

## Impact of Patents and Other Incentives on Biotech Product Development

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### Biotechnology:

- ◆ More than one-fifth of newly launched medicines and increasingly, medical devices, as well as diagnostic products and genetic testing services are now biotechnology-derived.
- ◆ New ways for diagnosis, prevention and therapy led to the creation of a new tier of biopharmaceutical companies, and contribute to the restructuring of the pharmaceutical industry and even of health care systems.
- ◆ Biotechnological research related to serious, chronic and rare diseases is exploiting the understanding of the basic disease mechanisms derived from the human genome project and other genomes.
- ◆ For the first time in history, biotechnology allows the development of a therapy for rare genetic diseases.

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### Patents:

- ◆ Protect inventions from unlicensed commercial competition.
- ◆ Are an incentive for investment into the subject of the patent, difficult to replace by other incentives.
- ◆ Play a crucial role in the development of the biotechnology industry.
- ◆ Enable the attraction of the kind of investments needed: guarantee the development of biotech inventions into commercial products or services.
- ◆ Ensure the advancement of science into benefits and welfare for citizens: patents force information to be made publicly available and allow it to be used in further research, fostering scientific progress.

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## Patents:

- ◆ Interplay between patent offices and courts guarantees a balance between patent rights and societal needs:
  - ◆ patent offices grant or deny rights based on patent law, and case law (developed by courts), but have no special competencies on issues of morality or public policy ;
  - ◆ courts deciding on validity and enforceability of patents have a strong consideration of public policy and societal context of a specific country;
- ◆ The concern that biotech patents would be too broad seems invalid today: the combination of patenting rules and their interpretation by the courts have prevented too broad patent rights (in analogy with the observation that few cows died as a result of the construction and operation of railroads).

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## Patents:

- ◆ Even if patents are granted, innovative products will not benefit patients if a health care system in a specific country is not granting reimbursement in a timely fashion: patents do not provide products, they are only enabling development.

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## Patents and the development of therapeutics:

- ◆ Patents may only result in commercial products after substantial further work, leaving only very few years of patent protection at the end.  
Examples:
  - ◆ monoclonal antibodies yielding the first therapeutics after a 20-year time lag;
  - ◆ gene therapy for which many patents have been filed, is not yet having products on the market : waiting for the ultimate vector and the clinical data to support an approval.

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## Patents and the development of biotech products:

- ◆ Since a living organism has only one genome, patents provide a time-limited, exclusive control over a gene, a therapeutic field,... for which there may not be an alternative.
- ◆ The development of a therapeutic, involving the identification of the active compound, *in vitro* safety and efficacy testing, the finding of dose and product specifications, *in vivo* clinical trials, manufacturing scale-up, validation and QA/QC etc... requires between at least 100 up to 800 million US\$, investment not attainable without patent protection .

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## Patents and the development of biotech products:

- ◆ It may be necessary for one company to have exclusive rights to a patent in order to develop a therapeutic, especially when the related disease is rare. Non-exclusive rights would not guarantee enough interest in the investment.
- ◆ It would be unfair to deprive investors from a just return on their investment which would stifle development of new therapeutics or diagnostics/prognostics needed by the affected patients.

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## Ethics and societal issues:

- ◆ To be patentable, an invention has to be novel, involve an inventive step, and be industrially applicable.
- ◆ The invention's applications cannot be contrary to morality or "ordre public".
- ◆ Mere discoveries are not patentable, e.g. methods for treatment of the body by surgery or diagnostic methods practised on humans, but then again this does not apply to products used in these methods.
- ◆ The definition of patentability of inventions ensures the advancement of science into benefits and welfare for citizens.
- ◆ One of the challenges in our society is to achieve consensus on the limitations of the application of new technologies, taking ethical and moral concerns into account.

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## Orphan drug regulations:

- ◆ Provide, although for a shorter time period, a "patent-resembling" market exclusivity incentive to industry.
- ◆ In the US, based on the Orphan Drug act, over 200 therapies for rare diseases have been developed, of which close to half are biotech-based complex biological products.
- ◆ Of all newly approved biopharmaceuticals over 1995-2000, 46 % were orphan drugs in the US.
- ◆ "Patent-like" incentives proven to be instrumental in creating a biotech industry in the 80's, as over 50% of all new biotech start-ups in the US were based on the Orphan drug act..

## Orphan drug regulations:

- ◆ In Europe, the first products based on the new orphan medicinal products regulation are now on the market, and 88 products have already been designated "orphan".
- ◆ Even more importantly, these regulations are providing medicines for patients with rare diseases which have been incurable hitherto.

