# Towards an *Orphan Drug* Policy for the European Union

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under a studry contract for the European Commission
(ETD/94/B5-4110/IN/38).

# Content

## I - INTRODUCTION AND METHODOLOGY

The treatment or improvement of pathological conditions each severely affecting a small part of the population, and without satisfactory solution, raises a number of delicate questions that neither modern society, the public health authorities, or the health research industry can afford to ignore, or to treat superficially.

The European Commission, perfectly aware of this, is proposing a wide consultation with the objective of defining and setting up, after finding the means, an aggressive and effective health policy.

This particular study, which it has requested, submits for reflection by the interested parties of the European Union, a set of points that need consideration. It is based on analysis of existing regulations, principally in the U.S. and Japan, and their effects, on various manifestations of interest, both at community level in the European countries and others, and on an examination of numerous publications.

The W.H.O., the pharmaceutical industry associations in Europe, the U.S. and Japan, individual firms or groups of firms, as well as patients associations, have kindly communicated their experiences in this area.

## II - DEFINITIONS & OBJECTIVES

### A Definitions and Review of the Situation

It is generally considered that a rare disease is one that does not strike more than 650 to 1000 people per million. The W.H.O. appear to have identified about 5,000, of which 4,000 seem to be linked to genetic factors. Many of these do not benefit from any support or aid, institutional or scientific, and are considered as orphans. Their symptomatic or causal treatment or better still, their prevention implies the need for a much deeper knowledge of the origin and the effects of the disease, as well as a search for "tools", medicinal, diagnostic and surgical.

Unfortunately such research is extremely onerous and risky,in the sense that the chances of success are very limited, and in addition, it comes within a domain which is to a great extent provided by the private sector.

It is also not accessible to charitable organisations, or patient associations that nevertheless ask for it. The cost, the difficulties, the heavy responsibilities, the pressures moral and public, the absence of foreseeable profit etc, ... are all elements that do not really prompt industrial or scientific sponsors to give much consideration.
Their inevitable lack of interest, even the withdrawal of the development of certain potential drugs have led to the idea of "orphan" drugs, in the same way as "orphan diseases" implies severe pathological conditions, either rare or affecting only a small portion of the population, or only spread among the poorest populations. It is as much the more fundamental research into these diseases and their causes(s), as on more specific research into treatments ( medical or otherwise), or finally on the development with a view to marketing of existing potential therapies that must be examined.

The first seems to be more the privileges of societies and public institutions within their research programmes, whilst the following ones are essentially the responsibility of industry, especially pharmaceutical. But the latter is subject to profitability restraints from which there is no escape. However one must admit that public institutions are more and more confronted with the same problems.

The W.H.O. devotes special attention to those diseases where no useful treatment exists and also to Tropical Diseases, which are not necessarily rare, but can be regarded as orphan diseases, since they tend to be "abandoned" because of the extreme poverty of those countries and affected populations, and of the dramatically insufficient medical infrastructure (Tropical Disease Research Programme). The W.H.O. acts through its regional offices and health ministries, but it also collaborates with numerous institutions, international and other organisations interested in health , non-government organisations and industry. Towards the latter it operates, to a great extent, through individual contacts with voluntary firms, known for their traditional interest in such research or their therapeutic "palette" in the matter.It offers its expertise in the area of those diseases as well as technical aid. Equally available is information on treatments used for those sick people who, whilst staying in the affected regions, contract a "Rare in the West" disease.

It also collaborated with the World Bank which published in 1993, an interesting report on "World Development".

With that in mind and in the setting of infectious or viral diseases, the case of vaccines merits special attention.

Incentive and support of R & D appears to be a moral obligation and a duty on the part of the Public Health Authorities.
More specifically regarding the drug (principal object of the present study) such an incentive should or could cling to the pursuit of objectives in the

most balanced possible way.

Everything leads to the belief that industry, as far as it is concerned, would bring its collaboration as well to seeking means, as to setting them up and exploiting them.

## B Objectives

- An humanitarian objective :

  by stimulating the interest of researchers and sponsors

- A Public Health objective :

  by encouraging

  * R & D of new curative/preventive drugs
  * development or possible exploitation of secondary properties or indications of known drugs
  * marketing/re-marketing of existing or abandoned drugs

  by ensuring their supply in sufficient quantities

  by preventing any increase of the frequency of the disease

  by informing beneficiaries and sick people of the existence and potential of certain drugs

  by ensuring their quick availability to those who need them

- A scientific objective

  by stimulating the development of knowledge on rare diseases, their cause(s) and possible treatments

  by specifying the epidemiological data, namely by establishing registers identifying rare diseases, their frequency, their extension or regression,

  by ensuring an appropriate classification

  by identifying, with the possible assistance of Universities and Academies, those linked to genetic factors, allowing a pre- or post-natal diagnostic, a surgical treatment or a possible genetic therapy (pre-competitive research)

  by envisaging the creation of centres of specific excellence (for selected

diseases)

- an economic objective : direct or indirect

  by proposing measures likely to boost the interest in Europe of the international Pharmaceutical Industry, as well as small and medium sized enterprises, thus increasing competition.

The global increase of knowledge, the development of biotechnologies, the analysis of the human genom, open new opportunities.

As regards the Pharmaceutical Industry, where the moral satisfaction that can often be achieved by free availability of essential products already procurable can be considered a duty, could invest - more reasonably - in their development and benefit in this respect from a more positive brand image.

