beings and in particular of clinical trials, including multi-centre trials, more particularly with regard to the application of good clinical practices referred to in Article 4.

NautaDutilh

2003

- Marketing authorisation applications are filed in Switzerland first, than in the EU, US and Japan
- A co-marketing/co-promotion agreement is concluded with BIG PHARMA #2
- Due to additional data requirements, the EMEA procedure is suspended



NautaDutilh

Questions:

- Can a second marketing authorisation be issued for BIG PHARMA #2?

Legal issues:

- Limitation of the number of MAs for the same companies (co-marketing / co-promotion agreements)

Co-marketing of centralized products

- Art. 82(1) Regulation 726/2004

  1. Only one authorisation may be granted to an applicant for a specific medicinal product.

  However, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product when there are objective verifiable reasons relating to public health regarding the availability of medicinal products to health-care professionals and/or patients, or for co-marketing reasons.

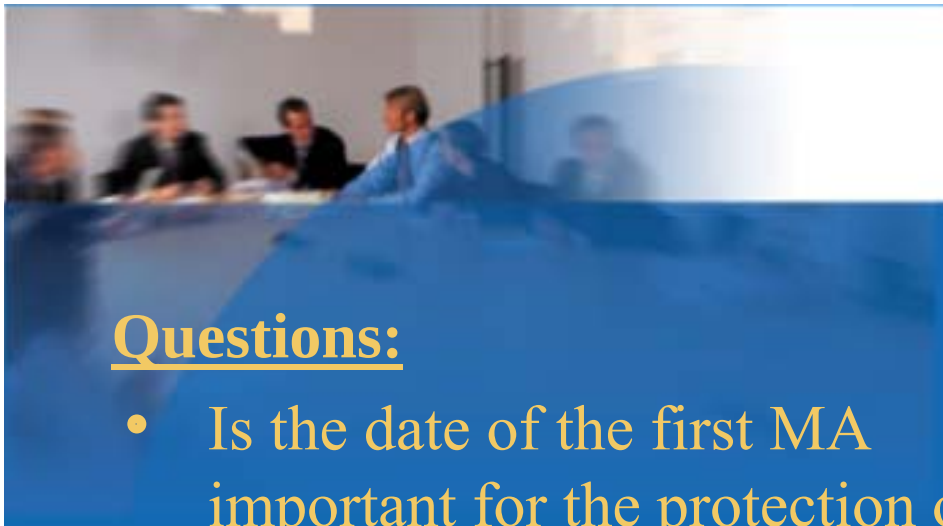
Co-promotion

- Art. 82(2) Regulation 726/2004 and Art. 98(3) Directive 2001/83 (as amended by Directive 2004/27)

  3. The Member States shall not prohibit the co-promotion of a medicinal product by the holder of the marketing authorisation and one or more companies nominated by him.

2003-2006

- 1 October 2003: A marketing authorisation is issued in Switzerland
- 2006: a positive CHMP opinion is issued and the Commission eventually approves the medicinal product of BIOTECH, with protein α as active ingredient
- One week later, the medicinal product of BIG PHARMA #2 (also containing protein α as active ingredient) is also approved



NautaDutilh

Questions:

- Is the date of the first MA important for the protection of the product?

Legal issues:

- 6-month period for filing the SPC application
- Starting point of duration of SPC in the Community (Swiss/Liechtenstein issue)
- Starting point of RDP in the Community
- Starting point of the decade for well-established medicinal use

NautaDutilh

Well established medicinal use

- Annex I, Part II, 1 Directive 2001/83

  Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

2006-2007

- Pricing and reimbursement procedures are initiated in the various Member States where necessary.

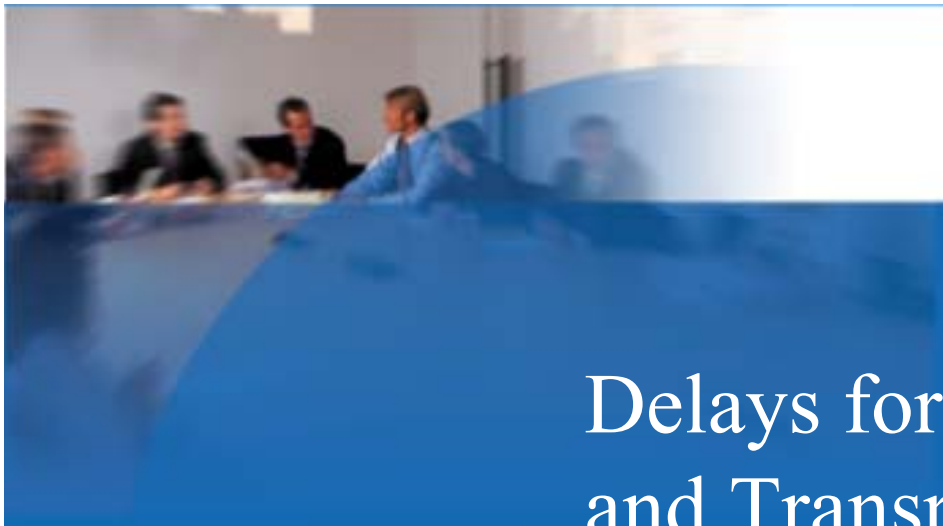
NautaDutilh

Questions:

- Is the level of price in Belgium important vis-à-vis other markets?
- How can I challenge a negative decision on reimbursement? What are the consequences of the absence of decision within the required time limits?
- Are the recent initiatives taken by Minister Demotte likely to influence pricing and/or reimbursement conditions?

Legal issues:

- Parallel distribution and price bands
- Absence of positive decision in due time and Transparency Directive
- Reference pricing
- Public procurement (Demotte proposal)



Delays for obtaining reimbursement and Transparency Directive

- Article 6(1) Directive 89/105/EEC

  Member States shall ensure that the decision on application submitted, in accordance with the requirements laid down in the Member State concern, by the holder of a marketing authorisation to include a medicinal product in the list of medicinal products covered by the health insurance systems is adopted and communicated to the applicant within 90 days of its receipt."

Absence of decision under Belgian law

- Article 35 bis §3 Act of 14 July 1994 regarding public health insurance

  In case of lack of a decision within 180 days off receipt of the application, the decision is considered positive, based upon the reimbursement basis, the reimbursement conditions and the reimbursement category proposed by the applicant.

NautaDutilh

2008-2016

- New indications are being authorized
- New supra-bioavailable pharmaceutical forms are developed
- A number of clinical trials results are published in scientific journals
- The patent department considers filing a patent on an important but undisclosed manufacturing step

NautaDutilh

Questions:

- Are the clinical data supporting the authorisation of new formulations, new indications, new doses of products protectable? Is it different for biological products?
- What should be taken into consideration when considering filing variations?
- Is it always appropriate to patent a manufacturing process of a biological compound?

Legal issues:

- Variations/line extensions and life cycle management strategies
- Abridged generic procedure and essential similarity
- Biosimilars rules

NautaDutilh

Global marketing authorisation

- Art. 6 Directive 2001/83 as amended by Directive 2004/27

  'When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).'

Generic medicinal product

- Art. 10(2)(b) Directive 2001/83 as amended by Directive 2004/27

  "generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Salts, esters and other derivatives

- Art. 10(2)(b) (et seq.)

