Die Zulassung von Ultra Orphans und die Rolle des COMP und CAT

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Orphan drugs in Europe

PERSPECTIVES

OUTLOOK

European regulation on orphan medicinal products: 10 years of experience and future perspectives

The Committee for Orphan Medicinal Products and the European Medicines Agency Scientific Secretariat

Abstract | In 2000, regulation on orphan medicinal products was adopted in the European Union with the aim of benefiting patients who suffer from serious, rare conditions for which there is currently no satisfactory treatment. Since then, more than 850 orphan drug designations have been granted by the European Commission based on a positive opinion from the Committee for Orphan Medicinal Products (COMP), and more than 60 orphan drugs have received marketing authorization in Europe. Here, stimulated by the tenth anniversary of the COMP, we reflect on the outcomes and experience gained in the past decade, and contemplate issues for the future, such as catalysing drug development for the large number of rare diseases that still lack effective treatments.

"Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by the careful investigation of cases of rarer forms of disease." (William Harvey, 1657)

It is estimated that the combined number of people suffering from a rare disease in Europe and the United States exceeds 55 million[1], and it is generally accepted that ~5,000–7,000 rare diseases exist, with approximately 250 new diseases being described on an annual basis[1,2] (see Orphanet for further details). However, data from literature searches suggest that the majority (>3,500) of rare diseases affect only a few patients worldwide[3]. This might be attributed, in part, to an improved knowledge of disease biology and genomics, which has resulted in the categorization of more prevalent diseases into several distinct diseases[4].

Historically, the small number of patients with a particular rare disease — and hence the low potential for pharmaceutical companies to achieve a return on their investment in the development of drugs to treat such diseases — was a major factor limiting industry involvement in the field[5]. However, starting with the introduction of the US Orphan Drug Act in the United States in 1983, legislation incorporating regulatory and economic incentives for orphan drug development has been introduced in several countries and regions, and this has had a substantial impact. For example, a recent assessment of the effects of the US Orphan Drug Act showed that in the 25 years following its introduction, ~250 drugs have been approved by the US Food and Drug Administration (FDA) for more than 200 rare diseases[6]. Similarly, in Europe, the adoption in 2000 of the European Commission (EC) Regulation Number 141/2000 of the European Parliament and the Council, the EC Regulation Number 847/2000, and the implementation of incentives (BOX 1) has also helped to stimulate the development of drugs for the treatment of rare diseases[7,8].

In Europe, the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) is responsible for reviewing applications from individuals or companies seeking 'orphan medicinal product designation' for products they intend to develop for the diagnosis, prevention or treatment of life-threatening or serious conditions that affect not more than 5 in 10,000 people in the European Union (EU). After evaluation of the application, the final opinion of the COMP is sent by the EMA to the EC, which is responsible for adopting a decision. In addition, the COMP advises the EC on policies and on drawing up guidelines on orphan medicinal products in the EU, and assists them in liaising internationally on these matters. The COMP is continually adding to and supported by the EMA expert network, which consists of 3,000–4,000 specialists, and was notably the first committee at the EMA to include patients' representatives as full members[9] (BOX 2).

In March 2010, the COMP held its 110th plenary meeting, which marked the tenth anniversary of orphan drug regulation in the EU. In this article, we discuss the outcomes of the first decade of this regulation and consider some of the challenges and opportunities for orphan drug development and regulation in the following decade.

Outcomes of the first decade

Orphan medicinal product designations and marketing authorizations in the EU. By the end of 2010, more than 850 positive opinions for orphan medicinal product designation had been adopted from the 1,235 applications that have been reviewed since 2000 by the COMP (TABLE 1). Designations for an orphan medicinal product are awarded for the treatment, prevention or diagnosis of a rare disease (also referred to as 'condition' in the context of orphan drug legislation). Designations may be awarded to multiple orphan medicinal products targeting the same rare disease; conversely, multiple designations may be awarded to one orphan medicinal product targeting different rare diseases. Therefore, a single orphan medicinal product could have more than one indication. However, this is rare; there is currently one orphan medicinal product with six indications and there are five orphan medicinal products with two indications.

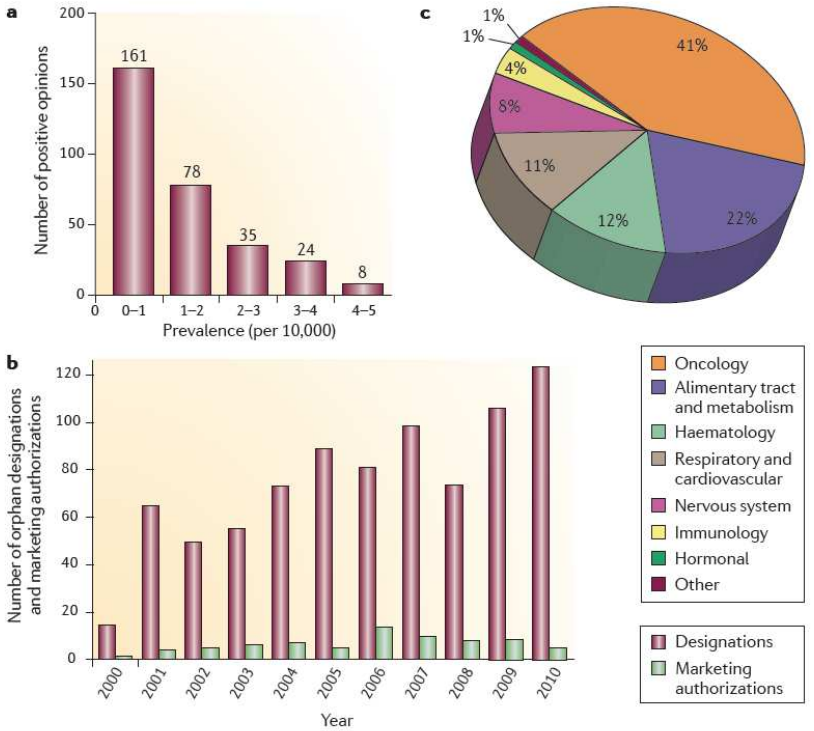


Figure 1 | **Statistics on orphan medicinal product designations and approvals in the European Union in the past decade. a** | Distribution of the prevalence of conditions for which designations for orphan medicinal products have been granted, considering only one designation per indication in those cases for which more may have been granted. This graph shows that 52% of orphan designations are awarded to medicinal products for diseases that affect fewer than 1 in 10,000 patients. **b** | Annual number of orphan drug designations and marketing authorizations from April 2000 to December 2010. **c** | Distribution of orphan drug marketing authorizations by therapeutic area. Out of the 63 designated orphan drugs that obtained marketing authorization in the European Union by December 2010, 41% are for oncology indications.

Orphan drugs: An emerging trend

CORRESPONDENCE

LINK TO ORIGINAL ARTICLE

Orphan products: an emerging trend in drug approvals

Timothy Coté, Aditya Kelkar, Kui Xu, M. Miles Braun and M. Ian Phillips

As highlighted in a recent News Feature, Rare incentives (*Nature Rev. Drug Discov.* 7, 190–191; 2008)[1], 2008 saw the 25th anniversary of the US Orphan Drug Act (ODA), which was promulgated in recognition of the economic barriers to developing drugs for rare diseases (defined as those that affect fewer than 200,000 persons in the United States)[2]. The ODA encourages the development of promising new compounds by providing significant fiscal benefits: FDA-enforced marketing exclusivity, tax credits and fee exemptions. These products are designated 'orphan products' by the FDA's Office of Orphan Products Development, and if shown to be safe and effective can be approved for marketing. As of 20 July 2009, 343 orphan products have been marketed to treat rare diseases[3]. By contrast, only 10 such products were approved in the 10 years preceding the ODA[4].

The ODA has been credited not only with offering new hope for those who suffer from rare diseases, but also with nurturing an expanding biotechnology sector and personalizing drug development[5,6]. In a time of relative contraction in the development of new small-molecule therapeutics, orphan drug development has emerged as a burgeoning sector of the pharmaceutical industry. This correspondence documents its growth.