## III THE MEANS

### A General Points

Judging by the steps that have already been taken in various countries, in particular in the United States and in Japan (see details infra), by the many analyses and comments available, it seems that the means envisaged (and that can be envisaged today) are all in the framework of a few fundamental concepts, very limited in numbers. And it is really the balance necessary to their materialisation that is the problem.

It appears commonly admitted :

* that without participation of the private Pharmaceutical Industry, R & D of (new) drugs remains totally insufficient, if not impossible.

* that if the latter, for reasons of humanity and/or prestige, is ready to make available free of charge certain drugs in its possession - under conditions remaining reasonable - it cannot ensure alone an intensive R & D, particularly expensive, with particularly high risks (difficulty of appreciation) and without any hope whatsoever of profitability at the end, while taking on greater and greater legal responsibilities (linked to making the drug available);

* that as a consequence, a close collaboration between responsible Authorities and research Industry should be set up;

* that this collaboration should extend to patient associations the role of which is essential (e.g. information);

* that this collaboration implies :

for public services :

the set up of financial, fiscal, scientific, regulatory incentives;

the acceptance of one end or the other information (see infra);

the reinforcement of the collaboration with academical institutions through financial assistance to fundamental research;

for industry :

the suggestion of adequate research programmes, their pursuit in consultation with the responsible Authority, the supply of possible products with the relevant information, even in the absence of a proper commercial profitability from the moment it accepts to take advantage of various incentives made available.

that the prime objective of Public Health protection suffers no infringement to the quality of evaluation of the dossier submitted for approval.

The expression in regulatory terms of these great principles is to be found more or less developed, in the various legislation presently in force.

## B In the United States

General Review

The **Orphan Drug Act** of 4.01.83 defines the objectives and main principles. As early as October 1984, it sets the conditions and limitations, envisaging clinical and pre-clinical experimentation, the designation to the status of "orphan drug", the protection granted to these products and the need for an early availability for some patients. Antibiotics and biological products are considered in this legislation and the "orphan disease" is defined as and illness affecting not more than 200.000 people in the United States.

In October 1985, a new amendment modified the approval conditions and a few later clarifications dealt with designation and subsidies.

Meanwhile, the FDA in collaboration with other government services, while preparing the application regulations, proposed - via the **Office of Orphan Products Development** (OPD), guidelines informing the applicants of the conditions for obtaining the designation of "Orphan Drug" and on assistance protocols. The available subsidies and terms of the request are published annually.

Very recently (on 29.12.1992), further to a request from the American Congress and after a wide consultation, the Food & Drug Administration (FDA) published, together with its interpretation, the modifications to the Orphan Drug Act and the procedures to be applied, under the title of **"Orphan Drug Regulations : Final Rule.**

This very detailed document is the more interesting in that it is based on some 8 years of experience and that it justifies the selected options.

In other words, it never tries to divert from the objectives sought early on in the legislation, i.e. give Industry sufficient incentives to promote R & D for new products (or the utilisation of properties or side effects of known substances) and give the patients, as quickly as possible, access to the potential treatment needed, while avoiding deviations such as laxity in the analysis of the benefit/risk connection, or undue profits or advantages for the Industry, or even utilisation of the legislation as blocking instrument to competition or scientific progress.

It must be noted that the FDA gives no consideration as to the price of the finally authorised drug; only the marketing authorisation (MA), its preliminary work and conditions falling within its competence.

In brief, this document comprises 6 chapters :

a. <u>General Points</u> :

Fields of application : establish standards and procedures concerning experimentation, the designation, the exclusivity period, the availability before marketing.

Definition of terms used : particularly the concepts of "clinical superiority" and the character of "novelty".

b. <u>Recommendations</u>

of the FDA - written or not - for experimentation (assistance protocols).

c. <u>Eligibility</u>

to the status of "Orphan Drug". It is to be noted that the "Orphan Medical Devices" or the "medical food" are not concerned by this legislation. All drugs are, including biological ones :

* Serious presumption of efficacy on a rare disease

* The product should however not be reserved exclusively for the treatment of the rare disease. It can concern the exploitation of a property, even of only a side effect of a commercialised product, or of the study for other indications.

* The disease cannot affect more than 200.000 people in the U.S. (or the product cannot be administered to more than 200.000 people in the U.S. - vaccines for instance).

* A product which is intended for more than 200.000 patients is also eligible if it cannot be reasonably expected that its commercial results cover the costs of the R & D for the indication studied.

* Control of the data on the frequency (prevalence) of the disease, or on the presumed non-profitability (with possible data on the justification of costs involved outside the U.S.).

* The applicant must be - or have as an agent - a permanent resident in the U.S.. The request may, or not, precede the Marketing Authorisation.

* Conditions for refusal, modification, transfer to another sponsor, of publication or dismissal of status. To be noted that an increase of the frequency of the disease does not lead to the dismissal of the status nor of the advantages linked to it, if the data was valid at the time of designation.

d. Exclusive approval

The FDA will not grant any Marketing Authorisation for the same product during 7 years dating from the product receiving the status of "Orphan Drug" to a product, except
in case of agreement from the holder
in case of revocation of status according to previous criteria
in case of suppression of the MA
in case of incapacity by the holder to supply the product in sufficient quantities.