  The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant.

Pharmaceutical form and bioequivalence

- Art. 10(2)(b) (et seq.)

  The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

Biosimilars (after 20 November 2005)

- Art. 10(4) Directive 2001/83 as amended

  4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.

The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

NautaDutilh

Case by case assessment

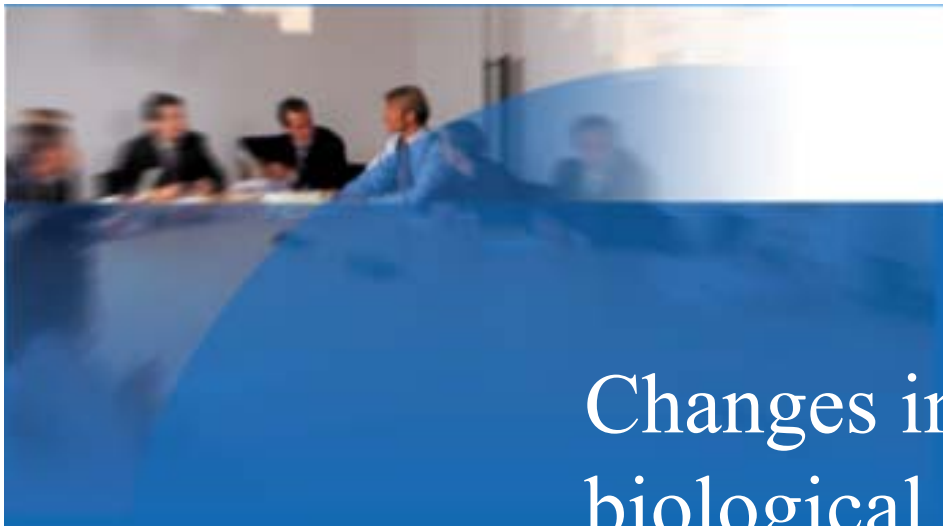
- Part II, 4 Annex I Directive 2001/83 as amended by Comm. Directive 2003/63

  Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

New indications of biological products

- Part II, 4 Annex I Directive 2001/83, as amended by Comm. Dir. 2003/63

  In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.



Changes in manufacturing process of biological product

- Point 3 of CHMP Guideline on comparability of medicinal products containing biotechnology derived proteins as active substance – Non-clinical and clinical issues (EMEA/CPMP/3097/02/final)

  In all situations, the company should justify that the change in the manufacturing process will not affect efficacy and/or safety of the product and that the data underpinning such justification will be assessed.

NautaDutilh

Corporate Workshop

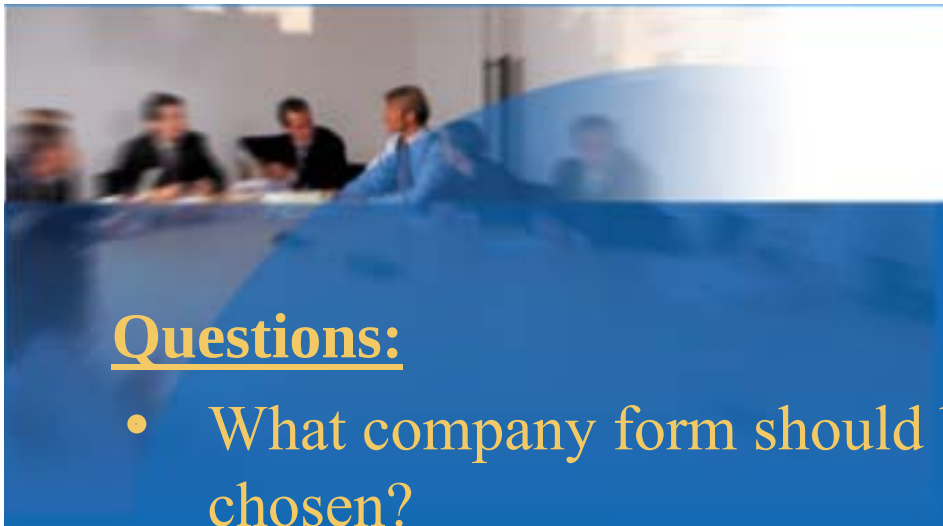
- Chair: Paul Van Dun (K.U. Leuven)

- Thierry Duquesne
- Elke Janssens
- Brent Springael
- Dirk Van Gerven

NautaDutilh

1991

- Prof. A. sets up BIOTECH
- BIOTECH's CEO is Prof. A
- Seed capital is provided by Prof. A., UNIVERSITY and regional subsidies
- A patent license agreement is signed between BIOTECH and UNIVERSITY re the ABC gene patent application



NautaDutilh

Questions:

- What company form should be chosen?
- Are there any particular issues if UNIVERSITY contributes know-how to BIOTECH?
- Any tax remarks?
- What are the labour issues further to the setting up of a company?

Legal issues:

- NV / BVBA / CVBA
- Valuation and contribution of know-how
- Regional subsidies
- Shares not representing capital
- ONSS/RSZ, family allowance fund, work permit, etc.

Relevant corporate law provisions

- Code on Commercial Companies:
  - Book VI on the BVBA/SPRL
  - Book VII on the CVBA/SCRL
  - Book VIII on the NV/SA

Relevant corporate law provisions

- Walloon Act of 11 March 2004
  - Art. 1 "In order to contribute to the durable development of the Region, the government can (…) grant incentives to SMEs that apply an investment program (…)."
  - Art. 2 "The incentives take the form of premiums, an exemption from real estate tax or a combination of both incentive forms. (…)"
  - Art. 3 "§1. In order to qualify for the incentive, the SME must have its seat in the Walloon Region and apply an incentive program as defined article 5 (…)."

    "§2. In order for the incentives to apply, the SME: (4°) must be a spin-off as defined in paragraph 6."

    "§6. A spin-off is an SME established by researchers, or university or industrial persons, starting from their research results."
  - Art. 5 "§3. Investments that are eligible for the incentives are investments in tangible and intangible fixed assets."

Relevant tax law provisions

- Article 115 Registration Tax Code

  Is subject to a 0.5% tax, the contribution of movable assets to a civil or commercial company having either its place of management in Belgium, or its statutory seat in Belgium and its place of management outside the EU, independent of whether the contribution takes place at incorporation or later. (…)

NautaDutilh

1991-1992

- Prof. A. now CEO of BIOTECH, continues to collaborate closely with his former team from UNIVERSITY, and in particular with Ms. B
- BIOTECH further employs researchers

NautaDutilh

Questions:

- Can BIOTECH protect itself with respect to its relationships with Ms. B and new employees?
- Any tax incentives for researchers?

Legal issues:

- Risk of poaching
- Remuneration
- Fringe benefit
- Specific clauses
- 50% payroll tax exemption

Poaching

- Article 17, 3° Employment Contracts Act of 3 July 1978

  An employee has the obligation to refrain in the course of his/her employment, and after its termination:

  - to divulge any trade or business secret, or any secret of a personal or confidential nature obtained by the employee during the performance of his/her professional activity;

  - to indulge or to co-operate in any act of unfair competition.