We used internal and publicly available data on first-time FDA approvals[5,7] from January 1983 through to December 2008. We categorized approvals as 'drugs' if marketing authorization was gained under a New Drug Application (NDA) or as 'biologics' if under a Biologics License Application (BLA). We further classified these approvals as 'orphan' or 'non-orphan', depending on whether the product held an antecedent orphan designation. Only new drugs and biologics were considered; we did not include efficacy supplements (applications for new indications of already approved drugs) or formulation changes.

In 1983, the year when the ODA was signed, there was 1 new orphan drug approval and no new orphan biologic approvals. FIG. 1 shows trends by 5-year periods for all 636 new drugs and 123 new biologics that were approved by the FDA between 1984 and 2008. Trends for orphan drug and biologic approvals were different. FIG. 1a shows that the number of orphan drugs approved remained relatively constant from 1984 through 2008 (with 31 approvals in the 2004–2008 period), but the number of non-orphan drugs approved peaked at 145 in the1994–1998 period and declined to 69 between 2004–2008. Consequently, the proportion of all drug approvals that are orphan drugs has increased from 17% (19/113) in 1984–1988 to 31% (31/100) in 2004–2008, and was 35% (6/17) in 2008. By contrast, FIG. 1b shows that approvals of both orphan and non-orphan biologics have generally increased from 1984 to 2008, and there was no meaningful trend in the proportion of biologic approvals that have orphan indications.

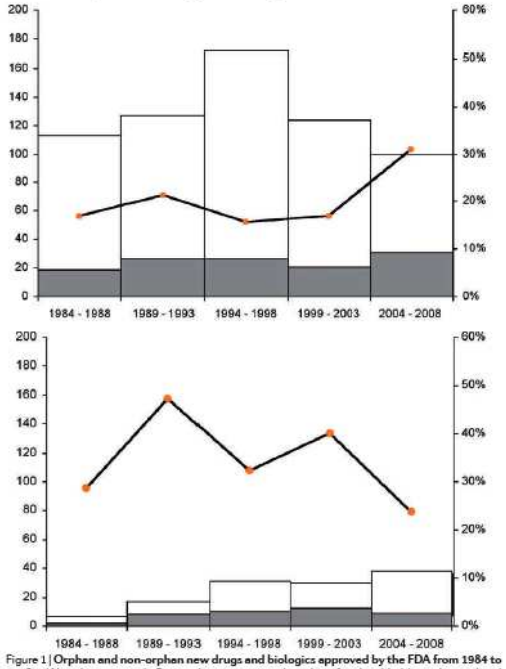


Figure 1 | **Orphan and non-orphan new drugs and biologics approved by the FDA from 1984 to 2008. a** | New drug approvals. Bar graph represents total number of orphan (dark bar at bottom) and non-orphan (white bar at top) new drugs approved every 5 years. Line graph represents percentage of new drug approvals that were orphan drugs in each 5-year period. **b** | New biologics approvals. Bar graph represents total number of orphan (dark bar at bottom) and non-orphan (white bar at top) new biologics approved every 5 years. Line graph represents percentage of new biologic approvals that were orphan biologics in each 5-year period.

Big pharma moves from 'blockbusters' to 'niche busters'

Since its passage in 1983, the US Orphan Drug Act has led to the approval of more than 350 drugs for around 200 rare diseases, mostly thanks to small biotech startups looking for a unique niche in the marketplace. Yet with the demise of big pharma's traditional business model, some of the world's largest drug makers are aggressively entering the rare disease sector.

"There's a trend toward the death of the blockbuster, so people are moving toward the niche buster," says Christopher Milne, associate director of the Tufts Center for the Study of Drug Development in Boston.

The latest company to enter the orphan market is New York–based Pfizer, which in June announced the creation of a new research unit devoted to developing and commercializing new biologics to treat rare diseases. The move follows GlaxoSmithKline's February announcement that the London-based firm was forming a similar stand-alone unit. Other companies, including the Swiss drug maker Novartis and Indiana's Eli Lilly, have made similar investments.

"It's the industry saying, 'where is there an unmet need, and how can I address it?'" says Edward Mascioli, who is heading up Pfizer's new unit, based in Cambridge, Massachusetts.

According to Milne's calculations, the share of orphan product approvals in the US by large biopharma grew from 35% ten years ago to 56% in 2006–2008, the last years that records were kept (*Tufts CSDD Impact Rep.* **12**, 1–4, 2010). Milne also found that only four orphan drugs were among the top 200 bestselling medications in the US a decade ago; by 2006–2008, the number had quadrupled to 16 orphan products, with annual sales ranging from $200 million to nearly $2 billion each.

With drying drug pipelines and increasing generic competition, the orphan drug sector offers several attractions for pharma. It provides tax credits on clinical trial expenses, grant funding from the US Food and Drug Administration (FDA), seven years of marketing exclusivity after an orphan drug is approved and a waiver of user fees. "The economics are much more attractive for rare diseases than they were in the past," says Usama Malik, Pfizer's head of business innovation. What's more, orphan drugs are often given high price tags to help recoup costs within the small market, which further boosts pharma's bottom line.

> "Society is turning away from us and saying, 'this is a raw deal'."

Beyond profitability, pharma's shift toward rare diseases also helps in the court of public opinion, notes Bernard Munos, a former advisor on corporate strategy for Eli Lilly (who retired last month). With few new drug entities emerging from the industry's pipeline, and more than 6,000 diseases affecting an estimated 25 million Americans still without a therapeutic option, "society is turning away from us and saying, 'this is a raw deal; this is not the covenant that we agreed to,'" Munos says. "Ultimately, the acid test of success for the industry is our impact on public health."

To complement the private sector, federal agencies are also searching for new ways to bolster research into orphan products. In March, for example, the FDA created the Rare Disease Review Group (which held its first public hearings this summer), and the regulatory agency has teamed up with the National Institutes of Health to run a rare disease investigator training course, scheduled for October. At the two agencies' request, the Institute of Medicine is also conducting a review of national policy for rare disease research and product regulation; recommendations are due next month.

Elie Dolgin

Advocates to bring rare disease philanthropy under one umbrella

NORTH BETHESDA, MARYLAND—Rare diseases, defined in the US as those occurring in fewer than 200,000 people in the country, collectively affect around 10% of individuals worldwide. Yet the majority of the public can hardly name a single rare disease. As a result, most orphan disorders fall under the radar and remain poorly funded.

Patient advocacy groups are one of the primary backers of research into rare diseases. But the hundreds of disease-specific foundations and organizations out there rarely work together to raise funds, and the rare disease landscape has remained fractured and siloed. To remedy the situation, the R.A.R.E. Project, an initiative launched in 2008 to raise awareness and accelerate the development of therapies for rare diseases, is rolling out a new platform to serve as a one-stop shop for innovative research into all 6,000-plus rare diseases.

"We're trying to bring new people in to care about rare disease," says Nicole Boice, founder and president of the Children's Rare Disease Network, part of the R.A.R.E. Project. "The idea in fact is that we will stimulate foundations to think differently about funding and research," adds R.A.R.E. Project CEO Jonathan Jacoby.

Modeled after services such as Kiva and Save the Children, where donors can precisely match their contributions to the specific project of their choice, R.A.R.E. is launching a website, called the Global Genes Fund, intended as a clearinghouse for rare disease philanthropy, where people can select projects to fund. Jacoby hopes that by bringing hundreds of research projects under one umbrella, individuals, foundations and corporations will be more likely to donate to multiple causes.

Last month, R.A.R.E. secured $50,000 for a beta version of the site, which the organization plans to make public later this year, Boice and Jacoby announced here at the Genetic Alliance annual conference on 16 July.

For projects listed on the page—which will be vetted through some as yet undefined criteria—supporters will be able to read an affected child's personal story, the details of the study and why the research is important, among other details.