The FDA informs the sponsor and the public by a list updated regularly with names and particulars of the holder of the recognised product.

e. Access to treatment

Besides the measures in case of insufficient supplies (temporary or final), an earlier "opening" of the access to the product by the patient is planned (by allowing him to receive the drug under investigation as a treatment and not for the purpose of research).

f. Information

Publication of the list (updated monthly) of authorised products and availability of additional information (to be determined by the FDA). However, the FDA will refuse to give any confidential or premature information.

It has also to be remembered that

upon obtaining the status of "Orphan Drug" a tax credit of 50% is obtained on the cost of clinical trials made in the U.S;

subsidies for conducting clinical experimentation can be requested (the available amounts are published annually - as an example they amounted to 12 million dollars in 1995). Clinical trials in phase 1,2 and 3 can expect subsidies up to $ 100.000 per annum for a maximum of 3 years, while trials in phase 2 and 3 could receive up to $ 200.000 during a maximum of 2 years;

and that no evaluation of environmental risk, presumptively considered as insignificant, is required;

The exemption of registration fees could, according to the FDA, be the subject of a later discussion.

Additional comments

It cannot be denied, even if the summary above is particularly short, that the legislation in question is very closely studied and aims to reach the determined objective (meeting a duty of state and of human nature) without calling upon a forced and unrealistic voluntary action, associating public effort and private effort, encouraging the latter significantly, but marking out the ways open to Industry for ethic, moderation, scientific progress, competition in the sector and in the different segments of the sector, to be preserved.

Already, prior to the **Orphan Drug Regulation of 1993**, which codified the procedures and practices of the **Orphan Drug Act**, applied by the FDA, results were not long in coming. According to the FDA, the stimulating combination of 7 years exclusivity, subsidies to research and tax credits, has lead to the development of new products by numerous small enterprises and while, before the signing of the law, two or three drugs a year could have been eligible to the title of "Orphan Drug" , an average of eight a year, approved and *marketed*, have been counted since 1984 (48 drugs for 58 diseases mentioned by the FDA on 28.01.91).

In March 1993, according to a publication of the Pharmaceutical Manufacturers Association in collaboration with the FDA's Office of Orphan Products Development, 488 designations to the status of Orphan Drug, 64 drugs approved and 189 drugs in development for a total of 132 sponsors were counted.End 1994, 682 designations were registered of which 110 products approved.

However, voices have begun to rise, denouncing the profit, excessive according to them, that the Pharmaceutical Industry would or could draw in certain cases of this legislation. Amendment proposals have been presented both to the Chamber and the Senate. They aim to :

* in principle reduce from 7 to 4 years, the exclusivity period granted;

* grant 3 additional years to products with a limited commercial potential (to be defined);

* make sure the frequency cannot exceed 200.000 patients during the 3 years following the application (or otherwise allow the approval of other products).

These amendments should, once accepted, have been published and in force before the end of 1994. But so far no modification of the law in that direction has taken place or is planned at short term.

The Pharmaceutical Industry, or at least certain segments of it, have denounced the flaws or incoherences which have appeared, such as : differentiation criteria, especially for the macromolecules for which the "chemical identity" cannot suffice on its own to grant or not a character of novelty, or also the concept of "clinical superiority" which remains very subject to interpretation, or finally the sometimes ambiguous relation between patent and exclusivity.

## C In Japan

General Review

As early as 29.06.1985, a circular from the Bureau of Pharmaceutical Affairs defined the concept of "Orphan Drug" and the nature of the dossier to be supplied to obtain a Marketing Authorisation. This circular comprised four sections :

a. Object :

To promote the development of drugs intended for the treatment of diseases affecting only a very limited number of people in Japan, but essential for their treatment, by proposing a simplified list of documents to be submitted to support the request.

b. Definition :

The recognition of status of "Orphan Drug" and the obtention of the attached advantages implies :

* a very low rate of frequency of the disease for which the drug would be indicated;

* no treatment must exist;

* it must be possible to grant the authorisation quickly, given the particular importance for the sick person.

c. Dossier

It should comprise :

* Data on the number of sufferers in Japan, on existing treatments, the possible usage of the drug abroad...

* The clinical file will have to content itself with the results of trials achieved in Japan next to any clinical data obtained from abroad (in accordance with the recommendations from the Bureau of Clinical Affairs).

* The results on stability studies can be submitted later on.

d. condition after marketing :

Obligation to supply any information to users on the efficacy and the tolerance. Obligation also to take all possible steps to collect a maximum of information on usage.

Additional comments

It would appear that these measures, which in fact only set out to alleviate the dossier in order to achieve an easier and faster availability of the product to the patient, have not obtained the result expected.

The authorities then considered an important recasting of the **law of 1979** to which, on 1.10.1993 important modifications have been suggested, in order to "better promote", "to adopt a more aggressive support policy for "Orphan Drugs".

From now on the *Ministry of Health and Welfare* (MHW), in consultation with the *Central Pharmaceutical Affairs Council* (CPAC) will be allowed to grant the status of "Orphan Drug" when the product - whether a new product or a new indication - appears to be of great value in case of usage and that less than 50.000 patients are affected in Japan.
The decision will be published, as well as the particulars of the sponsor and the target indication.