Non compete clause

- Art. 65 §2 Employment Contracts Act of 3 July 1978

  In order to be valid, a **non-compete clause** must comply with the following conditions:

  - the clause must be in writing;

  - it must relate to similar activities;

  - it must be limited in scope to the territory on which the employee can effectively enter into competition with the employer within Belgium;

- the period of validity may not exceed 12 months from the expiration or termination of the employment contract;

- it must provide for the payment by the employer of an amount equal to at least half the employee's gross remuneration for the duration of the non-compete obligation, unless the employer waives the non-compete clause within 15 days following termination of the employment contract.

Remuneration

- Art. 2 Remuneration Act of 12 April 1965

  All benefits paid to an employee by an employer as compensation for the work performed in the context of an employment contract.

Tax exemptions for research

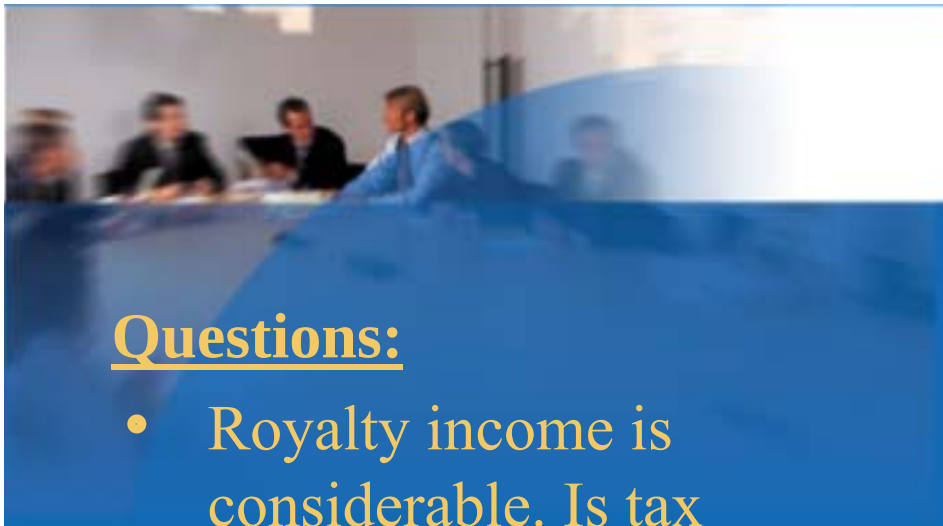
- Art. 366(2) Act of 27 December 2004

  The same [50%] exemption from remittance [of payroll tax] is granted to enterprises that pay or grant wages to researchers that are working on research projects in connection with cooperation agreements with (…) universities or colleges of higher education, established in the EEA, or recognized scientific institutions. Such exemption only applies to payroll tax on wages that are paid in the context of the research project during the period of that project and to the extent they relate to an effective employment in that research project.

NautaDutilh

1994

- Royalty income from the use of BIOINFORMATICS' technology is rapidly growing. The technology is licensed to multiple pharmaceutical companies