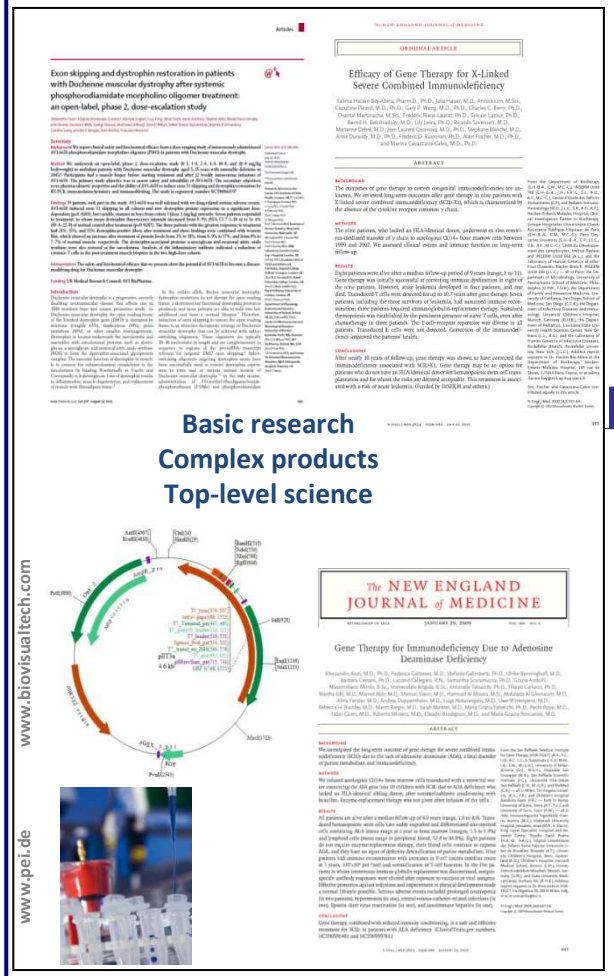
"The challenge with rare diseases is that they're rare, and there aren't that many families that can raise money," says Geraldine Bliss, research chair of the Phelan-McDermid Syndrome Foundation. "A concept like [the Global Genes Fund] is really great because it allows you to reach beyond your immediate circle of support."

"The rare disease community is large enough and deserving enough to have an effort like this and to succeed at it," Boice says. "It's time, it's really time."

Elie Dolgin

Committee for Advanced Therapies (CAT)

Our environment: The „academic gap“ and „small company gap“



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Complex products
Top-level science

Regulation 1394/2007
(„ATMP regulation“)

Directive 2009/120/EC
amending Directive 2001/83/EC
(”revised Annex I”)

Marketing
authorisation

Translation into a medicinal product
(”translational medicine”)

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The ATMP landscape in Europe

commentary

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

Romaldas Maciulaitis[1,2], Lucia D'Apote[3], Andrew Buchanan[3], Laura Pioppo[3,4] and Christian K Schneider[1,5,6]

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The first two authors contributed equally to this work.

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Molecular Therapy vol. 20 no. 3 march 2012

Analysis of the EudraCT database (2004-2010):
318 trials with ATMPs

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Paper calls for continued support for development of advanced therapies

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News

13/03/2012

Paper calls for continued support for development of advanced therapies

The European Medicines Agency needs to continue reaching out to academic institutions, charities and small companies developing advanced-therapy medicines, according to a paper published in the journal *Molecular Therapies* earlier this month.

The paper, written by members of the Committee for Advanced Therapies (CAT), its secretariat and other European Medicines Agency staff, found that the main sponsors of clinical trials of advanced-therapy medicines performed in the European Union (EU) between 2004 and 2010 often have limited financial resources and a limited capacity to navigate regulatory procedures.

It argues that this causes a translational gap between development of these medicines and reaching later regulatory milestones, and that regulators need to continue working towards closing this gap in a proactive manner.

The paper emphasises the numerous ways in which organisations developing advanced-therapy medicines can engage in dialogue with the Agency and receive guidance on regulatory procedures. These include scientific advice, meetings with the Innovation Task Force, and classification or certification of medicines as advanced-therapy medicinal products by the CAT. The CAT has also run focus groups to discuss aspects of the development of advanced-therapy medicines with its stakeholders, and organised a scientific workshop with learned societies.

Advanced-therapy medicines are medicines that are made from genes and cells. They may offer groundbreaking new treatment opportunities for many diseases and injuries. All advanced-therapy medicines intended for marketing in more than one EU Member State are authorised centrally via the European Medicines Agency, following scientific evaluation by the CAT.

The analysis presented in the paper, which looked at clinical studies in the EU Drug Regulating Authorities Clinical Trials (EudraCT) database, found that over three-quarters of the advanced-therapy medicines under development were cell-based medicines. Most medicines were being studied in cancer, followed by conditions affecting the heart, blood vessels and blood.

Related information

- Clinical development of advanced therapy medicinal products in Europe: Evidence that regulators must be proactive
- Advanced therapies
- Committee for Advanced Therapies (CAT) work programme 2010 - 2015 (18/11/2010)

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The ATMP landscape in Europe

commentary

Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive

Romaldas Maciulaitis[1,2], Lucia D'Apote[3], Andrew Buchanan[3], Laura Pioppo[3,4] and Christian K Schneider[1,5,6]

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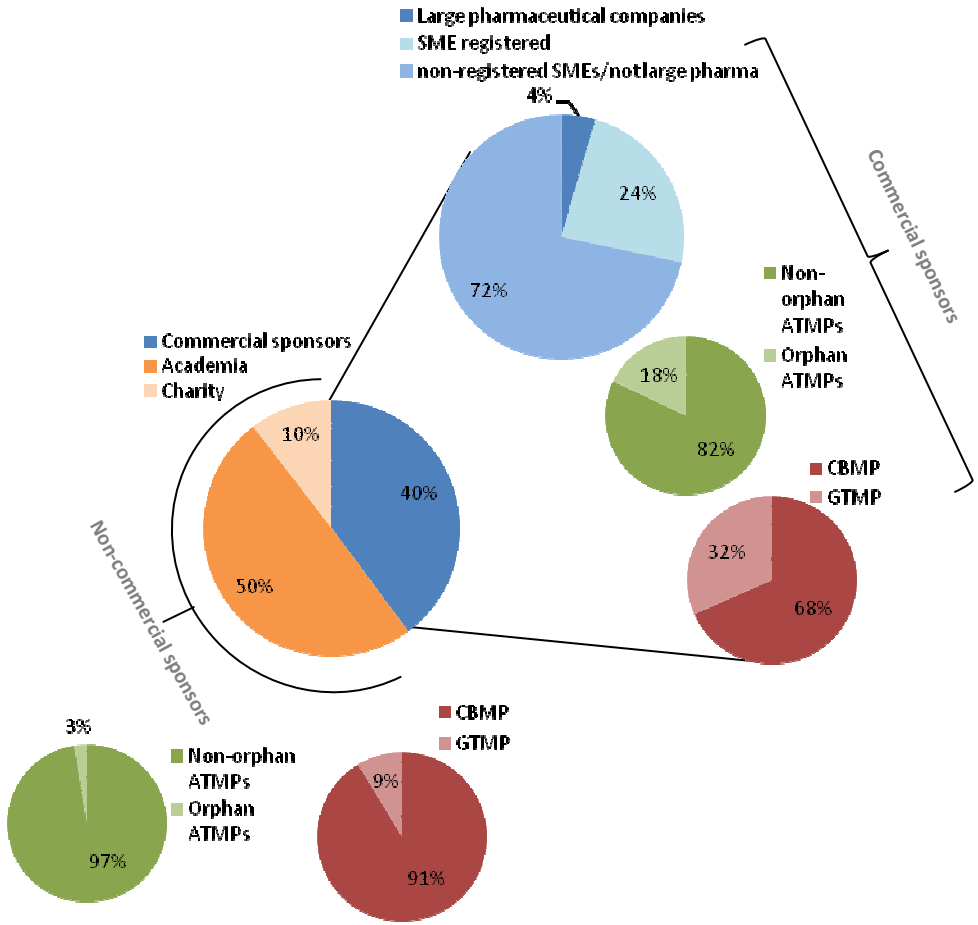