Once this status is granted, the "Drug Fund for Side Effects Relief and Research Promotion" (Drug Foundations) will bring its financial assistance for R & D, as well as technical advice to firms. The latter will also benefit from a tax relief (6%) on R & D expenses (except those financed by the Fund) and a maximum of 10% reduction on the tax rate of the firm, as well as an extension of the re-examination period which, presently from 4 to 6 years, will extend up to 10 years. The modifications of the law also anticipate an accelerated procedure for the Marketing Authorisation and a reduction of the dossier content.

(Flow-Chart of the proposed system in annex).

The status can be withdrawn if :

* the number of patients in Japan exceed 50.000;

* the medical need regresses (availability of another treatment, for example);

* the experimentation is not carried out;

* or if the holder infringes the law.

The "Drug Foundation" will receive funds from the Government and from beneficiaries of subsidies, as soon as the latter will have made profits from their orphan drugs.

The Pharmaceutical Industry has presented the Bureau of Pharmaceutical Affairs with a petition entitled "Needs to clarify the requirements relative to the designation of Orphan Drugs and measures to be taken concerning these products".

The JPMA (Japanese Pharmaceutical Manufacturers Association) :

* requests that the status of Orphan Drug be recognised for any product meeting the criteria defined and for which an application has been filed by a firm;

* considers a global donation from Industry as participation to the supply of starting subsidies;

* is opposed to the *proposal* of a 3 % tax for "Orphan Drug Companies" on the turnover exceeding 1 billion Yens/year during 10 years;

* considers as acceptable the payment of 1 % of sales over 100 million Yens per year, until the time when the government subsidy will have been repaid;

* expects in return tax relief, priority in the examination of dossiers and a liberal approach to questions on subsidies, price and reimbursement.

It is premature to give a verdict on the results of the implementation of these measures. There was mention of 15 drugs having obtained their status since 1987, but it appears from a first investigation that these measures essentially aim at rationalising, simplifying and accelerating the procedures while safeguarding, as much as possible, the quality, efficacy and safety of the product. On the other hand, the "incentives" for industry are modest, precarious and temporary and result much more in *allowing financially* the industrial effort that instigate or promote it.

However, since the revision of the law, 69 products provided by 50 firms appear to have received the status of orphan drug. On the other hand, the MHW has proposed, for 1994, the availability of subsidies to an amount of about 4 million dollars.

## D Elsewhere

General Review

There seems to be no regulatory measures to draw the attention. However it cannot be denied that there is concern everywhere on the matter. As an example :

In Singapore : the authorities and the Pharmaceutical Industry have agreed on a basic programme.

## E In Europe

General Review

No specific legislation has been set up nor, to date, even proposed. In some (large) countries, a precise mention is introduced in the official texts.

a. In France :

The **Law of 8.12.1992** modifying book V of the Public Health Code relative to the Pharmacy and drug, article 21, provides for the exceptional *use* of certain drugs, when they :

* are intended for treatment of severe pathologies, while no alternative therapy exists, if their efficacy is strongly presumed in view of the results of therapeutic trials which they have undergone for a marketing authorisation application (compassionate use);

or

* are intended for patients affected by rare diseases and if no drug already authorised in the sense of article L.601 and likely to act as a substitute (orphan drugs)

and

* the use of these drugs is authorised, for a limited time, by the Minister in charge of Health, with prior agreement of the holder of the drug' exploitation right in the case outlined in the first paragraph of this article. This authorisation can be suspended or withdrawn if the conditions outlined in this article are no longer met, or for reasons of public health.

The Decree 94-568 defines the granting, renewal, suspension and withdrawal from temporary use conditions for these drugs.

Definition, Classification, Prevalence deserve to be specified. For instance, it has been suggested to make the following modifications :

Orphan Drugs : are intended to diagnose, prevent, treat severe pathologies, *without it being reasonably possible to absorb the costs of development and distribution*, as long as their efficacy.....

Drugs possessing orphan indications : are drugs already registered but whose usage has shown the therapeutic interest in other rare or severe pathologies, at different dosage than those registered and when there exists no therapeutic alternatives.

In other words, the suspicion of an orphan indication can derive from an "extensive" usage of a drug, through a step-by-step approach by the physician, in non-registered indications because they were not supported by a sufficiently structured experimentation. The latter must be promoted and supported, if indicators flicker seriously.

On the other hand, a very recent law (11th January 1995), modifying the list of specialities subject to reimbursement to social beneficiaries, confirms the intention of the French Authorities to set a procedure for "exceptional drugs", and underlines the absence of documented clinical studies specific to "*orphan indications*".

In this particular case, the purpose is certainly not to promote R & D, nor even marketing of drugs for orphan diseases, but only allow access of a particular product to patients suffering from an orphan disease. The point is to give a socio-economic follow-up to the "authorisation for exceptional use of a drug in a non registered *indication*", according to the above mentioned law.

Let us indicate here that research organisations such as INSERM, the CNRS and others have set up information and training activities and also act somewhat like "opinion promoters" in favour of a greater activity in the area of rare diseases.

b. In Spain :

Article 34 of the law 25/1990 of 20.12.1990 on drugs considers that the Government can adopt special measures in relation to their manufacture, their economic, fiscal, distribution and release regime, concerning "drugs without any commercial interest".

c. In the United Kingdom :

In the field of research, there is a definite collaboration between academic authorities and industry; in particular, the Medical Research Council and some industries work on programmes (diseases in developing countries). In some particular cases, requirements before Marketing Authorisation are limited subject to commercialisation for low populations and availability of further data.

d. In Germany :

In 1990, Parliament, supported by the BPI (Bundesverband der Pharmazeutische Industrie) proposed to the Federal Government that the possibilities for promoting R & D of orphan drugs be studied and that consecutive measures be implemented without delay. Parliament also requested the problem be taken to European level.