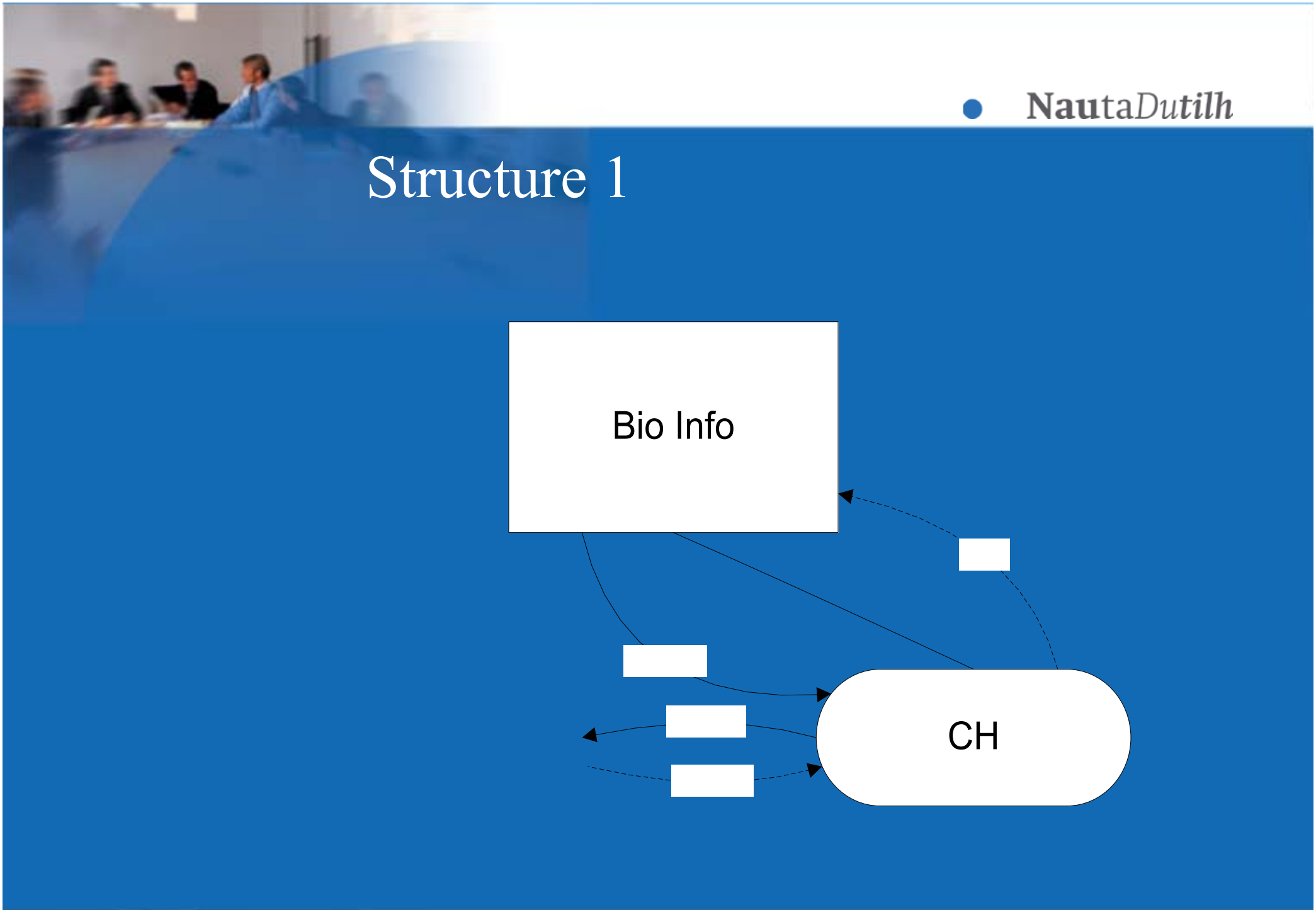
NautaDutilh

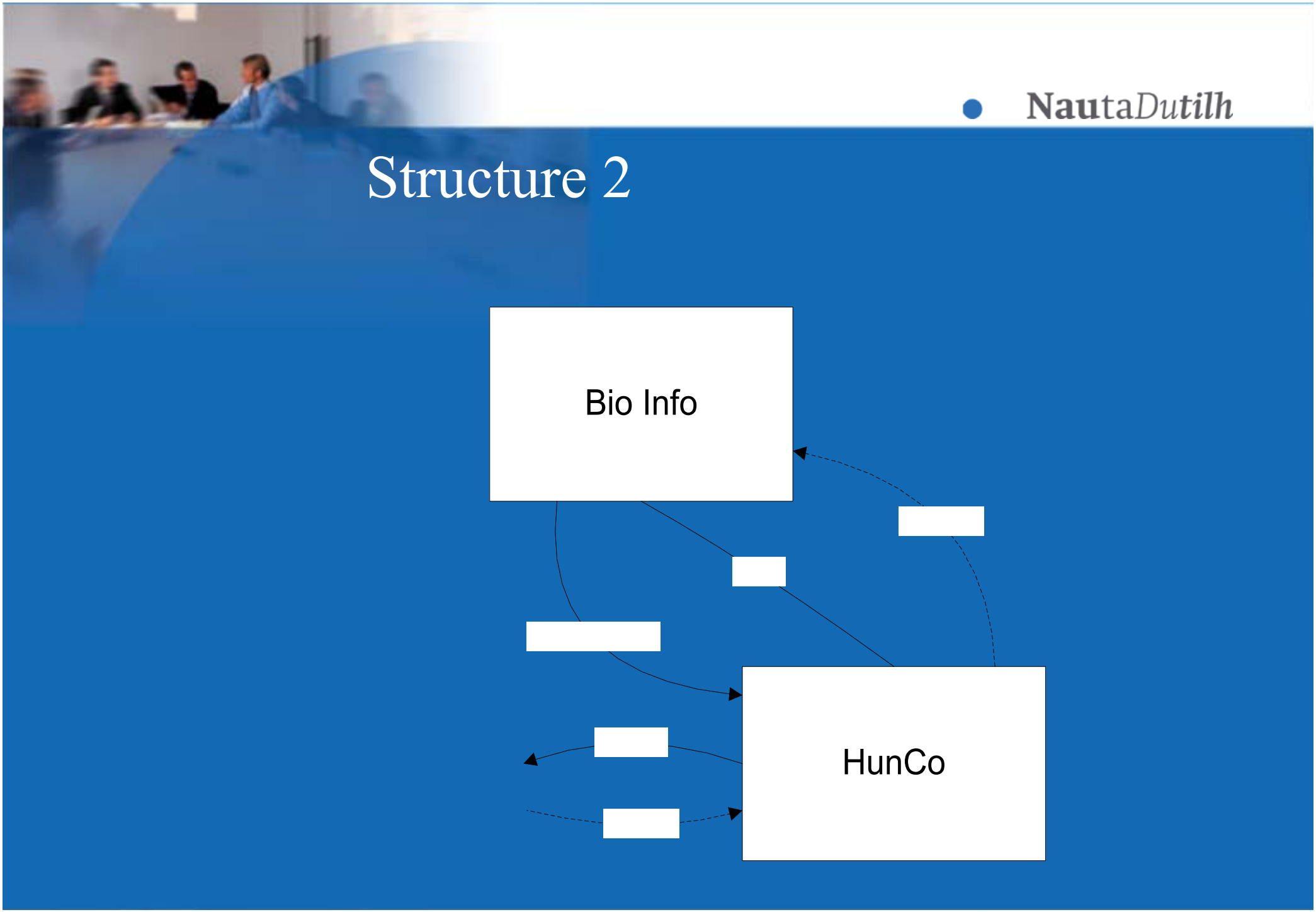
Questions:

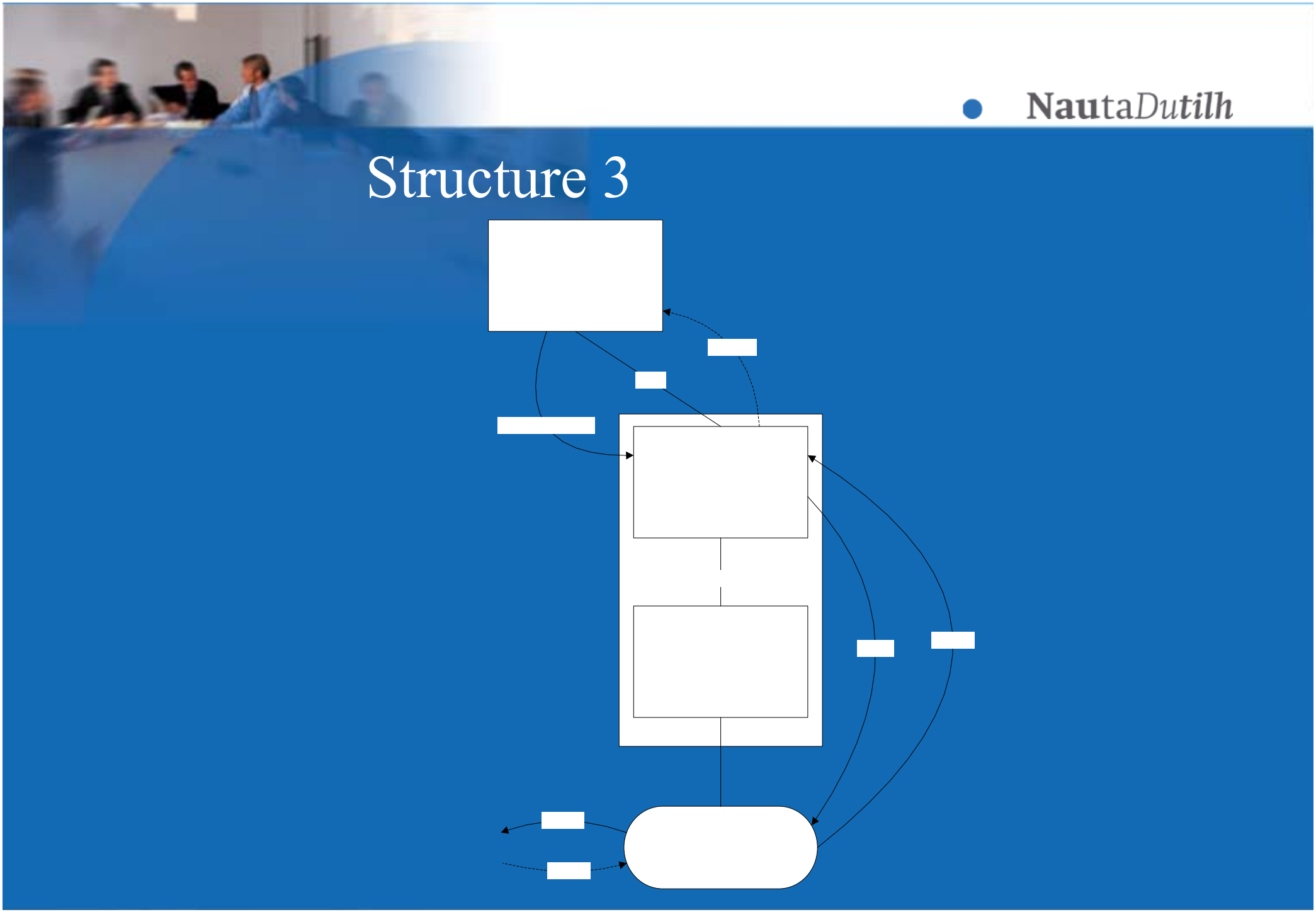
- Royalty income is considerable. Is tax optimisation possible?

