

Study on orphan drugs

Phase II

**Considerations on the
application of article 8.2 of EC
regulation
No. 141/2000 concerning orphan
drugs**

We thank all those persons who were kind enough to give their time to help with this report, in particular François Cornu for his valuable help throughout the project.

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Introduction

The European Union adopted a specific stance on Orphan Drugs in 1999 in the form of regulation EC 141/2000. It aims at promoting the research, development and commercialization of orphan drugs in Europe, thereby improving the management of patients with rare diseases.

The incentive nature of this regulation is unanimously recognized and has been validated by its positive outcome after 5 years of existence.

Up to the present, the Committee of Orphan Medicinal Products (COMP) has registered 191 orphan designations and 15 Marketing Authorizations have been granted to orphan drugs by the Committee for Proprietary Medicinal Products (CPMP). These results are even higher than during the first four years of the American Orphan Drug Act (1983-1986), which included 93 designations and 17 Marketing Authorizations.

In addition, the dynamics of these first four years is positive, with a constant number of new designations every year and new MA's increasing by 25 to 30% per year (Figure 1).

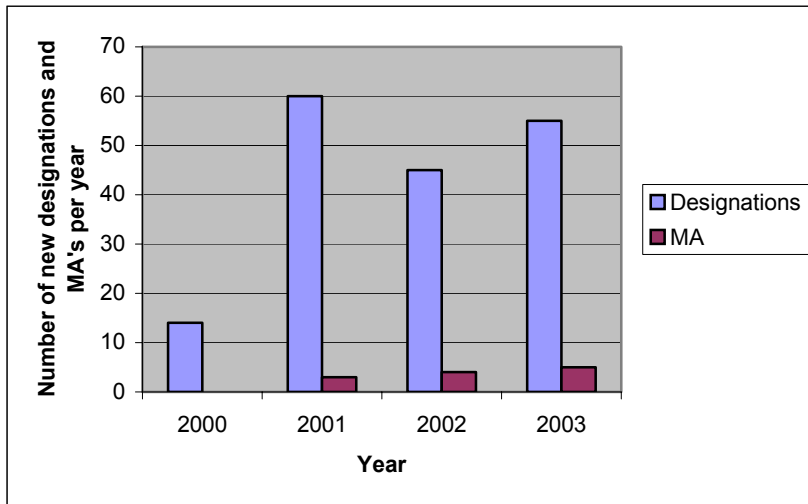


Figure 1: Trends in the number of designations and Marketing Authorizations of orphan drugs since 2000

It should also be noted that this regulation has favoured the formation of a start-up incubator (since about 80% of the sponsors are small and medium size companies). European research has also been stimulated (as about 80% of the products were designed initially in Europe based on European research).

Of all the incentives the regulation offers, by far the most important is the guarantee of market exclusivity for the 10 years following the MA. This is of obvious interest for drugs that are not or are no longer protected by a patent. We have also been informed many times that this commercial exclusivity has a very important psychological impact for all Orphan Drugs, including the most innovative ones. It encourages investors to commit funds to young companies while encouraging older and larger companies to start *ad hoc* development, both to promote a positive corporate image concerning rare diseases, and also to accelerate the marketing of new products in order to reduce the of return on investment times. Finally, orphan status in some countries can facilitate the reimbursement of these medicines by health insurance systems, which is evidently an engine for market development. It

should nonetheless be remembered that this aspect is true only in the European countries that have effectively implemented a genuine policy in favour of Orphan Drugs.

The European regulation's 10 year limit provides greater incentive than its American counterpart, which only grants market exclusivity for 7 years (see appendix 1). The success of Orphan Drug development in Europe is partly due to this aspect.

Article 8.2 of the regulation mentions that "this [market exclusivity] period may be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria [of designation] laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity". The Commission is responsible for establishing detailed guidelines for the application of this article. In particular, the Commission would like to have a tool for evaluating the profitability of an Orphan Drug after 5 years on the market.

The precise goal of the mission confided to ALCIMED is to propose possible options for measuring the profitability of an orphan product after 5 years of commercialization. It should be stated here that the aim of this report is not to take a stand or to judge the profitability level of a given product.

This mission was conducted by questioning the parties with a vested interest in orphan drugs: pharmaceutical executives with Orphan Drugs on the market, as well as their representative authority, the EBE (Emerging Biotechnology Enterprise), representatives of health authorities of the different Member States (involved in both drug evaluation and reimbursement, and in management of « Orphan Drugs » at the national level), associations of patients and their European alliance Eurordis, the EMEA and the COMP. Several experts not specialized in orphan drugs have also provided assistance.

We thank everyone for their cooperation. We will try to faithfully convey their points of view.

As yet there is no consensus among the parties on an acceptable and feasible tool for measuring the profitability of an Orphan Drug. This is why this report proposes possible options, or families of options, that should be considered as key discussion points in future working meetings with the various players involved.