In 1993, the Health Minister invited the Industry to a new discussion but this concentrated on the question of antidotes in case of intoxication, given the withdrawal of some of them for economic reasons.

e. Elsewhere

The Nordic Council proposed, in 1985, a programme with a view to collecting some information on rare diseases and the patients groups suffering from rare diseases in Scandinavia.

In Denmark, the Health Minister has founded a research centre for rare diseases and handicapped people. In addition, in December 1993, the National Health Council suggested an appropriate organisation for hospitals (diagnosis and treatment). Bearing in mind the low incidence, only two centres were recommended to be established. One of them, the Centre for Rare Disorders and Disabilities, was created in December 1994, in association with the Department of Pediatry at the hospital concerned. The other is planned for 1995.

In Sweden, the status of orphan drug does not exist but a particular procedure is open for drugs of great medical value for which the sales forecast is low.

The Apoteksbolaget, which administers some 800 pharmacies, provides the manufacture and the distribution (through a few specialised units) of non-commercialised orphan drugs. It takes on if necessary, the galenic formulation, takes care of documentation and organises R & D programmes in collaboration with the doctors. In 1990 the Swedish Medical Products Agency suggested a policy for orphan drugs to the Government and to the Pharmaceutical Industry which to date remains without concrete follow-up.

But it is in Sweden that an interesting initiative has been launched by a few pharmaceutical firms, i.e. the creation in 1988 of "*Swedish Orphan AB*". Its mission is described as follows :

"To provide patients, healthcare personnel and the pharmaceutical industry with an independent global network, specialising in the development, marketing and distribution of Orphan products for the treatment of rare disorders"

An international "*Orphan*" network has been set up (associations in Sweden, Denmark, Finland, Norway, France, United States, Japan, Australia) and some contacts established with more than 20 different pharmaceutical firms and associations.

Through this network, which is oriented towards certain therapeutic areas, clinical experimentations have been carried out as well as actions of marketing, advice and support for the obtention of a Marketing Authorisation.

f. At Community level (Within the European Union) :

Although the Union is not yet equipped with any specific legislation concerning Orphan Drugs, it is certainly not from unawareness or disinterest, but because of "helplessness" in front of administrative, political, and economic barriers, consequent upon the division of the Unions's territory.

Now that the internal market for drugs is becoming a reality, and a unique marketing authorisation is instituted, nothing whatsoever justifies such a gap in the European Union, neither from an ethical point of view nor even from an economic point of view. The size of the population not only justifies it, but even requires it; the centralised system of Marketing Authorisation allows it so well at the level of granting the authorisation as on that of dialogue and technical support; the R & D programmes are thinking about it and must become concrete and develop and the intellectual and industrial protection is virtually harmonised.

The fact remains of course that any subsidy or possible fiscal incentives, should avoid the traps of discrimination between countries. Furthermore - and it is very important -the risk that national systems of price and reimbursement fixing in some Member States compromise the final economic balance sheet.

However that may be, the European Union for drugs lives nowadays to the rhythm of a very sophisticated legislation applied to any drug and in which is found, here and there, some allusion to a possible exemption - but always subject to interpretation - to the prescriptions of normal procedures.

It is not possible to talk of "incentive" to R & D in this matter, on the contrary the few "alleviations" of the requirements that can be hoped for according to Directive 91-507 are far too uncertain and too late in the development process. They cannot on their own persuade a firm to launch itself, in this difficult adventure of developing a drug for an orphan disease, if it does not itself have sufficient means. In any case, it is an *adaptation to the epidemiological and scientific reality* that has to be envisaged, maybe even case by case.

Since 1987, and considering that an orphan drug represents a significant interest in the therapeutic field, the procedure known as "concertation" is accessible to it. It would appear to be the same for a new way of administration, considered as innovative, of a known drug, but, being a new indication, it would be the same only if the therapeutic interest it represents is know. The conditions of access to the centralised procedure which took effect on 1.01.1995 being identical, this reflection is worth mentioning. In any case, the admissibility decision being in the hands of the Committee of Proprietary Medicinal Products (CPMP), an "uncertainty" remains... that precise criteria as to the designation of "orphan drug" remove.

The draft regulation on fees collected by the European Agency for the Evaluation of Medicines authorises, in its article 6, the suppression of the fee (possibly partial and only on the advice of the Director assisted by the Committee of Proprietary Medicinal Products). However appreciated this initiative may be, it remains completely insignificant in relation to the investments made,and moreover only affects the cost of marketing of the result of a research having *ended up* in the development of a marketable drug, and cannot be considered as an incentive to R & D, but at the most, an incentive to the decision of marketing a drug of which the firm would have successfully finalised the development prior to marketing.

For any new drug, authorised by the centralised procedure,there also exists a protection of data spread over 10 years. This protection would of course apply to orphan drugs should a Marketing Authorisation be applied for and obtained through this procedure. Although this protection is essential, it can however not be compared to a market exclusivity such as granted and used in the United States for a non-patent drug. On the other hand it should be firmly guaranteed for all the data in support of a new indication of an existing product.