Legal issues:

- Licensing structure – tax consolidation


NautaDutilh
Structure 1
Bio Info
CH


NautaDutilh
Structure 2
Bio Info
HunCo



NautaDutilh

Structure 3

NautaDutilh

1996

- A professional manager is named CEO
- Prof. A. is named CSO
- Incentive plans are discussed

NautaDutilh

Questions:

- Does hiring self-employed persons have particular labour law consequences?
- What type of incentive plans can be envisaged and what are their tax / labour law consequences?

Legal issues:

- Risks
- Sanctions
- SOP
- Discounted shares
- Stock Appreciation Rights (SARs)
- Phantom options
- Profit shares
- Royalty related bonus

Relevant tax and labour law provisions

- Art. 42 Act of 26 March 1999 on Stock Options

  §1. The advantages received pursuant to the professional activity of the beneficiary, in the form of an ***option*** granted (whether or not free of charge) constitute for the latter a professional income that is taxable at the time of grant, when he has not used the option for the exercise of his professional activity.

Relevant tax and labour law provisions

- Art. 48 Act of 26 March 1999 on Stock Options

  The advantage received pursuant to the issue of ***discounted shares*** pursuant to article [609 of the Company Code] [*i.e., at the occasion of a capital increase in favour of the personnel*] are not regarded as an advantage for the purposes of art.2(1)(3) of the Act of 12 April 1965 regarding the protection of the employees remuneration.

Relevant tax and labour law provisions

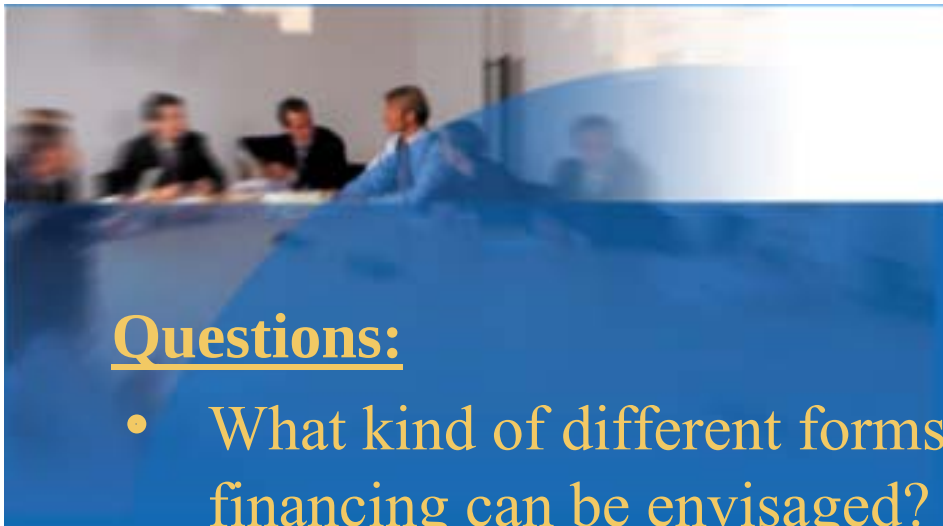
- Art. 49 Act of 26 March 1999 on Stock Options

  The advantage received pursuant to the issuance of ***stock options*** granted at the occasion of a capital increase pursuant to article [609 of the Company Code], or with the issuance of ***discounted shares*** pursuant to that article, are not regarded as a taxable advantage for the beneficiaries.

NautaDutilh

1998

- Preclinical tests show that protein α is efficient in blocking the over-expression of the ABC gene. Cancer tumour size is reduced in animals. Phase I clinical trials results are encouraging
- BIOTECH is looking for new financing to support further clinical testing in humans



NautaDutilh

Questions:

- What kind of different forms of financing can be envisaged?
- What must BIOTECH take into account from a tax perspective?

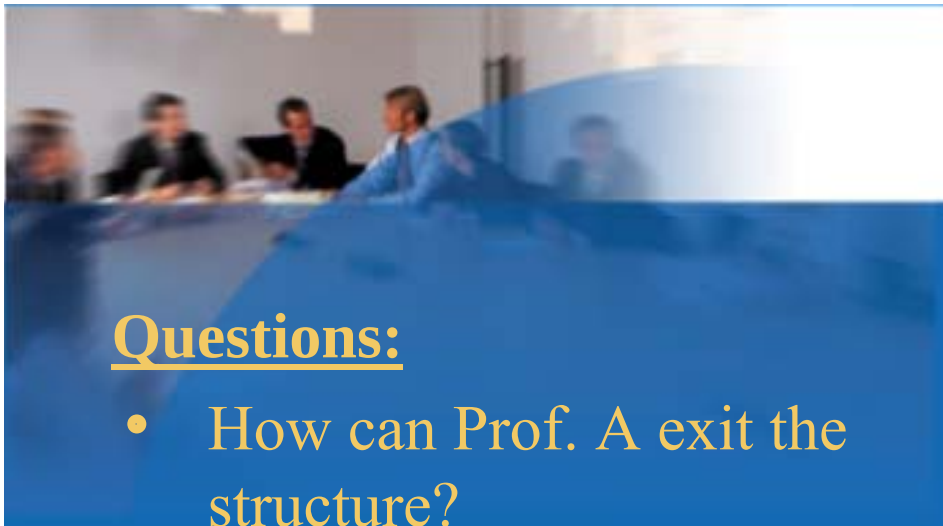
Legal issues:

- Warrants; convertible bonds; convertible shares; non voting shares; founder or bonus shares
- Loan
- Ratchet clauses
- Debt vs. Equity
- Withholding tax exemptions

NautaDutilh

2003

- Marketing authorization applications are filed and a co-marketing/co-promotion agreement is signed with BIG PHARMA #2
- Prof. A. decides to exit from BIOTECH



NautaDutilh

Questions:

- How can Prof. A exit the structure?
- What are the tax concerns when exiting the structure?

Legal issues:

- Put option
- Tag along
- IPO
- Capital gains taxation

Relevant tax provisions

- Art. 90 Income Tax Code of 1992

  "Miscellaneous income includes:

  (9°) capital gains on shareholdings in Belgian companies that are realized pursuant to the sale to non-resident entities, when the transferor (…) has held at any time during 5 years preceding the sale (…) directly or indirectly more than 25% of the shares of the company of which the shares are transferred."

NautaDutilh

Commercialisation Workshop

- Chair: Alain Van der Cruyssen (BBA)

- Massimo Gonnella
- Olivier Lemaire
- Maarten Meulenbelt
- Florence Verhoestraete

NautaDutilh

2006

- The medicinal products of BIOTECH and BIG PHARMA #2 are authorised. A marketing campaign is initiated by the respective sales forces of the two companies
- Further clinical trials are conducted. Physicians are regularly invited to scientific and commercial conferences

NautaDutilh

Questions:

- What are the consequences of providing support to academic sponsored trials? Can I control study results?
- What are the rules for the promotion of medicinal products?
- Can we invite doctors to scientific conferences or provide small gifts or samples of medicinal products?
- Can I direct promotional campaigns to patients?