During the course of our investigations, we received a large number of comments from the parties concerned by article 8.2. We have decided to use these as an introduction to the discussion covering the actual measurement tools.

The first comment is essential, since it is shared by all the parties encountered: is this the right time to pose the question of profitability of Orphan Drugs?

The regulation is in fact still young and all the aspects it contains have not yet been implemented, in particular national incentives. Accessibility to Orphan Drugs in the former Europe of 15 and even more so in the current Europe of 25, still requires considerable work and is undoubtedly the current priority. This is even truer given that we have very little experience with the actual marketing of Orphan Drugs.

The second question posed involves the potentially harmful impact of the application of article 8.2 on the development of new orphan drugs in Europe. Even if it were justified, withdrawing market exclusivity would risk substantially reducing the attractiveness of the regulation for the pharmaceutical industry, not least by simply eliminating the psychological value of this incentive. Additionally, the application of this measure would surely have an extremely negative effect on the implicated sponsor's image most likely engendering a spill over effect on the other Orphan Drug developers, even going as far as to discourage the initiatives of new potential sponsors. Furthermore, reducing exclusivity to 6 years as proposed by article 8.2 would increase competition between Europe and the United States, where the exclusivity period lasts 7 years.

Finally, it seems evident that the main objective of a Member State's submission to the Commission for application of article 8.2 would be to control health expenditures via better price control of Orphan Drugs which are currently judged to be costly by some. Yet the correlation between withdrawing market exclusivity and the price decrease of Orphan Drugs, however, has not been established. The goal would essentially be to enable the introduction of direct competition to a sector in which by definition it is not possible at the current time. But there are numerous reasons for thinking that withdrawing exclusivity at 5 years would not enable this competition to be introduced.

First of all, most orphan products are protected by patents or the data protection system, and withdrawing market exclusivity would thus preclude placing « me-too » products on the market.

Next, even if the product were no longer protected in this manner after 6 years, what company would risk starting product development for market penetration without the certainty that exclusivity would effectively be removed?

Concerning the onset of product development after exclusivity ceases, this is possible but 4 years seems a short time to develop, register and launch the commercialization of a competing product. Even in the case of a pure generic, it would require at least bioequivalence studies in cases where original clinical data are not protected.

It is more probable that competitors would prepare to market their product after 10 years. For example, this is the situation for 30% of cases in the United States after expiry of the 7-year commercial exclusivity (see appendix 1).

There are nevertheless two possible scenarios for the introduction of competitors after 6 years. The first is the existence of a generic product on the market that is indicated for other non-orphan pathologies at the time commercial exclusivity is

withdrawn. This situation is nevertheless relatively improbable since in this case purchasers would acquire the generic product at a low cost for the orphan pathology, rather than one with a formal Marketing Authorization (MA).

The second situation is the existence of products developed for the orphan indication, but that did not receive an MA because of similarity with another already authorised product. This case could occur but it would remain rare.

It is also clear that there is no direct link between price and market exclusivity. Thus, there are drugs currently on the market that have orphan status in the United States but not in Europe, and that target the same rare diseases as certain European Orphan Drugs. The cost of these medicines, lacking European market exclusivity is nevertheless high and sometimes in the same order of magnitude as the corresponding European Orphan Drugs (see phase I of this study). Prime examples of this are Gaucher's disease and pulmonary hypertension.

Finally, market exclusivity does not prevent competition, as is the case today for pulmonary hypertension. The introduction of new orphan treatments in this indication has not resulted in a decrease in net cost.

Globally, these considerations explain why some players think that article 8.2 should purely and simply not be applied. The risks run (i.e. loss of attractivity) appear to outweigh the real potential benefits.

This is also consistent with the American experience: even if American legislation contains no measure for the revision of orphan status or the withdrawal of commercial exclusivity as a function of profitability (appendix 1), solutions have been considered to limit the period of commercial exclusivity. These solutions were rejected by President Bush Senior, who said in the 90s: « I believe that we should not imperil the success of this regulation, that is largely due to the existence of market exclusivity ... Weakening the provision of 7 years of exclusivity would certainly

discourage the development of orphan drugs we desperately need ». At the present time, the FDA refuses to re-evaluate Orphan Drugs for any criterion whatsoever during the 7 years of commercial exclusivity (appendix 1).

In spite of this and independently of the above considerations, the ALCIMED mission indeed involves defining a tool for measuring profitability, the theme that we will now discuss in detail.

I. Definition of the concept of profitability and of the scope of its evaluation

In order to determine the profitability of an orphan drug at 5 years, we should first define the concept of profitability as well as the scope within which this measurement must be made.