## Genetic testing:

- ◆ Since the 60's: cytogenetic testing (chromosomes).
- ◆ Since the 90's: molecular genetic testing looking for mutations in human genes.
  - ◆ single gene disorders result in the absence of a critical protein, or the presence of an abnormal protein. Examples: cystic fibrosis, muscular dystrophy, Gaucher's disease, Huntington disease;
  - ◆ many, more common, disorders have a genetic component, which may involve several genes.
- ◆ Development costs for genetic tests are steeply increasing.

## Genetic testing:

- ◆ Before a genetic test is ready for routine diagnostic use, it should have been tested for its clinical utility, with the aim:
  - ◆ to assist the medical staff in the diagnosis and the treatment.
  - ◆ to help in the counseling of a patient (and sometimes to his family members), in a non-directive and professional way.
- ◆ It is a specialized service, in competition with academia as well as with other commercial entities, with a very large personnel cost component: to reduce cost per test substantially is only possible by economy of scale, or by automation (e.g. also e-business).

## Genetic testing:

- ◆ Increasing technical and development complexity justifies a high initial price for a novel genetic test:
  - ◆ increasingly complex test development and royalty stacking from licenses on technology platforms, genes, mutations, etc.;
  - ◆ the need for more and higher quality epidemiological and genetic population data;
  - ◆ increasing regulatory costs, also for home-brew tests, which include stricter QA/QC requirements as well as certification costs for the laboratory;
  - ◆ increasing need for clinical counseling.
- ◆ Only larger, commercially oriented laboratories may be equipped to deliver the quality of the test results expected by society at an affordable price.

## Genetic testing:

- ◆ Costs related to increased liability are additional guarantees to take quality and QA at heart.
- ◆ Licensing of genes and technologies for genetic testing:
  - ◆ non-exclusive rights result in royalties on gene patents and must-have technologies from 1 to 4%, with outliers to over 10 %;
  - ◆ exclusive rights result in royalties from 6 to 10%, up to over 20%;
  - ◆ outlicensing for commercialization of patent rights will largely depend on the available market, and the medical need for the test;
  - ◆ esoteric, highly complex and specialized tests are more likely to be licensed in an exclusive manner.

## Genzyme Corporation and patents

- ◆ Genzyme is developing therapeutics for rare genetic disorders as one of its prime targets.
- ◆ Genzyme Genetics, is one of the largest providers of genetic testing services in the world. E.g. our test for cystic fibrosis, testing simultaneously for the 87 most common mutations.
- ◆ Has not participated in the patent "landgrab" with patent attorneys filing patent claims on every sequence coming out of our proprietary gene identification technology.
- ◆ Is actively protecting genes, sequences and other biological entities such as cancer antigens, based on specific information regarding their utility.
- ◆ Aims to develop improved diagnostics, therapeutics or prophylactics for unmet medical needs.
- ◆ Out- and in licenses a number of intellectual property rights.<sup>P. 16/19</sup>

## Genzyme Corporation and licensing

- ◆ In the genetic testing arena, granted rights are mostly non-exclusive.
  - ◆ rights are depending on the market of which the territory, the rarity of the disease and the disease field are components;
  - ◆ getting or granting exclusive rights may still be appropriate to make the resulting service economically viable, while still fitting our company image;
  - ◆ the opinion of the medical profession and of the involved patient groups are of high importance and carry a high weight in our decision-making process;
  - ◆ outlicensing e.g. patent rights for p53, and for MSH-2 and APC genes in colon cancer diagnosis.

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## Genzyme Corporation and licensing

- ◆ In therapeutic fields, or for therapeutic targets, our strategy is to license exclusively or non-exclusively based on the characteristics of the claims and in a field-limited manner.
- ◆ In the research field, Genzyme actively encourages use of its technology: see licensing strategy related to our SAGE (Serial Analysis of Gene Expression) technology, providing access under appropriate agreements without fees for the academic researcher, but requiring fees for commercial access.

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## Trends:

- ◆ New strategies of combining biotech with informatics bring biotech intellectual property issues closer to those of the software industry.
- ◆ Data mining and manipulating of data sets from databases replace wet laboratory work, and put more emphasis than before on confidentiality and privacy of patient data used in research or clinical trials.
- ◆ Tissue banks and ownership of clinical tissue is another area with growing need for data and knowledge protection, creating its own issues and challenges.
- ◆ There is increasing participation of patient advocacy groups in the process from research to product.

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### 1. Introduction.