Legal issues:

- Liability of (co-)sponsor and right to "control" results of trials made by third parties
- New Belgian law on promotional activities
- Information to patients

Promotion of medicinal products to health professionals (current Act)

- Current Article 10 Medicines Act of 25 March 1964

  § 1 It is prohibited when supplying medicines to directly or indirectly offer benefits or advantages. It is prohibited for manufacturers, importers and wholesalers of medicinal products to offer or grant directly or indirectly advantages or benefits to persons qualified to prescribe medicines. It is forbidden to request or accept such advantages or benefits.

§ 2 Without prejudice to the provisions of § 1, persons qualified to prescribe those medicines may be compensated for tasks performed when clinical trials or other scientific studies are carried out".

Promotion of medicinal products to health professionals (new rules)

- Art. 10 Act of 1964 as amended by Act of 18 November 2004 on combating the excessive promotion of medicines (not yet in force)

  §1. It is prohibited, in the framework of the supply, the prescription and the administration of medicines, to directly or indirectly promise, offer or give pecuniary advantages or benefits in kind to wholesalers, persons qualified to prescribe, supply or administer medicines and institutions where medicines are prescribed, supplied or administered. […]

NautaDutilh

Inexpensive benefits and advantages

- New Art. 10 Act of 25 March 1964

  This prohibition does not apply to:

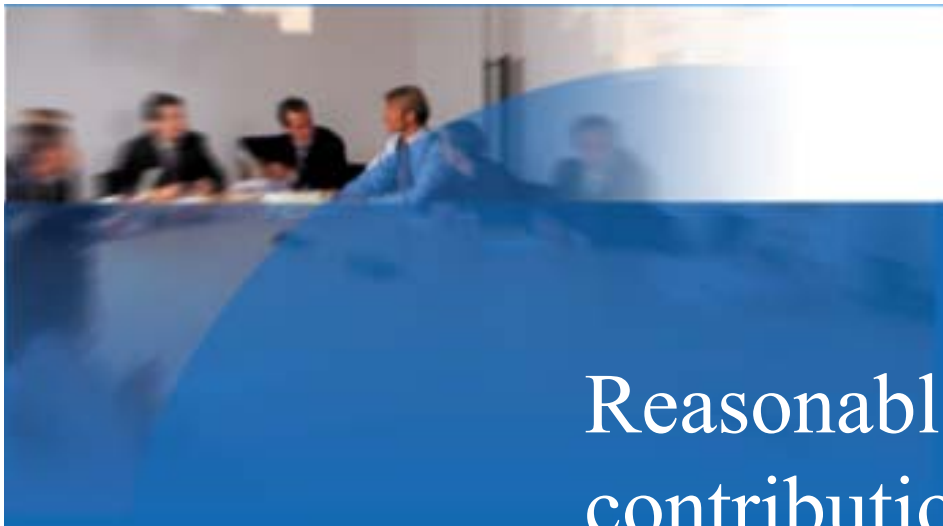
  1° Benefits and advantages which are inexpensive and relevant to the practice of medicine, pharmacy or veterinary medicine.

Invitation to scientific events

- New Art. 10 Act of 25 March 1964

  This prohibition does not apply to:

  2° The invitation to and paying for the participation, including the hospitality, in a scientific event of the natural and legal persons mentioned in § 1, including the veterinary sector, provided the event complies with the following conditions (*5 cumulative conditions*). […]



Reasonable compensation for scientific contributions

- New Art. 10 Act of 25 March 1964

  This prohibition does not apply to:

  3° Without prejudice to Article 18, § 2, of the Decree n° 78 of 10 November 1967 on the exercise of the healthcare profession, the compensation of legitimate tasks with a scientific character, insofar as this compensation is reasonable. Reference is maid in particular to clinical trials mentioned in Article 2, 7° of the Act of 7 May 2004 regarding experiments on human beings.

NautaDutilh

2007

- BIG PHARMA #1's product has received a positive opinion from the CHMP. The sales forces of BIG PHARMA #1 are distributing copies of non peer reviewed scientific journals to physicians
- BIG PHARMA #1 is also promoting the advantages of protein β as compared to protein α

NautaDutilh

Questions:

- Can I use non-published studies to promote my products?
- Can I use re-prints of published articles?
- Is it allowed to communicate about a medicinal product which has not yet been authorised?
- Is comparative advertisement allowed, and under what circumstances?
- What are the remedies against a competitor's unlawful advertisement?

Legal issues:

- Off label promotion
- Copyright issues
- Comparative advertisement without head-to-head clinical trial results
- Possible (legal) actions before Commission of Deontology and/or commercial courts

Off label advertisement

- Art. 9 § 1 Act of 25 March 1964

  Any advertisement relating to a medicinal product which is not yet registered or which has been suspended or withdrawn from the market pursuant to Articles 7 and 8, is prohibited.

Advertisement of medicinal products

- Article 2, § 1, 3° Royal Decree of 7 April 1995 regarding the promotion of medicines

  Any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products.

- It shall include in particular:
  - the advertising of medicinal products to the general public
  - advertising of medicinal products to persons qualified to prescribe or supply them
  - visits by medical sales representatives to persons qualified to prescribe medicinal products or supply them

- the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal
- sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products, and in particular payment of their travelling and accommodation expenses in connection therewith.

Information v. advertisement (1)

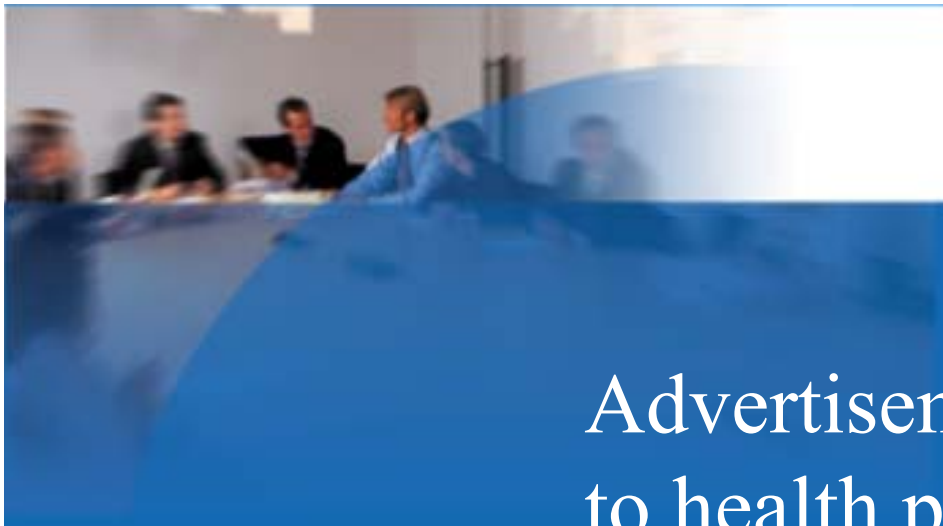
- Art. 9 §1, 2nd al. Act of 25 March 1964

  Any advertisement directed to the public is prohibited when it related to a prescription only medicinal product (…).

Information v. advertisement (2)

- Art. 11 Act 25 March 1964

  The King may regulate information directed to the public or to physicians, nurses, or persons exercising a paramedical profession or veterinary medicine.