Small companies and orphan drugs are at risk

Eur J Clin Pharmacol
DOI 10.1007/s00228-009-0756-y

SPECIAL ARTICLE

Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency

Jan Regnstrom · Franz Koenig · Bo Aronsson · Tatiana Reimer · Kristian Svendsen · Stelios Tsigkos · Bruno Flamion · Hans-Georg Eichler · Spiros Vamvakas

Received: 25 September 2009 / Accepted: 28 October 2009

Abstract
Purpose To identify factors associated with success of Market Authorisation Applications (MAAs) for pharmaceutical drugs submitted to the European Medicines Agency (EMEA), with an emphasis on the Scientific Advice (SA) given by the Committee for Human Medicinal Products (CHMP).
Methods MAAs with a CHMP decision (outcome) between 1 January 2004 and 31 December 2007 were included in the analysis. Factors evaluated were: company size, orphan drug (OD) status, product type, existence of SA, compliance with SA, therapeutic area and year of outcome. Compliance with SA was retrospectively assessed with reference to three critical clinical variables in pivotal studies: choice of primary endpoint, selection of control and statistical methods.
Results Of 188 MAAs with an outcome, 137 (72.9%) were approved, whereas 51 (27.1%) were not approved or were withdrawn by the company. In the simple logistic regression analysis, company size [odds ratio (OR) 2.96, 95% confidence interval (CI) 1.92; 4.56, $p<0.0001$) was positively correlated with a positive outcome, whereas OD status (OD vs. non-OD: OR 0.38, 95% CI 0.19; 0.77, $p=0.0067$) was negatively correlated. A total of 59 (31.4%) MAAs had obtained SA related to one or more of the three critical variables. Thirty-nine of these were assessed as being compliant with SA. Obtaining an SA per se was not associated with outcome (SA vs. no-SA: OR 0.96, 95% CI 0.49; 1.88, $p=0.92$), but complying with SA was significantly associated with positive outcome (compliant with SA vs. no-SA: OR 14.71, 95% CI 1.95; 111.2; non-compliant with SA vs. no-SA: OR 0.17, 95% CI 0.06; 0.47, $p<0.0001$). Stepwise regression analysis revealed that company size and SA compliance were independent predictors of outcome. The proportion of the MAAs that had received SA increased from 22% in 2004 to 47% in 2007. Company size and product type were associated with the frequency of requesting SA (26, 33 and 46% for small, medium-sized and large companies, respectively; 16, 39 and 48% for known chemical substances, new chemical substances and biologics, respectively). Factors related to compliance with SA were company size and OD status (25, 60 and 84% for small, medium-sized, and large companies, respectively; 77 and 38% for non-OD and OD status, respectively).
Conclusions The strong association between company size and outcome suggests that resources and experience in drug development and obtaining regulatory approval are critical factors for a successful MAA. In addition, obtaining and complying with SA appears to be a predictor of outcome. Based on this analysis, companies, particularly smaller ones and those developing orphan drugs, are recommended to engage in a dialogue with European regulators via the SA procedure. Obtaining SA early in development and at major transition points as well as compliance with the advice given by the CHMP are recommended.

Keywords Drug approval · Drug development · Regulatory · Scientific advice

Jan Regnstrom and Franz Koenig contributed equally to this paper

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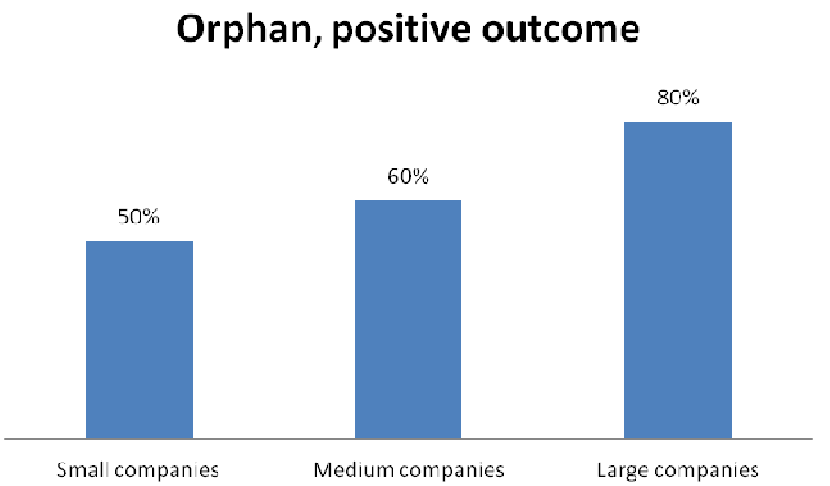
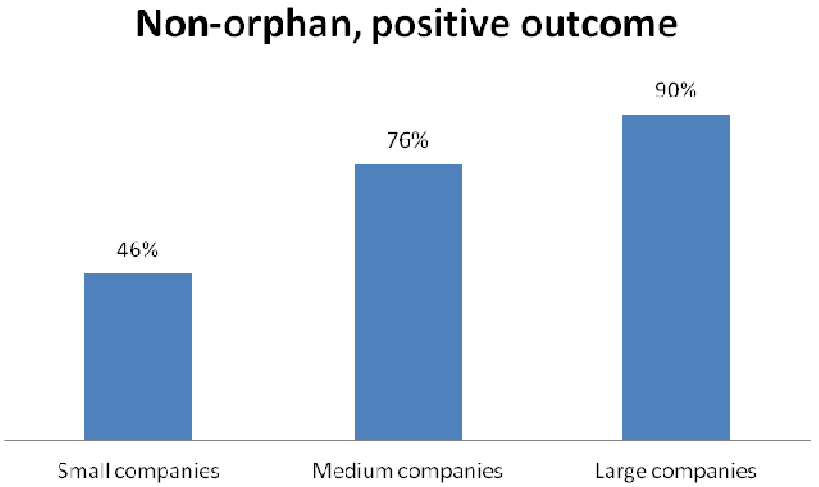
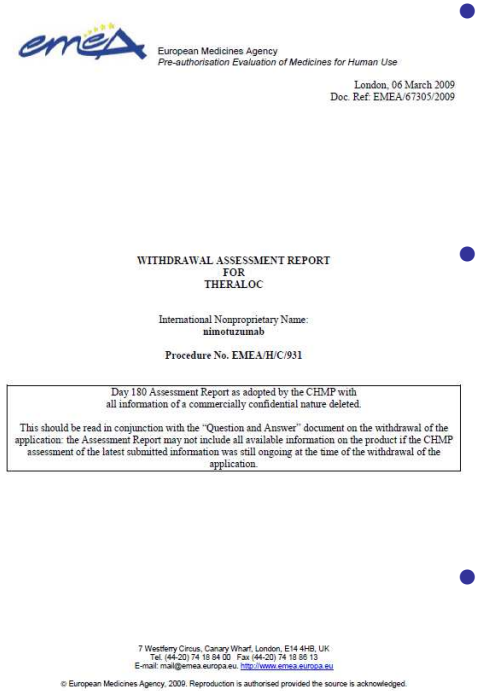




Reasons for failure? Case studies



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 06 March 2009
Doc. Ref: EMEA/67305/2009

WITHDRAWAL ASSESSMENT REPORT
FOR
THERALOC

International Nonproprietary Name:
nimotuzumab

Procedure No. EMEA/H/C/931

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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- **Anti-EGFR monoclonal antibody**
- **Indication: treatment of children and adolescents with recurrent high-grade glioma in patients where no other therapeutic options are available or appropriate except symptomatic treatment**
- **CHMP concerns:**
  - **Quality issues (27 major Quality objections and 73 other concerns)**
  - **Pre-Clinical issues**
  - **Lack of clinical Pharmacodynamic and pharmacokinetic data**
  - **Lack of efficacy demonstration**
  - **Lack of data on immunogenicity**
  - **High rate of SAEs and possible relationship to Theraloc**
- ***"The applicant has presented only one pivotal, uncontrolled clinical phase II study with 47 patients."***
- ***"The value of this study and the interpretability of study results were questioned because of the lack of a comparator."***
- ***"The major objection on efficacy and the lack of a comparator (…) was addressed (…) with a historical control group. The data provided and comparison between these two groups did not show evidence of benefit in term of overall survival."*)***