More than one-fifth of the many new medicines launched each year are now biotechnology-derived, and increasingly, medical devices, as well as diagnostic products and genetic testing services also use biotech techniques. New ways for diagnosis, prevention and therapy have not only led to the creation of a new tier of biopharmaceutical and technology companies, but also contribute to the restructuring of the pharmaceutical industry and even of health care systems. Biotechnological research related to serious, chronic and rare diseases is exploiting the understanding of the basic disease mechanisms derived from the human genome project and other high-tech genetic studies, as well as other genomes. For the first time in history, biotechnology allows the development of a therapy for some of the rare genetic diseases, and the number of such therapies is increasing, based on the orphan drug regulations in the US, Japan and Europe. These regulations provide, although much shorter in time, a "patent-resembling" market exclusivity incentive to industry. Since the 90's, molecular genetic testing, looking for mutations in human genes, is increasingly being used to detect genetic defects, and is complementing or even replacing cytogenetic testing. Single gene disorders result in the absence of a critical protein, or the presence of an abnormal protein. Cystic fibrosis, muscular dystrophy, Gaucher's disease or Huntington disease are examples of disorders caused by a single gene. For cystic fibrosis, more than 900 mutations, most of them very rare, have been found. Many, more common, disorders have a genetic component, which may involve several genes.

### 2. Patents, orphan drugs and biotechnology.

A patent protects an invention from unlicensed commercial competition, and is as such an incentive for investment into the subject of the patent, which is difficult to replace by other incentives. A broad patent on a novel technology may only result in commercial products after substantial further work, leaving only very few years of patent protection at the end. Monoclonal antibodies are a good example of such novel technology yielding the first commercial therapeutics after a 20-year time lag. However, diagnostic applications of monoclonals had been pursued for a long time. Gene therapy is another example of a technology for which many patents have been filed, but without products on the market as the ultimate vector to deliver the genes is still under development, and the clinical data to support an approval are not yet there.

Since the biotechnology industry is requiring high levels of investments, patents play a crucial role in its development, because such intellectual property enables the attraction of the kind of investments needed. In addition, patenting of biotech inventions brings along some unique issues. Each living organism has only one genome, and a patent would provide a, be it time-limited, exclusive control for a company or an institution over a gene, a therapeutic field,... for which there may not be many if any alternative.

However, such exclusive rights are so far the only guarantee for the development of such invention into a commercial product or service from raw research data. Development of a therapeutic product, involving the identification of the active compound, *in vitro* safety and efficacy testing, the finding of dose and product specifications, *in vivo* clinical trials, manufacturing scale-up, validation and QA/QC etc... requires between at least 100 up to on average 400 million US\$, a level of investment which is not attainable without patent protection.

Development costs for genetic tests are also steeply increasing, because of the population statistics required on the one hand, and the royalty stacking coming from licenses on technology platforms, genes, mutations, research tools etc... on the other hand. The increasing technical and development complexity needed justifies a high initial price for a novel genetic test. Moreover, before a genetic test is ready for routine diagnostic use, such a test should have been tested for its clinical utility, meaning that the test should assist the medical staff in the diagnosis and the treatment or the counseling of a patient. Providing diagnostic or predictive genetic testing is indeed not just the provision of a test result, but also of non-directive and professional genetic counseling to the patient and sometimes to his family members. Counseling is a necessary but also costly part of the service. Genetic testing is a specialized service, with as a consequence a very large personnel cost component, and therefore much less opportunity for cost reduction. It would be unfair, and therefore detrimental to efforts in this field, to deprive investors from a just return on their investment in this field, thereby stifling developments of new tests or of new therapeutics needed by the affected patients.

In the US, based on the Orphan Drug act, over 200 therapies for rare diseases have been developed, of which close to half are biotech-based complex biological products. In Europe, the first products based on the new orphan medicinal products regulation are now on the market, and 88 products have already been designated "orphan". This "patent-like" incentive not only has proven to be instrumental in creating a biotech industry in the 80's, as over 50% of all new biotech start-ups in the US were based on the Orphan drug act. It also provided much needed medicines for patients which have been incurable hitherto. Of all newly approved biopharmaceuticals over 1995-2000, 46 % were orphan drugs.

### 3. Genzyme's strategy in licensing.

One of the characteristics of Genzyme Corporation is that it has not been participating in the gene patent "landgrab". It has not had patent attorneys filing patent claims on every sequence coming out of our proprietary gene identification technologies. This attitude differentiates us from other groups that may have rushed to protect every partial gene sequence, even before they knew what the sequence relates to. Genzyme has however actively protected genes, sequences and other biological entities such as tumor antigens, for which we have specific information on utility, aiming to develop improved diagnostics and/or more efficient and safer therapies for the underlying disease.

Genzyme does outlicense a number of patents in the cancer field, such as for p53, and for MSH-2 and APC genes in colon cancer diagnosis. In the genetic testing arena, these licenses are mostly non-exclusive, but Genzyme recognizes that getting or granting exclusive rights on a gene or a cancer antigen, also for diagnostic genetic testing, may be appropriate or even needed to make the resulting service economically viable while still fitting our company image, depending on the market of which the territory, the rarity of the disease and the disease field are components. It has to be specified that the opinion of the medical profession and of the involved patient groups will be of high importance and carry a high weight in Genzyme's decision-making process.