Whatever the case may be, the first question is to be capable of financing and proceeding to the R & D of the drug and thus it is at a much earlier stage than the MA, that action must be taken, i.e. find, propose and make available sufficient financial incentives. International firms as well as small and medium enterprises should have access to it and the quality of development (in biotechnology, for instance) should be supported, mainly with the latter.

Indeed, as mentioned above, directive 91/507 of 19.07.1991 modifying the annex to directive 75/318 allows for exemptions to the necessary documentation to support demands relative to the efficacy and harmlessness, if the indications considered appear so rarely that the applicant cannot reasonably be requested to supply complete information (i.e. an adaptation of the requirements to what is reasonably possible).

However it is a text which is very much subject to interpretation. The dialogue which should start between the applicants and the European Medicines Agency well before entering the dossier of marketing authorisation application, would at last, allow this text to be used to the full as long as it ends up in precise commitments.

The heavy responsibilities lying on the firms aggravated by the legal uncertainty cannot be forgotten. They are likely to lead a firm to abandon the marketing of a drug which was unable or could not - in the present state of knowledge - meet the usual standard of safety and pharmacovigilance.

Within the scope of a more fundamental research on orphan drugs, there is also a Community interest in **Research Programmes** partially subsidised. In this way the recent programme Biomedicine and Health, in its chapter 4 : "socio-economic impact", mentions by name in point 4.6: rare diseases, and in the pharmaceutical research concerning clinical experimentation it mentions : "including an inventory of rare diseases, and a register of so-called "rare" drugs.

The Biotechnological programme can also have an influence on the matter.

On the other hand, a Workshop on "European Clinical Trial Network", organised by the Commission in November 1992 took note of the difficulties, (among others, recruitment of patients), of a valid clinical study for such products and identified the absence of financing as one of the main barriers.

Finally, the "Groupe de Conseillers pour l'Ethique de la Biotechnologie" mentions in 1994 : "According to this equal access principle, a special status could be attributed at European Level to orphan drugs and diseases (as already done within the Biomedical and Health Research Programme of the European Commission)".

g. Patient Associations.

Patients and parents of victims, faced as they are with the difficulties and hesitations of industry, beneficiaries etc, have created or participated in, patient associations, foundations and charitable organisations in order to take advantage of appropriate treatments for their disease. At the same time as requesting better attention to the needs and rights of patients, affected by rare and severe pathologies, by way of adequate support measures from political authorities, they try to give active collaboration to the improvement of treatment and care.

To this effect, they make the most of existing products by intervening, if possible, in facilitating their availability and use. They also seek the development of excellence centres and infirmation centres. In the United States, NORD (National Organisation for Rare Disorders) collaborates closely with the Office of Orphan Products Development, and has an important data base available.

In Europe, very many national associations exist, directed towards one or several particular pathologies. But a grouping at European level, or at the level of specificity, does not yet exist, although some moves to collaboration between them are appearing (example: European Alliance of Genetic Support Groups in the Netherlands).

This does not prevent some of them being very active and willing to collaborate. The importance of the privileged contact they enjoy with patients and their families, must not be underestimated.

During a conference in 1991, organised by RTMDC (Research Trust for Metabolic Disorders in Children), problems encountered in the usage of non commercialised drugs were clearly identified, namely: source of supplies, purity, pharmaceutical formulation, toxicity testing, monitoring and legal issues amongst others.

As a consequence, one of the speakers at this conference suggested that, an "Administration" of orphan drugs was something to be envisaged.

## F. Vaccines

As stated above, the interest of vaccines in many tropical diseases considered as orphan has not escaped the attention of the WHO. It is in the framework of the Children Vaccine Initiative Task Force "Relations with Development Collaborators" which included industrialists, that a categorisation of vaccines has been proposed. It says : "New vaccines, whose use is likely to be restricted to developing countries what might have termed "*Orphan Vaccines*". Such vaccines, if adopted as CVI targets are likely to require heavy donor support". In the United States, still within the scope of the CVI: "Achieving the vision" 1993, the committee recommends that an entity, tentatively called "National Vaccine Authority" (NVA) be organised to advance the development, production and procurement of limited commercial potential but of important Public Healthneed.

A reminder here of firstly :

the importance of the European Industry in the vaccine industry and its dominant involvement in the supply to developing countries;

and secondly :

that this industry has, on several occasions, fulfilled its mission of preventive protection in Public Health by supplying vaccines or serums against infectious rare and severe diseases, with no hope of financial return on investment (examples are : vaccine against brucellosis of mediterranean shepherds, vaccine against leptospirosis of sewage workers... to name only two).

## IV CONCLUSIONS

If the economic impact on Society of rare diseases as a whole deserves a serious analysis and probably justifies the investment of public funds to get to better know and treat them, the moral obligation to seek appropriate treatments and means of prevention is unanimously recognised as well as the absolute necessity to lead Industry in this direction.

It is thus only the means that need to be investigated.

But the magnitude of difficulties encountered - scientific, experimental, financial, ethical - linked most of the time as well to the lack of knowledge as to the rarity of the disease and to the risk inherent to any new medication, does not allow to be satisfied with timid measures. The research effort is enormous and particularly delicate, because it would not be tolerable that these rare patients be treated, without the quality of the drug and its harmlessness having been reasonably appraised. In addition there is the risk of failure that must be kept in mind and which, already determining the orientation of research in view of drugs potentially interesting economically, which has here a new dimension in the absence of any hope of profitability.