**) "Data shows that [in] the Theraloc group all died in a shorter period of time than the historical control group."*

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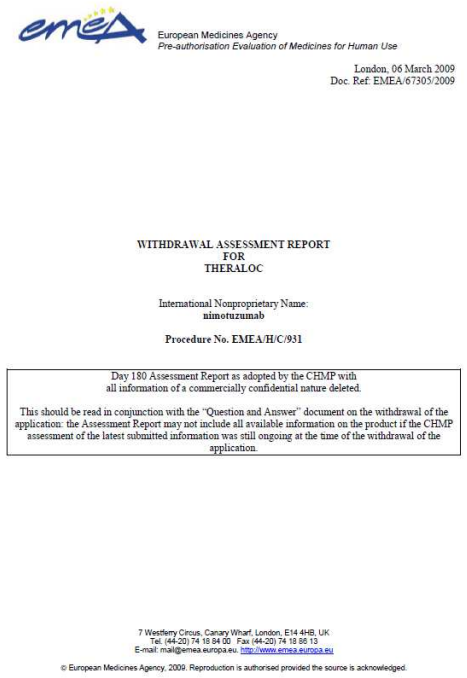

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 06 March 2009
Doc. Ref: EMEA/67305/2009

WITHDRAWAL ASSESSMENT REPORT
FOR
THERALOC

International Nonproprietary Name:
nimotuzumab

Procedure No. EMEA/H/C/931

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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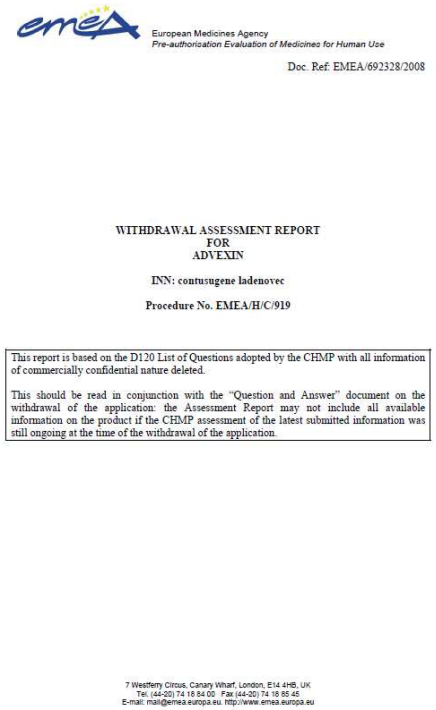
- *"It is not clear why there was no reference arm, as best supportive care or temozolamide, which is approved for glioma."*
- *"There is discrepancy between studied patients and the proposed indication."*
- *"(…) there is a possibility that all the patients were not maximally treated, although the proposed indication is for patients where no other therapeutic options are available or appropriate except symptomatic treatment."*
- *"Most responders were observed in the subgroup of patients with a diffuse intrinsic pontine glioma. The confidence intervals were wide due to the small numbers of patients."*

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063198.pdf

Reasons for failure? Case studies



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

Doc. Ref: EMEA/692328/2008

WITHDRAWAL ASSESSMENT REPORT
FOR
ADVEXIN

INN: contusugene ladenovec

Procedure No. EMEA/H/C/919

This report is based on the D120 List of Questions adopted by the CHMP with all information of commercially confidential nature deleted.

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- Adenoviral vector (Ad5CMV-p53) containing a functional copy of the human p53 gene
- Indication: treatment of Li-Fraumeni cancer patients (mutation of tumour suppressor p53; predisposes to various cancer types). Prevalence: 0.05 per 10,000
- No specific treatment; current treatment is adapted from the protocols for sporadic cancer therapy.
- However, due to the p53 defect in patients with Li-Fraumeni syndrome, these therapies may be associated with a high risk of secondary malignancies.
- Problem with chemotherapies targeting DNA and working via p53 activation ("gatekeeper" of the cell cycle).

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063080.pdf

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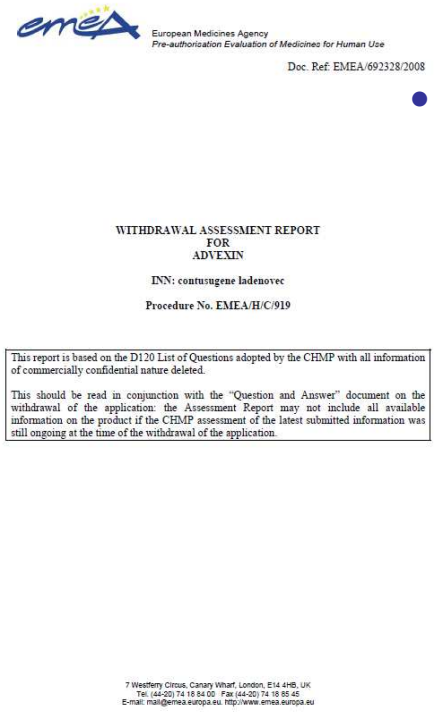

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- **Indication: treatment of Li-Fraumeni cancer patients (mutation of tumour suppressor p53; predisposes to various cancer types). Prevalence: 0.05 per 10,000**
- ***The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:***
  - ✓ *Clinical benefit of Advexin was not demonstrated*
  - ✓ *Correlation of p53 expression in tumours and clinical response to Advexin treatment was not convincingly demonstrated.*
  - ✓ *Clinical data on biodistribution, shedding and transmission, presented in the dossier, are judged to be not valid. Signals of biodistribution in various organs, body fluids shedding and transmission seen in the studies were not adequately addressed in the further development program of Advexin.*
  - ✓ *The data do not conclusively allow further recommendations regarding the posology such as the duration of therapy, monotherapy vs. combination therapy, type of combination therapy.*
  - ✓ *The safety data base does not allow comprehensive evaluation of the safety profile due to its small size and methodological limitations in generating the data*
  - ✓ *New uncharacterized open reading frame (ORF) in the vector sequence*
  - ✓ *Insufficient analysis of replication competent adenovirus (RCA)*
  - ✓ *Lack of GMP certification and import licence*
  - ✓ *Lack of validation data on the release tests of the drug product*
  - ✓ *Lack of demonstrated consistency of lots with respect to the ratio of infectious particles to total particles and manufacturing changes during product development*
  - ✓ *DP manufacturing process is not fully validated*
  - ✓ *Lack of sufficient stability data*
  - ✓ *Unclear role of RCA in the mode of action of Advexin*
  - ✓ *Lack of adequate biodistribution analysis*
  - ✓ *Possible germ line integration of vector DNA*
  - ✓ *Lack of adequate repeat dose toxicity analysis*
  - ✓ *Several deficiencies in the data and evaluation for assessment of the environmental risk*

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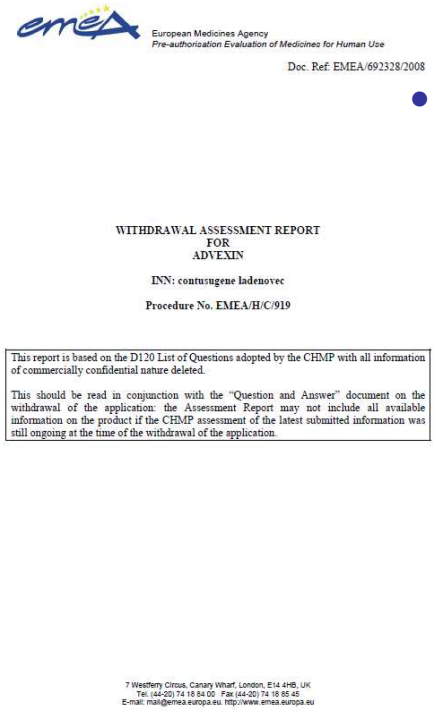
Reasons for failure? Case studies