Concept of profitability

It is not as straightforward as that to speak of the profitability of a product, since there is no true definition of this term from an accounting standpoint, or at least concerning the legal information required to be published by the company. We generally speak of the profitability of a company, which involves a portfolio of products and a set of activities that are then consolidated. Accounting that includes all revenues and expenditures related to a given product exist at certain levels, e.g. a distribution subsidiary or the branch of the company responsible for sales. In this case, however, costs such as Research and Development are not factored in. In addition, this « product-specific » accounting is an in-house management tool for the company and has no legal bearing. It is not publicly available, even from companies listed on a stock exchange, and is not audited, as are legal accounts. Even if made available, it would be difficult to verify this type of product-specific accounting.

It is interesting to bear in mind that the principal health care system that evaluates the profitability of medicinal products is the English PPRS system (Pharmaceutical Price Regulation Scheme) that reasons at the company rather than the product scale. Furthermore, to our knowledge, there is no system in the world that evaluates the profitability of a given product.

For all these reasons, we consider here that the term « profitability » very generally means what the company gains as benefit from a given product. The tools proposed

will enable this profitability to be assessed, but will not enable absolute numbers to be obtained. We will thus speak rather of profitability indicators.

ALCIMED will propose two types of indicators:

- The first involves considering profitability as the difference between revenues and costs. Several sub-types of indicators will be proposed
- The second type involves considering that profitability is largely dependent on revenues, and that the « sufficiency » of profitability can be legitimately estimated on the basis of sufficiency of revenues.

Indications considered

One of the questions raised is to determine if the profitability of a medicine after 5 years should be measured in terms of only one orphan indication, if it should be measured in terms of all its orphan indications, or if it should be measured in terms of all of its indications.

This question can be posed, for example, for medicines such as Glivec that currently have two orphan indications, or for Onsenal that has just been accepted for an orphan indication whereas it is largely used for non-orphan indications. It is highly probable that similar cases will increase in the medium/long term.

This is a key question, especially in the perspective of evaluating profitability, since inclusion of non-orphan indications in this evaluation would clearly affect the level of profitability.

Since the orphan designation is given for a (product x indication) couple, it now appears clear that the measure of profitability must involve only an orphan indication. In the case of Glivec, this means that profitability should initially be evaluated for chronic myeloid leukaemia 5 years after the MA, granted on November 7, 2001,

followed by another evaluation 6 months later for gastrointestinal stromal tumours for which the MA was granted on May 24, 2002.

This reasoning is more faithful to the regulation but is also more complicated, since for all Orphan Drugs benefiting from other indications, this would involve precisely identifying elements of profitability of the orphan indication from amongst the overall profitability elements of the product, regardless of the measurement method used.

In the same sense, the question was brought up concerning revenues resulting from non-MA prescriptions of these products. Even if the magnitude of this type of prescription is often low in the pharmaceutical industry (beyond a certain limit, the company would be wise to apply for an extension of indication in order to be able to promote its product), the « *off-label* » may generate non-negligible revenues for the company. At this stage, there are several considerations to take into account:

- For the majority of Orphan Drugs currently on the market, there is little risk of off-label prescriptions since the action mechanisms and/or the benefit/risk ratio of these products are such that their efficacy within other pathologies is difficult to envisage, e.g. the case of enzyme replacement therapies.
- Off-label prescriptions are not in the hands of the Industry, which could consider itself to be « penalized » for occurrences over which it has no control.
- It would be consistent to exclude this source of revenues from the evaluation of profitability with respect to the regulation (designation for a (product x indication) couple).
- Including this source of revenues on the other hand, would incite the Industry to develop tests and promote research on other indications, which is also an objective of the regulation. If « *off-label* » products are included in the evaluation of profitability, there is in fact an increased risk of seeing market exclusivity withdrawn. In order to maintain this exclusivity, the company may want to conduct specific development and obtain an MA for the indications concerned.

- In any case, monitoring off-label prescription is more or less possible by using prescription surveys conducted by institutes such as IMS, but this is not always easy and reliable, even for the drug company.

We should also mention that, in contrast to « *off-label* », product donations exist within the framework of humanitarian actions, which are « negative revenues » for the company. These donations should be included in the elements considered in a precise and comprehensive measure of profitability.

Products concerned

In light of the regulation, the Industry considers that profitability should only be determined for products designated on the basis of financial criteria. This amounts to allowing the company to decide on the best way to evaluate the profitability of a product. At the present time, no calculation method has in fact been proposed, even in the July 2003 communication of the Commission, which defined the modalities for examining the financial criteria. It can thus be imagined that the company in question would be requested to submit a « profitability » dossier at the time of the designation, that it would defend in front of a committee of experts who would judge the relevance and veracity of the approach proposed. The same committee would also be the sole judge of the level of « sufficiency » of the calculated profitability. Profitability at 5 years would be judged on the basis of the same elements as those initially provided, by determining that forecasts were effectively met. At this stage, it should be noted that currently in Europe, no medicine has been designated as orphan on the basis of « profitability » criteria only. Very few medicines have been designated based on this criteria in the United States either (2 out of about 250 designations in all), regardless of their much greater experience in the field as the American regulation dates from 1983.