On the other hand, present technological developments open opportunities never equalled before. Admitting that some 4/5th of rare diseases have a genetic origin, biotechnology and analysis of the human genom, to give but one example, will revolutionise the perspectives and offer major assets.

But the interweaving of humanitarian, social, economic, industrial and scientific objectives demands the interpretation of the usual notions of risks (sanitary and financial), cost (global on healthcare), profitability (recovery of the investment whether successful or not, and legitimate profitability) and of responsibility (of the authorities, the investigator and the industrialist).

In other words, the thing to do is to *consider a health policy completely specific and sustainable for the different actors.*

The success of measures taken in the United States allows to consider that they have enabled a true social advance.

The exacerbated fear of some of too great a "generosity" towards the Industry should not lead to the amputation of their beneficial effects while trying to avoid perverse effects (real or estimated).

Japan, through the application of a somewhat different philosophy, is in turn trying to reinforce the tendency by somewhat easing the load on the Industry of part of the financial investment which is absolutely too heavy and too long.

Alone among the regions most advanced in pharmaceutical R & D, Europe has to date remained silent. The importance and the quality of its Pharmaceutical Industry would make inexcusable the maintenance of a passive attitude. It is now responsible, in the field of Public Health, for a population of more than 370 million inhabitants, which is markedly more than the United States and Japan. That this responsibility be shared with the Member States should no longer be a constraint, at least on regulatory level, when concertation and collaboration mechanisms are implemented, that financial assistance could be envisaged at community level and that socio-economic aspects deserve priority attention.

It has also to be underlined that the European countries with low populations would be hard pushed to find a national solution, but that from now on they are - with their counterparts of the other Member States - actors in this search for a solution.

Europe cannot be satisfied with waiting for positive fallouts from incentives to R & D set up in other continents, especially as the distribution of rare diseases can be quite variable and priorities different in every region. The specificity of Industries also deserve consideration and it is one of the aspects exploited by the WHO.

Spontaneous industrial initiatives, either by isolated firms acting alone or in collaboration with the WHO or other Authorities and Research Centres, or by groups of firms trying to overcome difficulties and uniting their efforts, are the obvious sign of their interest and their desire to succeed. They are the indicators of a positive reaction to well conceived and sufficiently incentive regulatory measures.

What are the measures to be discussed ?

First, four "levels" will have to be considered :

* the Union (the Member States) and its obligation to protect Public Health;

* the patients, their needs and their rights;

* the Industry (and other research centres), its possibilities and its rights;

* the social institutions (state and private insurance), their obligations and/or financing means when the product is available.

Next, consideration will have to be given to :

* the fundamental research (on the diseases) and the disclosure of knowledge;

* research and development of new products;

* the development of indications of known products;

* the marketing of existing or abandoned products.

The inventory of measures taken, or envisaged elsewhere, is already enlightening, even if adaptations at European level of additional initiatives or imaginative solutions could be beneficial. As a reminder, it has to be mentioned:

<u>In Pre-Normative</u> :

- Listing (descriptive ?) of rare diseases and an Information Centre on the state of research and the location of sick people (possibly with the help of patients associations or of a European organisation of the same type as NORD in the United States (National Organization for Rare Disorders) which has an impressive data base available.

- Epidemiological data base and determination of the frequency.

- List of drugs recognised as orphan, currently in use or being developed, or even presently used in other indications or of which the development has been interrupted.

- Complementary studies requested to IPTS (Institute for Prospective and Technological Studies)

- Determination of the criteria for admission to the status of orphan drug :

  character of novelty :

*new drugs* (on the basis only of the chemical structure, or taking into account the impact of minor molecular modifications ?)

*new indications*

*new way of administration of known drugs*

*particular indications* of a new product under development for other indications

character of non-profitability :

Presumption of insufficient ROI (Return on Investment) taking into account the investment in R & D that has not succeeded as well as the one which had a happy ending

frequency (prevalence) of cases :

in absolute numbers or in percentage of the population (e.g. < 0,1% on the territory of the Union which would be a less arbitrary fact the more so taking into account the widening of the European Union

criteria of revocation/preservation of the status :

if increase in frequency

if a new "clinically superior" therapy is detected, with - lacking a definition - interpretation given to those terms

if the drug becomes commercially viable

<u>In procedural and regulatory</u> :

- Dialogue with Industry (upon presumption of clinical activity)
- Support (help) in the development and the follow-up of experimental protocols
- Determination of the minimum content of the MA application dossier :

Possible exemptions in chemical/pharmaceutical
toxico/pharmacological
clinical
environment

- Possibility (obligation) of

  introducing, after marketing, a periodical profit/risk report

  defining the rules of pharmacovigilance applicable to these products

- Acceleration of the procedure (in the interest of the patient)

- Initial and periodical fees exemption

<u>In intellectual property</u>

- Patent and Supplementary Protection Certificate to be adapted if necessary

- Sufficient exclusivity period after marketing authorisation (very strict conditions to authorise the suppression of this exclusivity)

- Confidentiality of new data added to the dossier

<u>In financial, fiscal and economic matter</u> :

- R & D public subsidy through subsidised research programmes,

  through pooling national subsidy with community administration

  through a call to the European Development Bank

  through obtaining a budget line granted by the European Parliament

  through aids collected by patient associations

  through information campaigns to the public with fund collection...