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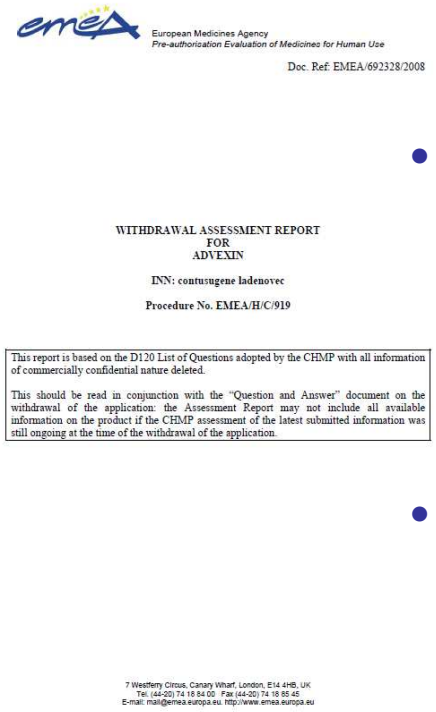

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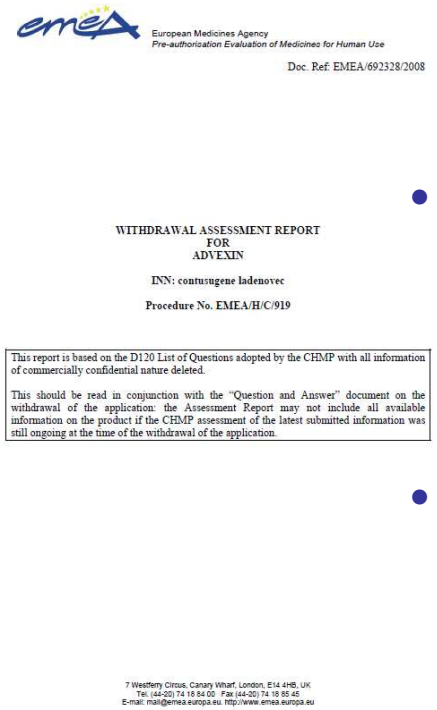
- *"No clinical study report was submitted. The applicant presented only a summary of a publication (Senzer et al 2007) describing p53 therapy in a patient with Li-Fraumeni syndrome."*
- *"Initially one accessible tumour was treated with Advexin. After 4 injections into this tumour, the patient received weekly 8 additional injections of Advexin over a 2-month period targeting tumours at other sites, including the pelvic extension of the primary vaginal tumour. In total, the patient received 12 injections over an approximate 5-month period."*
- *"By FDG-PET/CT scan, complete remission of the treated tumour was observed, with the untreated lesions showing further progression. Immunohistochemistry of the tumour was performed, pre-treatment and 7-day post-treatment, to evaluate expression of molecular markers associated with p53 mechanisms of action. The analysis revealed that the p53 signalling pathway was intact in the tumour. Furthermore a relationship between treatment response, radiographic findings and molecular markers of p53 tumour suppression was reported."*

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063080.pdf

Reasons for failure? Case studies



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- *"The correlation between abnormal p53 expression in pre-treatment samples and clinical outcome was evaluated in a post-hoc analysis and the evaluated samples represent a subgroup of enrolled patients."*
- *"However, the applicant failed to demonstrate convincingly the correlation of p53 expression in tumours and clinical response to Advexin treatment; the limitations are small sample size, sub-group analysis, post-hoc analysis and overall validity of the data (see also "Pharmacodynamics")."*
- *"The data can be seen as hypothesis generating and need to be confirmed in larger, well designed, GCP compliant clinical studies. This has not been accomplished."*

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063080.pdf

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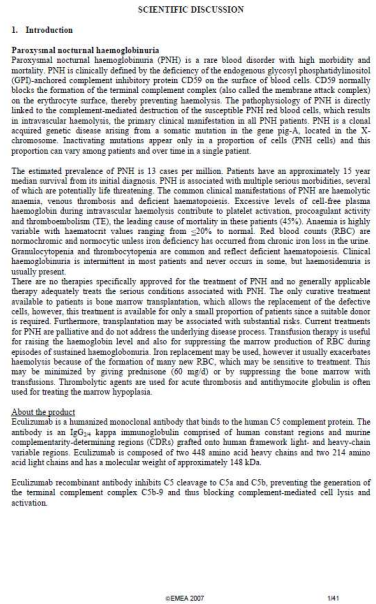


SCIENTIFIC DISCUSSION

1. Introduction

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare blood disorder with high morbidity and mortality. PNH is clinically defined by the deficiency of the endogenous glycosyl phosphatidylinositol (GPI)-anchored complement inhibitory protein CD59 on the surface of blood cells. CD59 normally blocks the formation of the terminal complement complex (also called the membrane attack complex) on the erythrocyte surface, thereby preventing haemolysis. The pathophysiology of PNH is directly linked to the complement-mediated destruction of the susceptible PNH red blood cells, which results in intravascular haemolysis, the primary clinical manifestation in all PNH patients. PNH is a clonal acquired genetic disease arising from a somatic mutation in the gene pig-A, located in the X-chromosome. Inactivating mutations appear only in a proportion of cells (PNH cells) and this proportion can vary among patients and over time in a single patient.

The estimated prevalence of PNH is 13 cases per million. Patients have an approximately 15 year median survival from its initial diagnosis. PNH is associated with multiple serious morbidities, several of which are potentially life threatening. The common clinical manifestations of PNH are haemolytic anaemia, venous thrombosis and deficient haematopoiesis. Excessive levels of cell-free plasma haemoglobin during intravascular haemolysis contribute to platelet activation, procoagulant activity and thromboembolism (TE), the leading cause of mortality in these patients (45%). Anaemia is highly variable with haematocrit values ranging from ~20% to normal. Red blood counts (RBC) are normochromic and normocytic unless iron deficiency has occurred from chronic iron loss in the urine. Granulocytopenia and thrombocytopenia are common and reflect deficient haematopoiesis. Clinical haemoglobinuria is intermittent in most patients and never occurs in some, but haemosiderinuria is usually present.

There are no therapies specifically approved for the treatment of PNH and no generally applicable therapy adequately treats the serious conditions associated with PNH. The only curative treatment available to patients is bone marrow transplantation, which allows the replacement of the defective cells; however, this treatment is available for only a small proportion of patients since a suitable donor is required. Furthermore, transplantation may be associated with substantial risks. Current treatments for PNH are palliative and do not address the underlying disease process. Transfusion therapy is useful for raising the haemoglobin level and also for suppressing the marrow production of RBC during episodes of sustained haemoglobinuria. Iron replacement may be used, however it usually exacerbates haemolysis because of the formation of many new RBC, which may be sensitive to treatment. This may be minimized by giving prednisone (60 mg/d) or by suppressing the bone marrow with transfusions. Thrombolytic agents are used for acute thrombosis and antithymocite globulin is often used for treating the marrow hypoplasia.

About the product

Eculizumab is a humanized monoclonal antibody that binds to the human C5 complement protein. The antibody is an $IgG_{2/4}$ kappa immunoglobulin comprised of human constant regions and murine complementarity-determining regions (CDRs) grafted onto human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Eculizumab recombinant antibody inhibits C5 cleavage to C5a and C5b, preventing the generation of the terminal complement complex C5b-9 and thus blocking complement-mediated cell lysis and activation.

- Monoclonal anti-complement C5 antibody
- Indication: Paroxysmal nocturnal haemoglobinuria (PNH) (CD59 deficiency, normally blocking the “membrane attack complex” = final stage of complement cascade activation) => Erythrocytes prone to complement-mediated lysis
- Acquired clonal mutation; 15 years median survival from diagnosis
- Prevalence: 0.1 in 10000
- Six clinical studies performed:

Six clinical studies provide the basis for establishing the safety and efficacy of eculizumab therapy in the PNH patient population. These studies included 195 patients from 13 countries.

Listing of All PNH Studies

Study Number	Phase/Design[1]	Duration/Status	Total Patients Enrolled
C02-001	2[2] / OL	12 weeks/Complete	11
E02-001	2[2] / OL (C02-001 Extension)	52 weeks/Complete	11
X03-001	2[2] / OL (E02-001 Extension)	104 weeks/Complete	11
C04-001	3 / R, DB, PC	26 weeks/Complete	87
C04-002	3 / OL	52 weeks/Ongoing 26 week Interim Complete	97
E05-001	3b / OL (C04-001, C04-002, and X03-001 Extension)	104 weeks/Ongoing	187

[1]R = Randomized; [2]Also referred to as Phase I studies;
DB = Double Blind; PC = Placebo Controlled; OL = Open Label.