For medicines designated on the criterion of prevalence, the Industry suggests that only prevalence should be subjected to revision after 5 years. In other words it would

be necessary to verify that the prevalence known at the time of designation and of the MA is still below 5/10,000, 5 years after granting the MA. The American example in fact shows that marketing a product could lead to the discovery of patients who were not initially counted. For example, in the case of Fabry's disease, it was found several years after the drug was first marketed that the pathology involved not only men, but women as well. In this case, prevalence doubled, even if it still remains below the threshold of designation in this particular case.

In the case of revision based on the initial designation criteria, the Industry admits that market exclusivity should be withdrawn if these criteria are no longer verified after 5 years.

There are thus several co-existing options today for the Commission:

- revise on a profitability basis only those products having been designated under the same criteria (solution recommended by the Industry);
- revise only those products for which an information note was deposited by a Member State, regardless of the initial designation criterion.

Given the current state of the regulation, all the parties concerned unanimously rejected the possibility of systematically revising the profitability of all orphan drugs.

We point out that the Industry solution is relatively simple to apply and circumvents any potential legal debate concerning interpretation of the law. On the other hand, even if it opens the path for applying article 8.2, it is not a total response to the objective of this study, namely proposing methods for evaluating the profitability of an Orphan Drug after 5 years of commercialization. This is why this approach will not be investigated further.

Geographic scope

The geographic scope of the evaluation should also be discussed. There are three options:

- reasoning on the European scale
- reasoning on the international scale
- reasoning on the national scale

International reasoning would currently appear to be the most applicable, since the entire health care sector is global, which in particular means that the elements composing the profitability of a product (costs and revenues) generally do not have a geographic localization. It is not rare that a product is discovered and developed pre-clinically in the United States, that its pharmaceutical and industrial development is conducted based on wherever the company's industrial competency is situated, and that its clinical development is carried out in several countries, generally in Europe and the United States, even in Japan.

But international reasoning is also open to discussion: can the European Union legitimately include data or facts not geographically European in its evaluations or decisions?

Finally, the question of national reasoning can be posed: if the demand for the re-evaluation of commercial exclusivity based on profitability came from a Member State or a group of Member States, should profitability be determined at the level of one or several countries? In this case, the obvious question posed is the geographic implication of withdrawing market exclusivity: could this decision be made at the national level? Even if this were the case, it is not certain that a competitor would appear only on the market(s) in question and that normal market rules would be re-established.

At first sight, reasoning on the European scale appears as the best compromise, and we will further examine its feasibility given the different profitability evaluation methods.

Time Frame

The evaluation of profitability after 5 years also requires the precise definition of the time frame in which this evaluation should be done: should we consider profitability during the 5th year taking only revenues into account and possibly the costs of that year? Or on the contrary, should we consider all costs and revenues during the entire period between the start of the development process up to the end of the 5th year of commercialization after obtaining the European MA? Depending on the options considered, the time frame to take into account will be discussed.

II. Evaluation of profitability

II. 1. General plan of profitability evaluation methods of an orphan drug

The evaluation of profitability schematically involves two steps: its measurement, followed by the evaluation of the result of the measurement in terms of the concept of sufficiency. It thus involves defining a method for each of these steps.

We have already said that the measure of profitability may be based on the determination of two indicators,

- a « revenues minus costs » indicator
- a « revenues » indicator

Regarding the estimation of the sufficiency level of the result obtained, it is necessary to operate by comparison with solid benchmark values recognized as valid by all the parties concerned. This comparative evaluation is consistent with the transparency desired by the European Commission. There are two broad types of comparators:

- an « external » comparator, e.g. a mean profitability value of the pharmaceutical industry, or that of a venture capital fund,
- a comparator intrinsic to the medicine evaluated, that would be a profitability value estimated at the time of the MA. This approach would require implementing a two-step procedure: evaluation at the moment the MA is granted and a second evaluation after 5 years of commercialization. Since this procedure is not included in the current regulation, its consequences will be discussed later.

In practice, details of the methods for measuring profitability based on the two broad types of indicators brings to light several sub-options that we will now clarify.

II.2 Profitability evaluation methods based on a « revenues minus costs » indicator

II.2.1 Precise evaluation, so-called **complete « accounting »** approach

This approach attempts to measure profitability so that it is as close as possible to reality for the company. In other terms, it attempts to determine the contribution of a given product for an indication, to the financial result of the company. Using this option, profitability is evaluated by taking into account all costs related to the development, manufacture and marketing of the product.

The accounting approach essentially poses the question of how to allocate costs to a product for a given indication, bearing in mind that, and with respect to its current cost accounting, these costs may be neither indication-specific nor even product-specific for the company.