NautaDutilh

Advertisement of medicinal products to health professionals

- Article 4, § 3 Royal Decree of 7 April 1995 regarding the promotion of medicines
  - The advertising of a medicinal product :
    - shall be verifiable
    - shall encourage the rational use of the medicinal product by presenting it objectively and without exaggerating its properties
    - shall not be misleading.

Comparative advertising

- Article 23bis, § 1 Act of 14 July 1991 on trade practices

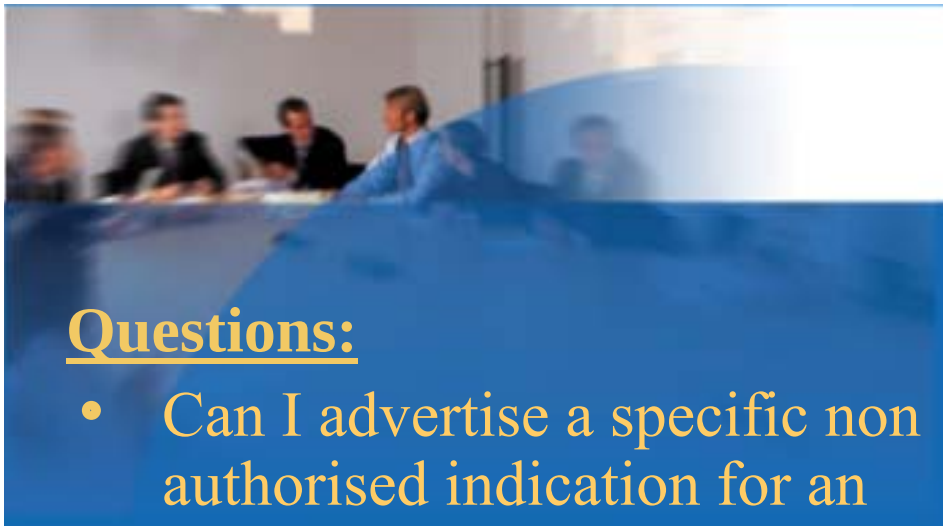
  § 1. Comparative advertising is permitted provided [if]:

  3° it objectively compares one or more material, relevant, verifiable and representative features of those goods and services, which may include the price.

NautaDutilh

2008

- BIG PHARMA #1's product is authorised by the EU Commission
- The protein α and β products are rapidly gaining market shares. Protein β is more and more prescribed to breast cancer patients (although it is only authorised for prostate cancer)
- BIOTECH decides to initiate patent infringement action against BIG PHARMA #1 on the basis of the ABC gene patent



NautaDutilh

Questions:

- Can I advertise a specific non authorised indication for an approved product (off-label)?
- How do I collect the proof of patent infringement?
- How can I block the sale of a competitor's product?
- Can BIOTECH rely on the protein α patent application? Is the EPO opposition against the ABC gene patent relevant?
- What about infringements abroad by Belgian companies?

Legal issues:

- Promotion of off-label indications and unfair competition actions
- Descriptive-seizure action
- Other legal actions

NautaDutilh

Descriptive-seizure

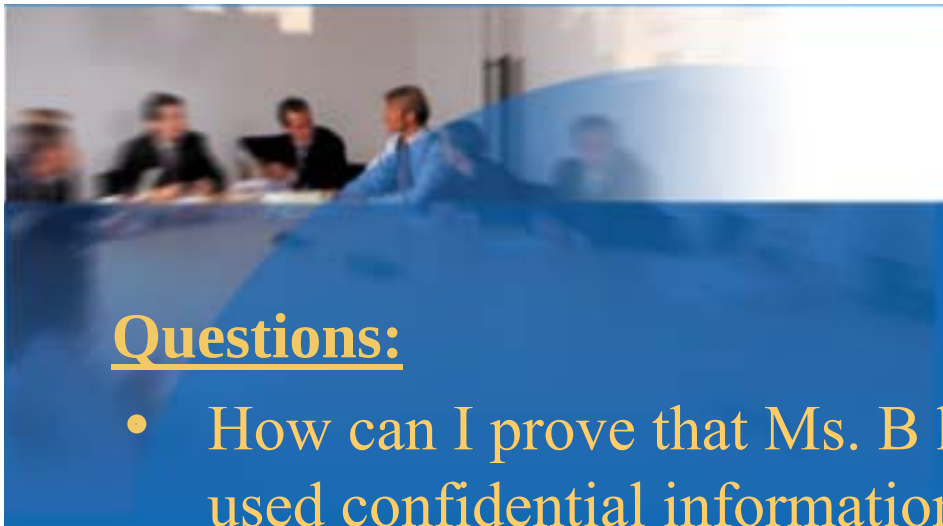
- Art. 1481 Judicial Code

  (…) court order (…) via an *ex parte* application, the holders of patents, supplementary protection certificates (…) as well as the holders of and applicants for new plant variety certificates (…) can have one or more experts appointed by the court to proceed to describe any devices, machinery, works, varieties, materials used to reproduce and multiply, and any other allegedly infringing objects and processes as well as any plans, documents, calculations, writings, plants or part thereof with a view to establishing the alleged infringement and any tools and instruments used directly in the production in question.

In the same order, the judge (…) can forbid the holders of the infringing goods from disposing of the same, consigning them to the custody of a third party, placing the goods under seal and, if the matter involves revenue, authorise preventive attachment of the receipts.

2009

- Ms. B. and BIG PHARMA #1 initiate an action in restitution of the protein α patent, alleging that the invention was made jointly by Ms. B
- BIOTECH starts a new action against Ms. B and BIG PHARMA #1 for breach of know-how, alleging that Ms. B used confidential information from BIOTECH when helping to the development of protein β



NautaDutilh

Questions:

- How can I prove that Ms. B has used confidential information from BIOTECH?
- How can I demonstrate that the information was confidential?
- Is a Court the appropriate forum for know-how litigation?

Legal issues:

- Importance of good CDA
- Maintaining good archives is essential
- Know-how litigation

NautaDutilh

2010

- BIOTECH and BIG PHARMA #1 settle their litigation
- Protein α products are parallel distributed from Poland and Norway into other EU Member States

NautaDutilh

Questions:

- Can I rely on my trademark rights to block parallel trade? Can a parallel trader use a different trademark? Is repackaging permitted?
- Can I rely on patent rights when the product was not patentable in a given Member State? Or EEA state?
- Can I refuse to supply wholesalers?

Legal issues:

- Parallel distribution issues
  - •Free movement of goods and Community exhaustion of IP rights
  - •Trademark
  - •Regulatory
  - •Patent (specific mechanism)
- Stock management programs
  - •Art. 81 and 82 EC

Free movement of goods principle (1)

- Art. 28 EC Treaty

  Quantitative restrictions on imports and all measures having equivalent effect shall be prohibited between Member States.

Free movement of goods principle (2)

- Art. 30 EC Treaty

  The provisions of Articles 28 and 29 shall not preclude prohibitions or restrictions on imports, exports or goods in transit justified on grounds of (…) the protection of health and life of humans (…) or the protection of industrial and commercial property.