For applications in therapeutic fields, or for therapeutic targets, our strategy is either to license exclusively to one commercial partner or to license non-exclusively based on the characteristics of the claims and in a field-limited manner. In the field of academic research, Genzyme actively encourages

use of its technology, as is proven by our licensing strategy related to our proprietary SAGE (Serial Analysis of Gene Expression) technology, by providing access to it under appropriate agreements without license fees for the academic researcher, while at the same time requiring license fees for commercial access to SAGE.

#### 4. Licensing of genes and related costs.

In the field of genetic testing, royalties for the inlicensing of patents on genes and must-have technologies will range from 1 to 4% for a non-exclusive license, with outliers to over 10 %, and ranging from 6 to 10%, up to over 20% for exclusive licenses. Outlicensing for commercialization of a genetic test will largely depend on the available market on the one hand, and the medical need for the test on the other. It is clear that esoteric, highly complex and specialized tests are more likely to be licensed in an exclusive manner as we discussed above. Being a service business, providing services in competition with academia as well as with other commercial entities, the only ways to reduce cost per test substantially is by economy of scale, meaning high volumes per test, and by automation, potentially including e-business opportunities in the future. An example of a higher volume test is the Genzyme test for cystic fibrosis, which simultaneously tests for the 87 most common mutations at the price of only 200 US\$, low compared to the prices asked for specialized tests such as for BRCA1 or neurological disorders, which range from 1-5000 US\$.

Prices in the genetic testing field will however experience upward pressure. The main factors contributing are the increasingly complex test development, the need for more and higher quality epidemiological and genetic population data, increasing regulatory costs, also for home-brew tests, which include stricter QA/QC requirements as well as certification costs for the laboratory, and increasing need for counseling. It is clear that only larger, commercially oriented laboratories will be equipped to deliver the quality of the test results expected by society at an affordable price. Potentially high liability-related costs act as a complementary guarantee that such laboratories do take quality and QA of their services at heart.

For the development of therapeutic products, in many cases it will be necessary to keep exclusive rights to intellectual property in the hands of one company, especially when the related disease is rare. Non-exclusive rights would not guarantee enough interest to invest the high amounts needed to develop a therapeutic.

#### 5. Ethics and societal issues.

To be patentable, an invention has to be novel, involve an inventive step, be industrially applicable. In addition the invention's patentability cannot be contrary to morality. Patentability of inventions ensures the advancement of science into benefits and welfare for citizens. It is one of the challenges in our society to achieve consensus on the limitations of the application of new technologies, taking ethical and moral concerns into account, and the issue around patenting of genes and other biological entities is part of this challenge. Patent offices are specialized offices, which grant or deny patent rights based on patent law, but do not have a specific consideration for public policy. Courts, which have to decide on enforceability of patents, are mostly non-specialized, having a consideration for public policy and societal context of a specific country. This way, the system guarantees a balance between patent rights and rights of commercialization based on patents.

Five or more years ago, there was a concern that many biotech patents would be so broad that they would dominate large fields. Today, this does not seem to be the case because the combination of the patenting rules and their interpretation by the courts seem to have prevented that to happen. The scenarios of scare tactics did not convert into reality, in analogy with the observation that few cows died as a result of the construction and operation of railroads. Patents also force information to be made publicly available and

allow it to be used in further research, and as such in general also foster scientific progress. Without patents, a culture of secrecy and non-disclosure would be created within the scientific community, protecting secrets like Coca-Cola successfully did. Moreover, the earlier mentioned success of the orphan drug regulations underline the importance of incentives for industry to develop much-needed products as solutions for unmet medical needs in our society. But even if patents are granted, innovative products will not benefit patients if the health care systems in a specific country are not granting reimbursement in a timely fashion.

#### 6. Trends, new strategies.

New strategies of combining biotech with informatics bring biotech intellectual property issues closer to those of the software industry. Data mining and manipulating of data sets from databases replace wet laboratory work, and put more emphasis than before on confidentiality and privacy of patient data used in research or clinical trials. The creation of tissue banks and ownership of clinical tissue is another area with growing need for data and knowledge protection, creating its own issues and challenges. The SNP consortium and similar initiatives and their complex interplay with front-line private genomics companies serve society by advancing knowledge and awareness alike.

Another trend is the increasing participation of patient advocacy groups in the process from research to product. Patients are not only active in the political debate, but become involved in the complex progression from research and development over patenting and licensing of inventions and regulatory committees to manufacturing of products related to their disease. Such patient groups are partnering with industry and researchers to progress science and advance developments of products for diagnosis and treatment in their field.

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