The analysis of a pharmaceutical company's financial statement shows the nature of expenditures paid out by the company for its activity. It is primarily a question of:

- Research and Development expenditures
- expenditures related to regulatory procedures
- manufacturing and logistics expenditures
- marketing expenditures
- miscellaneous administrative expenditures (management, accounting, human resources, information systems, ...)
- expenditures for patents and licenses.

Now, considering the question of costs imputable to a given product for a given indication, the following comments can be made:

- at this stage, the question of which expenditures should be included in this evaluation is relevant. If the revenues from a product are evaluated only for the orphan indication, should costs not directly related to the indication also be included? And even in the case of an evaluation covering all the indications of a product, it is reasonable to suppose that the Industry has committed costs not correlated with a particular product, but that must be included in the estimation of company profitability. One example of this is R&D costs for products that will never reach the market: these costs are an important part of Industry R&D expenditures. In comparison to other manufacturing sectors, the failure rate at various steps in the development of a medicine is very high in the pharmaceutical industry.
- every product marketed by the company must bear the burden of a part of the costs that by definition are not directly related to that product. This involves primarily:
 - o general administrative expenditures (IT, accounting, management, real estate, ...),
 - o research expenditures (in the sense of the discovery of active molecules). It is difficult to correlate these expenditures with an indication, since it is almost impossible to precisely determine which costs are effectively at the origin of the new active molecule,
 - o development expenditures for all ongoing programs that have only a limited chance of ending up in the commercialization of a medicine. These expenditures are extremely high, since the failure rate of products under development is very high in the pharmaceutical industry,
- for those expenditures that can be directly correlated with a given product, a certain proportion of them is not specific to an indication. More precisely, all expenditures related to manufacturing the medicine are shared by all the indications of the product. This category includes expenditures for industrial

development (formulation, process development, industrial investments required for manufacturing the product), as well as variable manufacturing costs (starting materials, labour costs, energy, waste management, quality control, ...). This category can also include costs related to the toxicological and pharmacokinetic evaluation of the molecule, that by definition are evaluations conducted on animals or healthy patients, and that can be valid for several indications.

- in summary, only clinical development expenditures (starting with phase II inclusive), regulatory expenditures related to the Marketing Authorization, to price and reimbursement procedures and to post-MA studies, as well as all marketing expenditures, are directly imputable to an indication.

In order to more accurately evaluate the real profitability of a product for an indication, it is necessary to add part of the other above-mentioned costs to those costs directly imputable to this indication. The question of allocation keys is the main obstacle to this method and can generate long discussions. But for a certain number of costs, it is possible to propose values that would be fixed percentages of easily identifiable amounts.

Here are several proposals:

	Nature of imputable costs	Proposed allocation keys
Costs shared by several indications	Industrial development and manufacturing costs	Distribution of total costs between indications, depending on the volume of product sold for each indication considered
	Toxicological and pharmacokinetic evaluation costs	Distribution of total costs between indications, depending on revenues generated by each indication considered
Costs shared by several products	Participation of the product in corporate R&D activities	Portion of industry revenues classically injected in the R&D processes. This part is applied to the sum of revenues generated by the indication considered starting from the date it was first marketed
	General administrative expenditures	Average of the portion of revenues that the industry allocates to its general administrative expenditures

In order for this approach to be complete, it is necessary to take into account subsidies and other types of assistance the sponsor could have benefited from to support his research (the Research Tax Credit is an example in France). These subsidies would be subtracted from costs, probably by the use of allocation keys.

The time frame considered for this indicator is:

- for product-specific costs: the period from the date of the first expenditure imputable to the target indication (start of phase II) up to the 5th year after the date of the European MA for the indication concerned,
- for revenues: the period from the date of the first commercialization up to the 5th year after the date of the European MA for the indication concerned.

Finally, it seems simpler to work at the global level for the evaluation of costs, and thus for revenues. An alternative would be to consider revenues in Europe, and costs on the basis of the proportion of total European revenues over total worldwide revenues.

The feasibility of this approach will first of all depend on the availability and validity of the figures used. The various sources of data and their validation will be discussed in chapter III.

The principal advantage of this approach is to enable direct benchmarking between profitability of the product considered and that of the pharmaceutical industry in general. If we consider that this approach represents the contribution of the orphan product to the overall profitability of the company, it becomes possible to compare the profit rate (profitability/turnover) to that of the pharmaceutical industry in general (for example by calculating the mean of net pre-tax results/ revenues of the leading 50 or 100 pharmaceutical companies). Nevertheless, considering the narrowness of the orphan drugs market, at least in terms of the number of patients, care is required when comparing profit in terms of only percentage, and perhaps we should also take into account the absolute value of the profit generated.