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf

Open questions

- **What is the "minimum" dataset for an approval for an ultra-orphan drug?**
- **How far can we depart from "usual standards"?**
  - ✓ **Can we accept publications instead of clinical study reports?**
  - ✓ **Can we accept post-hoc analyses of subgroups, even if biologically or medically plausible?**
  - ✓ **Which statistical methods? If any?**
  - ✓ **Do we accept "hypothesis generating data" as sufficient proof for an approval…**
    - …under exceptional circumstances?
    - …under the "conditional approval" rules?
- **Can we feasibly revoke a license once granted in case positive benefit-risk is questioned?**
  - ✓ **Where is the burden of proof? With CAT/CHMP or with the Applicant?**

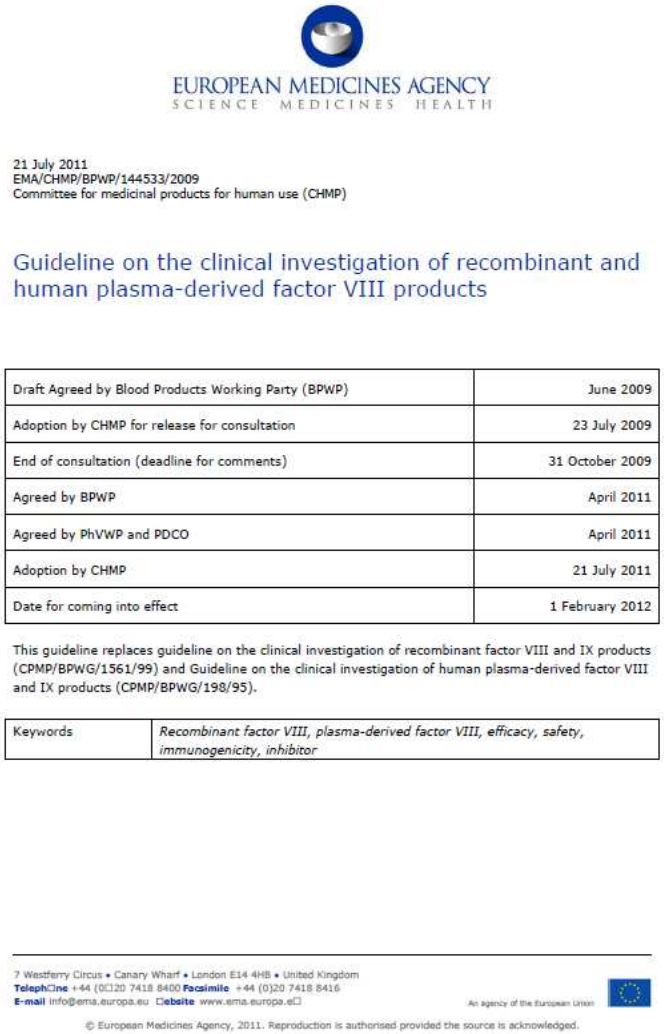
CAT/CHMP are aware!

Quotes from Protocol Assistance procedures:

- *"In this rare condition sample size is less a question of statistical considerations but of relevance and impact of the clinical effects of the treatment and the feasibility to recruit patients into a clinical trial. If the study results are compelling and the study planning and conduct is of high quality, the planned sample size might be sufficient in this specific situation."*
- *"Due to the rarity of the condition a randomized clinical trial is hardly possible and the use of an external control is an acceptable alternative for judging the treatment effect (see also the document 'Guideline on Clinical Trials in Small Populations' (CHMP/EWP/83561/2005))."*
- *"(…) the proposed sample size could be acceptable if the results of the study are robust and clearly indicate clinically relevant findings for the primary endpoint. Furthermore in this situation the totality of evidence presented would be carefully considered."*
- *"The proposed historical cohort from 1995 - 2005 is not endorsed. A more recent historical cohort from the last few years could, however, be acceptable subject to the applicant being able to demonstrate that the comparison is reliable and not subject to important biases commonly associated with this type of comparison."*

But we have to learn more!

Can we learn from blood products?



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMA/CHMP/BPWP/144533/2009
Committee for medicinal products for human use (CHMP)

Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products

Draft Agreed by Blood Products Working Party (BPWP)	June 2009
Adoption by CHMP for release for consultation	23 July 2009
End of consultation (deadline for comments)	31 October 2009
Agreed by BPWP	April 2011
Agreed by PhVWP and PDCO	April 2011
Adoption by CHMP	21 July 2011
Date for coming into effect	1 February 2012

This guideline replaces guideline on the clinical investigation of recombinant factor VIII and IX products (CPMP/BPWG/1561/99) and Guideline on the clinical investigation of human plasma-derived factor VIII and IX products (CPMP/BPWG/198/95).

Keywords	*Recombinant factor VIII, plasma-derived factor VIII, efficacy, safety, immunogenicity, inhibitor*

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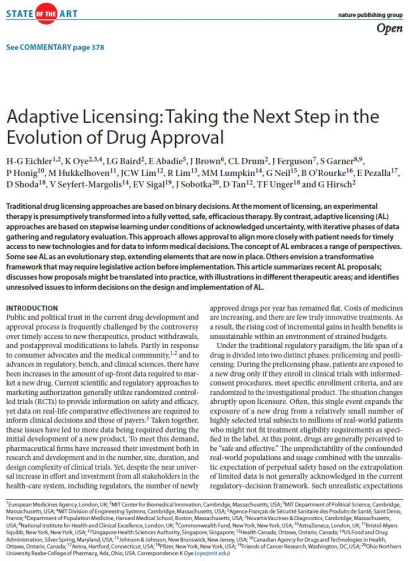
- **Haemophilia A (F.VIII deficiency): Prevalence 2:10000**
- ***"Efficacy needs to be demonstrated in clinical trials to be conducted before marketing authorisation combined with the commitment to perform (a) post-authorisation investigation(s) to collect additional clinical data and to bridge in the long-term between the outcome from clinical trials and from routine use."***
- ***"In view of the limited availability of patients suffering from haemophilia A, data from pre-licensing studies only are considered insufficient to estimate all aspects of therapy with factor VIII products, especially with respect to immunogenicity. Therefore, to collect additional clinical data and to ensure consistency in the long-term between the outcome from pre-authorisation clinical studies and from routine use, a post-marketing investigation should be performed."***

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500063080.pdf

Adaptive licensing – attractive for orphan drugs?



STATE OF THE ART

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See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals; discusses how proposals might be translated into practice, with illustrations in different therapeutic areas; and identifies unresolved issues to inform decisions on the design and implementation of AL.