- Encouragement of research and technical development efforts and support of policy towards cooperation agreements between firms, joint-venture, merging of research departments, etc.. (Art 130 F of the Treaty).

- Reduction of the firm's taxation rate

- Immediate deductibility of investment in R & D (on orphan drugs)

- Tax rebate on R & D spending

  these last three proposals to be envisaged in common with all the Member States

- Levy of any tax or occasional or annual fee on the product

- Prices negotiated on previously defined basis and which take into account particular specificities of this type of drug.

  Particular attention will have to be given in these matters in order to avoid the appearance of discrimination, protectionism, as well as the de facto invalidation of economic incentives granted to Industry by subsequent, misplaced restrictions of price or reimbursement in order to maintain the incentives to commercial success.

In "administrative" matter

The total or partial realisation of such initiatives will inevitably require the creation of consultation bodies, expert committees (decision-making or not in highly technical matters), of administration bodies, even surveillance committees, not counting liaison committees.

Much caution and precision will have to be given to the allocation of the tasks to avoid administrative heaviness, loss of time, unnecessary costs and waste of work and repetitive talk.

This is of course about the setup of a complex *specific health policy for **orphan diseases***, compatible with an industrial policy for the sector and a policy of stimulation of competition and support to the development of biotechnology.

On the legal level, a "basic" text (Regulation ?) defining clearly the objective of promoting the R & D in orphan diseases and their treatment, followed by execution directives or guidelines, more adaptable to the needs and experience would be a wise proposition. In this way the financial or technical aids (assistance protocols) could only be obtained after satisfying a series of requirements codified by those guidelines. Inversely, once obtained, they could not be questioned again or annihilated by subsequent requirements, the objective being to allow the sponsor to better outweigh the risk he will have to take and to guarantee him a minimum of security and continuity of the conditions in which he is operating.

With the objective of obtaining a marketing authorisation, the Committee of Proprietary Medicinal Products could create a "godfather" group, capable and keen to cooperate with Industry, from the time of "presumption" of an interesting activity up to the final phase of marketing authorisation. Moreover it could propose specific requirements and procedures for the orphan drugs by deviating, if useful, from measures applied to other drugs.

The difficulty is to find, besides the necessary funds, a right balance in the attribution of costs between beneficiaries (State, Society, Patients, Industry) while keeping incentives sufficient for the effort.

Another important problem is that incentives in the final phase (for instance marketing) such as the price, remain national prerogatives while subsidies and simplification of procedures which could be dealt with at community level, can be insufficient if the acceptance of the principle of entitlement to a reasonable profit in case of success is not recognised. In any case, the hope for a profit remains the best stimulation to research and competition, itself able and necessary to control prices.

On the other hand, to give priority to the development of already existing products which are not exploited or only exploited for other indications, could not be favourable to obtaining rapid results.

Europe should be sure to avoid the pitfall of a too rigid interpretative application of some legal texts.

In the field of orphan drugs, one must analyse, beyond promotion and support to R & D and MA, what happens or could happen at either end. At one end, the suspicion of a particularly interesting indication of a known product is not the sole result of knowledge developed in the laboratory or during clinical experimentation, but also of the information issued from the utilisation of the drug by the health professional. To erect barriers to the therapeutic freedom of the well informed physician, by administrative or other constraints on the use of drugs, can prevent the "revelation" of the orphan indication.

At the other end, the rarity of cases and often the precarious conditions of the patients, make the analysis of information obtained through the pharmacovigilance very uncertain and the benefit/risk ratio will be set in a very finely shaded context.

With this in mind, it seems essential to plan a narrow collaboration with patients associations when they exist, even encourage them. With them and through them attempts should be made to establish a much closer communication between patients and researcher. The experimenter must be able to identify patients likely to participate in clinical research. The patients as far as they are concerned will have to have a guarantee of confidentiality and be as well informed as possible. The drug under investigation can be their only chance, their only hope. On the other hand, the uncertainties about its security, its efficacy, secondary effects that it can generate must be explained to them. The very likely geographical dispersion of the patients implied in a clinical experimentation on an orphan drug, might justify to standardise the structure of the document by which they give their consent.

However, this analysis allows the affirmation that measures in this matter are indispensable, and that the duty of Public Health Protection require them. Expected for a long time, they now have a character of urgency if the Union does not want to be accused of accepting dependence from abroad.

Moreover, these measures should not be too feeble, by fear of ending in a failure as well at human level as on economic level. Patients cannot be nurtured with deceptive hopes. Their confidence (and their possible participation in experimentation) cannot be deceived. And, economically, subsidies, investments or other insufficient measures which do not allow the risk to be taken, nor the intensity or duration of the research effort, would be a waste.

It is, as often the case, in the accumulation of a series of incentives and in the balance achieved between the different needs, interests or obligations (the interest of the patient remaining a priority) of the various partners that lies the key to the success of a project of such magnitude.

In any case it would be regrettable for the European Union, for its credibility and for the prestige of its research industry, not to develop a series of first class measures and that, in a few years, the result of some 500 orphan products presently being developed, would be scientifically and financially, the prerogative only of the United States and Japan.

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