In the framework of this approach, it is also possible to envisage comparators outside the pharmaceutical industry. For example, we could consider that an Orphan Drug must have the same profitability for the company as that expected by a venture capitalist for a biotechnology company. The level of risk in both cases is very high

and directly correlated, since venture capital is often behind the financing of the development of innovative medicines. A venture capital fund that invests in a biotechnology company at a stage of average maturity (starting at the time the concept has been proven) and for 4 to 5 years, expects to recover about 6 times its initial investment when it sells its shares in the company. Longer term investments are rare in the venture capital world, but it is conceivable to work with investors to decide on the minimal level of profitability for a 10 to 15 years investment that is closer to the period we spoke about between the onset of a medicine's development and its 5th year of commercialization.

Once this threshold is established, it could be used as a reference for deciding on the sufficiency of profitability of an Orphan Drug at 5 years.

II.2.2 Other approaches eliminated

With an eye towards simplification, in particular concerning quantifying costs, we have investigated other approaches that considered only publicly available data, easily identifiable, and that can be calculated or verified by a public authority.

Two types of data can fulfil this criterion: expenditures related to phase II and III clinical trials, and product manufacturing costs. These expenditures can be estimated on the basis of:

- the mean cost per patient of a phase II and a phase III trial and of the number of patients included in the trials
- the mean industrial cost price for a similar product in terms of manufacturing (chemical synthesis and classical formulation, biotechnology production, other).

Even so, deducting one or both of these costs from revenues remains too rough and the result cannot properly be validated when next to the comparators. This is why these alternative approaches were not considered further.

On the other hand, it is interesting to estimate the costs of phase II and III clinical trials, that can be used in a method based on a revenues indicator, used as a modulator, and not a subtractor as here (see §II.3.1).

II.3 Methods for evaluating profitability based on a « revenues » indicator

The reasoning principle of this option is the following: the « sufficiency » of a product's profitability can be judged by comparing its total sales after 5 years with that of comparable, non-orphan products 5 years after their commercialization. The working hypothesis is that if a product is still on the market after 5 years, this means that it is sufficiently profitable for the company marketing it.

This option thus considers that sufficiency of profitability is judged by comparing it to the « classical » pharmaceutical industry.

The notion of « comparability » used to define products that will be used as reference is based primarily on three criteria that can be taken into consideration to varying degrees, depending on the desired level of sophistication of the analysis:

- the type of research conducted on the molecule (molecule obtained from the proprietary research of the sponsor, molecule purchased as a license by the sponsor, reformulation of an existing active ingredient, ...)
- the manufacturing process of the product (classical chemical synthesis, biotechnology production, other)
- the size of the company marketing the product, in order to take into account its capacity or lack thereof to share costs not specific to a product.

We propose two approaches that differ by their level of precision in the comparison.

In all cases, the size of clinical trials in terms of number of included patients should be included in order to modulate the revenue compared, since this is a major cost

factor in the evaluation of profitability, and since by definition orphan drugs are subjected to clinical assessments with a small number of patients, it will be difficult if not impossible to find comparable products from this point of view.

II.3.1 Detailed « revenues » approach

The following procedure is proposed:

- For each type of orphan product analyzed, a comparable group of non-orphan medicines is defined. It would be useful to first publish the groups of products to which future orphan drugs will be compared. These groups would be created on the basis of the typology of currently designated orphan products, which would lead to relatively rapid announcement of the constitution of the comparison group. For example, “biotech” type non-orphan products obtained by in-house research totally conducted by small companies could constitute the first group. A second group would be composed of products whose active ingredient was obtained by chemical synthesis and that underwent pharmaceutical reformulation by small companies. A third group would be composed of products chemically synthesized by international pharmaceutical houses, that were the subject of extensions of indications. And so on. This procedure is very close to the classifications used in price setting systems that use a reference price, as is the situation in several European countries (BAK in Germany, "Tarif Forfaitaire de Responsabilité" and "Groupes Génériques" in France, ...)
- On the basis of the analysis of sales figures of products of this group, corrected for the estimated amount of phase II and III clinical trials, using a method that remains to be defined, a turnover « sufficiency » threshold would be defined.
- The comparison would be between the turnover of the orphan drug concerned, corrected by the estimated amount of its phase II and III clinical trials, and the previously defined sufficiency threshold.

This approach could either be conducted on total turnover for the first 5 years or on 5th year turnover.

The accuracy and acceptance of this approach would be based on the relevance of the choice of comparability criteria and the resulting tree structure of comparable products, and on the level of cooperation implemented to establish its rules.

There are several advantages to this approach:

- facilitates access to required data, e.g. via IMS
- no complicated consideration of cost allocation
- principal cost factors continue to be taken into account, since the comparators are chosen in the basis of criteria corresponding to these cost factors
- company size taken into account
- possibility of working at the European or even national scale.

The approach nevertheless has the following disadvantages:

- considerable work is required to determine the sufficiency threshold of revenues via the analysis of medicines chosen as being comparable, and it should probably be revised on a regular basis
- it is more global in comparison to an accounting notion of product profitability.

II.3.2 Broad « **revenues** » approach.