Repackaging and trademark issues

- Art. 7 First Council Directive 89/104/EEC

  1. The trade mark shall not entitle the proprietor to prohibit its use in relation to goods which have been put on the market in the Community under that trade mark by the proprietor or with his consent.

  2. Paragraph 1 shall not apply where there exist legitimate reasons for the proprietor to oppose further commercialization of the goods, especially where the condition of the goods is changed or impaired after they have been put on the market.

NautaDutilh

Specific Mechanism

- Annex IV, Chapter 2, Act of Accession

  With regard to the Czech Republic, Estonia, Latvia, Lithuania, Hungary, Poland, Slovenia or Slovakia, the holder, or his beneficiary, of a patent or supplementary protection certificate for a pharmaceutical product filed in a Member State at a time when such protection could not be obtained in one of the abovementioned new Member States for that product, may rely on the rights granted by that patent or supplementary protection certificate in order to prevent the import and marketing of that product in the Member State or States where the product in question enjoys patent protection or supplementary protection, even if the product was put on the market in that new Member State for the first time by him or with his consent".

"Any person intending to import or market a pharmaceutical product covered by the above paragraph in a Member State where the product enjoys patent or supplementary protection shall demonstrate to the competent authorities in the application regarding that import that one month's prior notification has been given to the holder or beneficiary of such protection".

Regulatory obligations for EMEA

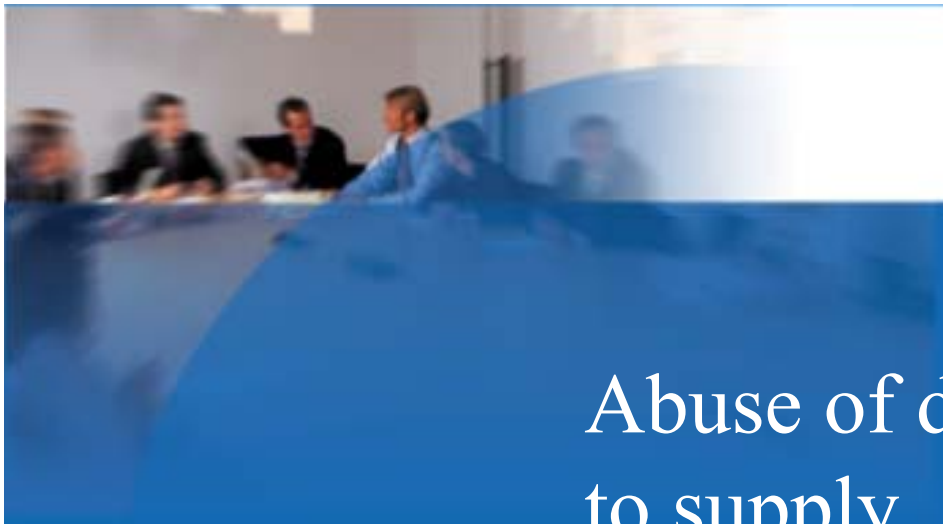
- Art. 57 (o) Regulation 726/2004

  (o) checking that the conditions laid down in Community legislation on medicinal products and in the marketing authorisations are observed in the case of parallel distribution of medicinal products authorised in accordance with this Regulation.

Agreements affecting trade between Member States

- Art. 81(1) EC Treaty

  1. The following shall be prohibited as incompatible with the common market: all agreements between undertakings, decisions by associations of undertakings and concerted practices which may affect trade between Member States and which have as their object or effect the prevention, restriction or distortion of competition within the common market (…).



Abuse of dominant position and refusal to supply

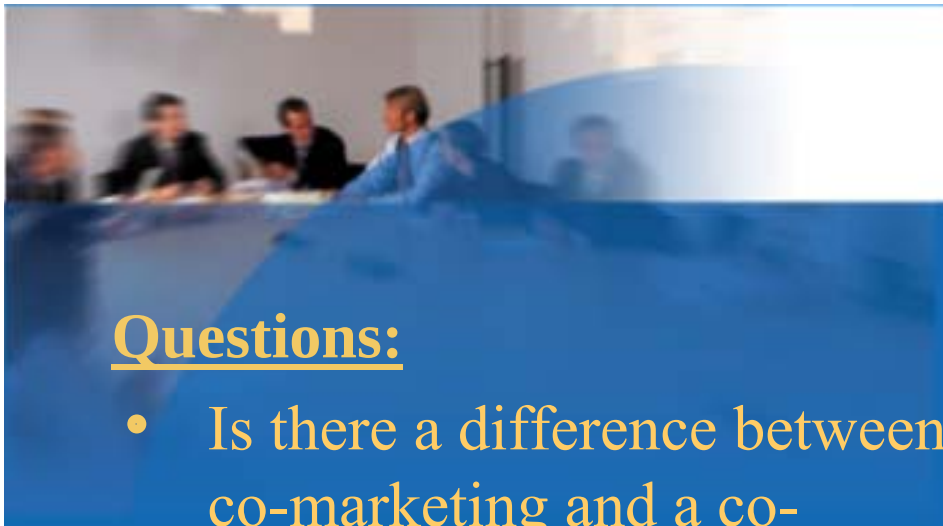
- Art. 82 EC Treaty

  Any abuse by one or more undertakings of a dominant position within the common market or in a substantial part of it shall be prohibited as incompatible with the common market insofar as it may affect trade between Member States.

NautaDutilh

2011

- The CEO of BIOTECH and BIG PHARMA #2 meet regularly in the context of their Alliances meetings. They discuss informally how to deal with parallel trade (e.g. fixing minimum prices in low price countries; tying products; rebates to hospitals; etc.)



NautaDutilh

Questions:

- Is there a difference between a co-marketing and a co-promotion agreement?
- Can partners in such agreements discuss price and other marketing issues in the same manner?

Legal issues:

- Difference between co-promotion and co-marketing
- Tying of products
- Competition law aspects

Anticompetitive agreements

- Art. 81(1) EC Treaty

  (…) and in particular those which :

  (a) directly or indirectly fix purchase or selling prices or any other trading conditions;

  (b) limit or control production, markets, technical development, or investment;

  (c) share markets or sources of supply;

(d) apply dissimilar conditions to equivalent transactions with other trading parties, thereby placing them at a competitive disadvantage;

(e) make the conclusion of contracts subject to acceptance by the other parties of supplementary obligations which, by their nature or according to commercial usage, have no connection with the subject of such contracts.

NautaDutilh

2014-2018

- 2014: generic applications can be filed with EMEA
- 2015: protein α patent expires
- 2016: 10 years RDP expiry
- 2017: 10 + 1 year RDP expiry
- 1 October 2018: SPC expiry (with Swiss MA date)
- 1 June 2020: SPC expiry (with EU MA date)
- Orphan indications; new therapeutic indications; etc

NautaDutilh

Questions:

- Can a biosimilar product be authorised without additional clinical data?
- Will the generic product have the same label as the reference product?
- How can I challenge a marketing authorisation for a biosimilar product?
- Can generic companies file a biosimilar MAA nationally?
- Will biosimilar be reimbursed as small chemical entities generics?

Legal issues:

- Abridged procedure and biosimilar products
- Orphan drug market exclusivity and off-label use
- Litigation against generic authorisation
- Centralised or decentralised abridged procedures