INTRODUCTION

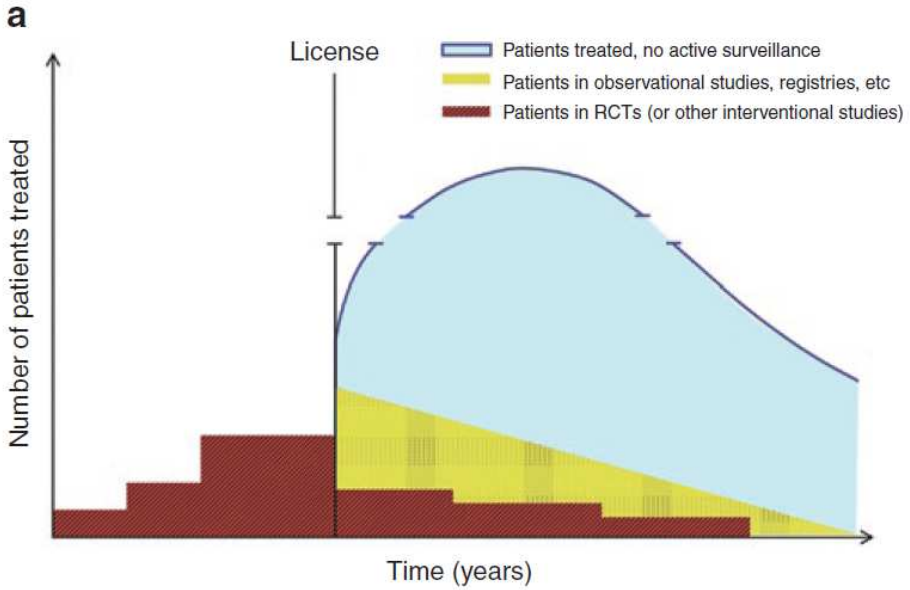
Public and political trust in the current drug development and approval process is frequently challenged by the controversy over timely access to new therapeutics, product withdrawals, and postapproval modifications to labels. Partly in response to consumer advocates and the medical community,[1,2] and to advances in regulatory, bench, and clinical sciences, there have been increases in the amount of up-front data required to market a new drug. Current scientific and regulatory approaches to marketing authorization generally utilize randomized controlled trials (RCTs) to provide information on safety and efficacy, yet data on real-life comparative effectiveness are required to inform clinical decisions and those of payers.[3] Taken together, these issues have led to more data being required during the initial development of a new product. To meet this demand, pharmaceutical firms have increased their investment both in research and development and in the number, size, duration, and design complexity of clinical trials. Yet, despite the near universal increase in effort and investment from all stakeholders in the health-care system, including regulators, the number of newly approved drugs per year has remained flat. Costs of medicines are increasing, and there are few truly innovative treatments. As a result, the rising cost of incremental gains in health benefits is unsustainable within an environment of strained budgets.

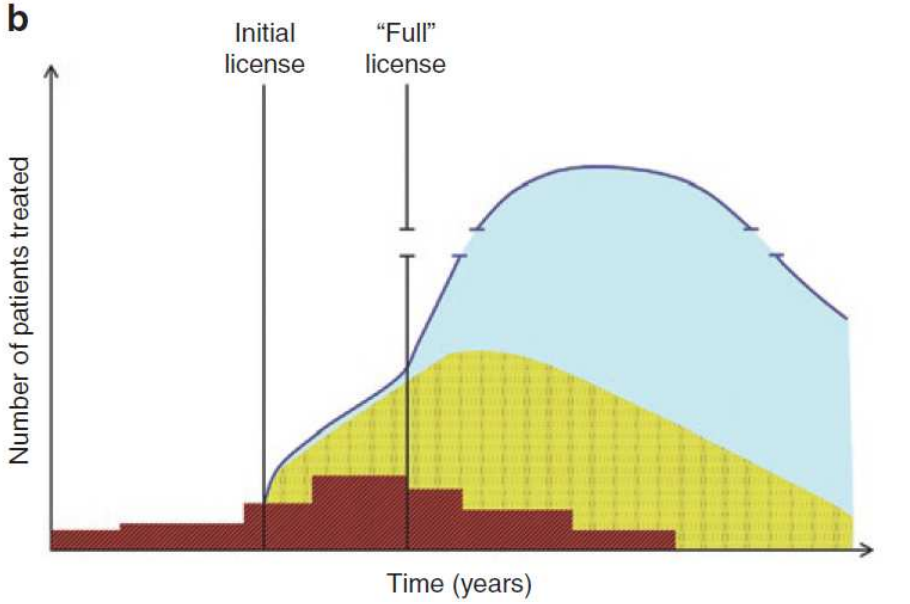
Under the traditional regulatory paradigm, the life span of a drug is divided into two distinct phases: prelicensing and postlicensing. During the prelicensing phase, patients are exposed to a new drug only if they enroll in clinical trials with informed-consent procedures, meet specific enrollment criteria, and are randomized to the investigational product. The situation changes abruptly upon licensure. Often, this single event expands the exposure of a new drug from a relatively small number of highly selected trial subjects to millions of real-world patients who might not fit treatment eligibility requirements as specified in the label. At this point, drugs are generally perceived to be "safe and effective." The unpredictability of the confounded real-world populations and usage combined with the unrealistic expectation of perpetual safety based on the extrapolation of limited data is not generally acknowledged in the current regulatory-decision framework. Such unrealistic expectations

[1]European Medicines Agency, London, UK; [2]MIT Center for Biomedical Innovation, Cambridge, Massachusetts, USA; [3]MIT Department of Political Science, Cambridge, Massachusetts, USA; [4]MIT Division of Engineering Systems, Cambridge, Massachusetts, USA; [5]Agence Française de Sécurité Sanitaire des Produits de Santé, Saint Denis, France; [6]Department of Population Medicine, Harvard Medical School, Boston, Massachusetts, USA; [7]Novartis Vaccines & Diagnostics, Cambridge, Massachusetts, USA; [8]National Institute for Health and Clinical Excellence, London, UK; [9]Commonwealth Fund, New York, New York, USA; [10]AstraZeneca, London, UK; [11]Bristol-Myers Squibb, New York, New York, USA; [12]Singapore Health Sciences Authority, Singapore, Singapore; [13]Health Canada, Ottawa, Ontario, Canada; [14]US Food and Drug Administration, Silver Spring, Maryland, USA; [15]Johnson & Johnson, New Brunswick, New Jersey, USA; [16]Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario, Canada; [17]Aetna, Hartford, Connecticut, USA; [18]Pfizer, New York, New York, USA; [19]Friends of Cancer Research, Washington, DC, USA; [20]Ohio Northern University Raabe College of Pharmacy, Ada, Ohio, USA. Correspondence: K Oye (koye@mit.edu)

Received 1 November 2011; accepted 2 December 2011; advance online publication 15 February 2012. doi:10.1038/clpt.2011.345

"Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made."





Orphans are on the top agenda

Published online 4 April 2011 | *Nature* 472, 17 (2011) | doi:10.1038/472017a

News

Rare-disease project has global ambitions

Consortium aims for hundreds of new therapies by 2020.

Alison Abbott

Prader–Willi syndrome. Fabry renal disease. Spinocerebellar ataxia. Few people have heard of these and the other 'rare diseases', some of which affect only hundreds of patients worldwide. Drug companies searching for the next blockbuster pay them little attention. But the diseases are usually incurable — and there are thousands of them.

This week, the US National Institutes of Health (NIH) and the European Commission launch a joint assault on these conditions, whose small numbers of patients make it difficult to test new treatments and develop diagnostic methods. The International Rare Disease Research Consortium being formed under the auspices of the two bodies has the ambitious goal of developing a diagnostic tool for every known rare disease by 2020, along with new therapies to treat 200 of them. "The number of individuals with a particular rare disease is so small that we need to be able to pool information from patients in as many countries as possible," says Ruxandra Draghia-Akli, the commission's director of health research.

> "We need to be able to pool information from patients in as many countries as possible."

At the launch meeting in Bethesda, Maryland, on 6–8 April, prospective partners will map out research strategies to identify diagnostic biomarkers, design clinical trials and coordinate genome sequencing in these diseases. Nearly all the rare diseases, of which there are an estimated 6,000–8,000, are the result of small genetic changes.

The meeting will also discuss the governance of the project, which is most likely to be modelled on the pioneering Human Genome Project. As such, the consortium is open to research agencies and organizations from all over the world. Representatives from countries including Canada, Japan and some individual European nations are all attending the meeting, and may join the consortium. Those wishing to participate will have to pledge a minimum financial contribution, which has not yet been agreed, and share all relevant data. Indeed, the project will have to overcome numerous obstacles to information sharing, such as the fact that physicians in different countries often use entirely different words to describe the same disease.

Draghia-Akli points out that the project could yield major benefits for the emerging field of personalized medicine — another political priority for the NIH and the commission — which also faces the challenge of small populations of patients.

Regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency rely on large, randomized and controlled clinical trials when deciding

"The International Rare Disease Research Consortium being formed under the auspices of the two bodies [the NIH and the European Commission] has the ambitious goal of developing a diagnostic tool for every known rare disease by 2020, along with new therapies to treat 200 of them."

Thank you for your attention!