The goal of this approach is to overcome the main difficulty discussed above: the choice of comparators. It involves proceeding with the same reasoning as above, without establishing groups, but by still comparing the Orphan Drug's turnover to an overall threshold above which it is judged that profitability is sufficient. This reasoning is based on the general consensus that a « blockbuster » is always profitable for the company. This threshold would be €500 million to €1 billion annually worldwide. Using a process of decreasing thresholds and referring to the sales figures of a panel

of non-orphan medicines, it would become possible to decide on « sufficient » turnover.

This approach has been considered in the United States as a reason to withdrawing exclusivity. Although the American threshold has been set at \$200 million in annual revenues but this approach has never been implemented (see appendix 1).

III. Data: sources, validation, evaluation of comparators

In all of the three options proposed above (complete “accounting” approach, detailed “revenues” approach and broad “revenues” approach), the strength of the evaluation hinges on both the method itself and the reliability of the data used.

There are two types of data:

- That used to calculate the profitability indicator of the product analyzed
- That used to calculate the value of the comparator.

For the calculation of the profitability indicator, it is best to gather the data in as much detail as possible in order to guarantee its reliability. As an example:

- for the three approaches, revenue data should be collected on a per country basis in the form of sales volumes (number of units sold) and unit price. The data should be collected separately for the product’s various pharmaceutical forms.
- for the complete “accounting” approach, industrial cost data should be collected along with details on the calculation method used (materials cost, depreciations of industrial investments, any included margin ...).
- for the complete “accounting” approach, clinical trial data should be accompanied by details and a substantiated evaluation of average cost per patient.
- ...

There are four ways to verify the data:

- validation by experts of the data communicated
- verification with publicly available data (for example, IMS for sales volumes and revenues or scientific publications of clinical trials)
- *ad hoc* studies by specialized consultants

- accounting audits ordered for this purpose. In this case, the question of whether a European authority is legitimately positioned for ordering this type of audit can be posed.

Concerning the data used to calculate the value of the comparator, at this stage it should be stated that the precise calculation mechanisms must first be adopted by a task force including the *ad hoc* experts engaged for this. This task force could in turn rely on studies and audits ordered in this context.

It is important here to return to comparators that could be used. In the « revenues minus costs » options, comparison with external values is done based on a profitability rate. It is reasonable to say, however, that this approach is valid only beyond a given absolute value: it is possible to realize a margin of 80%, but if turnover is €1 million, can it reasonably be said that profitability is sufficient? This limitation of the « revenues minus costs » approach could act in favour of the « revenues » option, that reasons rather in terms of absolute value.

IV. Procedures for the evaluation of profitability

The evaluation of profitability can be done in one or two steps, depending on the option selected concerning the nature of the comparator at 5 years (« external » comparator or comparator « intrinsic » to the product).

In the case of the one-step evaluation, it would be conducted at the end of the 5th year with no preliminary work up. There is a major risk to this approach in that it does not allow the company to prepare its defence in the case of an eventual unfavourable decision. In order to avoid this, it would undoubtedly be necessary to plan on an exchange between the authority conducting the evaluation and the sponsor during the evaluation process so that it becomes possible for the sponsor to justify itself if the evaluation's conclusion appears unfair.

A two-step evaluation would occur as follows:

- The first step, at the moment the MA is granted, involves evaluating a forecast profitability and deciding on its sufficiency. This initial profitability would be used as the comparison point five years later.
- The second step, after 5 years, would try to verify that profitability at this time corresponds to the forecast.

This two-step process comes down to agreeing with the company at the outset on a sufficient level of profitability, beyond which market exclusivity is no longer necessary.

By definition, this is not suited for medicines already on the market. If the two-step option was chosen, it would be necessary to work on a case-by-case basis in close cooperation with the drug companies in order to agree on a specific evaluation method for the 15 orphan drugs already authorized in the EC.

There are a number of advantages in using the two-step process.

First of all, the strategy would be preventive rather than abrupt, with a brutal, final decision on the profitability or lack thereof of an orphan product 5 years down the track.

This process is very close to price-volumes agreements practiced in several Member States and could be used as a starting point for European brainstorming on a reference price. This price could initially be defined with a group of volunteer Member States desiring to work together on the medical and economic evaluation of the medicine. Several representatives of Member States have agreed to the principle of this type of cooperation. Seeing this price would have no obligatory value, making it available could help non-participating Member States to negotiate the price of Orphan Drugs for their country, while maintaining their individual subsidiary-specific principles. For participating nations, discussion on EC-wide pricing would result in:

- sharing scientific experience on the pathologies considered. In the case of rare diseases, it is not uncommon that all countries do not possess the experience necessary to evaluate a new medicine. Working on the Community level would ensure that Member States participating in the initiative have access to the necessary knowledge;
- giving weight to Member States in negotiations, since the size of the corresponding markets would be larger.

In addition, Orphan Drugs could thus become a field of experimentation for common methods for the medical and economic evaluation of medicines.

It is also a procedure that would satisfy the Industry, for which establishing a reference price would undoubtedly accelerate national discussions and the marketing of their product accordingly.

Also mentioned were the advantages of an initial evaluation in implementing indicators for better monitoring patient access to orphan drugs. The notions of price and profitability are in fact closely linked to that of volumes of product sold (number of

packs for example) and thus with the number of patients treated. In these initial discussions with the Industry, all players clearly wish to include forecasts of volumes and numbers of patients treated, and to ensure that these parameters are monitored. It was requested that 'per country' monitoring system be implemented, that would facilitate the analysis of orphan treatments penetration in European populations. This tool would constitute a great step forward in encouraging Member States to have orphan drugs achieve maximum acceptance by their health care systems.

This monitoring could accompany initiatives currently taken by the Industry and by the EMEA to improve the system of evaluation and epidemiological surveillance of rare diseases and to uncover synergies with the current work of Orphanet ordered by the COMP, on a public orphan drug database.

Some orphan drugs players questioned during this study suggested that a European authority, to be defined, could have a triple role in this context:

1. Implement article 8.2 by managing the profitability of orphan products with an intervention at the moment of the MA and another after 5 years of commercialization
2. Define a European reference price with no obligatory value for the Member States.
3. Centralize forecast evaluations and the surveillance of volumes of medicine sold, the number of patients treated, and the epidemiology of rare diseases in all European countries.

The question of which authority should be responsible for profitability evaluation can be posed in the present context. There are three possible authorities in Europe: the COMP, the EMEA and the Commission.

In any case, it should be remembered that the current role of the COMP and the EMEA is essentially scientific and that the introduction of an economic aspect would require changing both the composition and role of these authorities.

The Commission already has a « Transparency Commission » that is currently the only group holding the role of addressing economic questions concerning medicines. However, this Commission is not specific to Orphan Drugs, which clearly cannot be evaluated like other products.

The simplest solution would undoubtedly be the creation of an authority dependent on the COMP and its scientific expertise in Orphan Drugs, whose domain would be primarily medical-economic and who would play this double role of monitoring profitability and addressing the problem of a European reference price.

V. Conclusion

In spite of the necessity for the unrestricted application of the European regulation on orphan drugs, and thus the definition of a method for the evaluation of the profitability of an orphan product in order to implement article 8.2, it is again important to state that this is surely not the most urgent measure for guaranteeing the success of this regulation.

Many consider that the priority should be providing patients with better access to orphan drugs via work on the reimbursement of these treatments. In addition, it is also extremely important to ensure the complete application of the regulation, in terms of the implementation of all incentives that are planned but not yet carried out in all Member States.

On the other hand, it is interesting to note that progress made on profitability evaluation has enabled solutions to be proposed that could have implications for and be of direct use to priority projects. A case in point is the monitoring of volumes of medicines sold, which would enable patient access to treatments to be monitored, and thus provide a tool for managing accessibility to these treatments. Similarly, the common evaluation of the price of Orphan Drugs, based on data shared with that required for profitability evaluation, could help to accelerate the marketing of products and thus increase accessibility to treatments. Finally, if the complete « accounting » approach option is adopted, the integration of aid and subsidy data in the evaluation of profitability would clearly enable the management of a more systematic implementation of the incentives planned in the regulation.

It is therefore certainly possible to implement tools, structures and procedures that would respond to the expectations of all payers concerned: European legislators, the Industry, patient associations, Member States.

When comparing the various approaches proposed, it appears that the “revenues minus costs” option is for sure the most complete and closest to the notion of profitability mentioned in the regulation. However it would be complicated and long to implement. The “revenues” option on the contrary is simpler in terms of data collection and validation, but above all with respect to the implementation of the procedure itself. The number of parameters to be considered is by far fewer than under the “revenues minus costs” option. This should drastically restrict discussions and potential disagreements between parties. The main question in this case remains the definition and calculation of the comparator, whose strength will be crucial to the success of such an approach.

Whatever the approach chosen, it is important to remember that wide consultation with all the players will be necessary and time consuming anyway. Yet it is also obvious that guidelines must be proposed by the European Commission before August 2006, which is the 5th birthday of the first orphan European MA. It would therefore be wise progressively implement the chosen approach. If the “revenues” option is adopted, why not for instance envisage the rapid implementation of the “broad” approach, before progressively adding items specific to the “detailed” approach. This would provide the advantage of an interval of several years for designing and simulating a system accepted by the majority of parties, while disposing of a method applicable as early as 2006. This option appears all the more necessary in a context where the current systems for economically evaluating ODs in place in Europe are extremely heterogeneous (see part I of this report for more details). Annual working sessions and consensus conferences involving all parties concerned could be a good way to make players work together that do not currently have common working methods on these topics.