Belgian Advisory Committee on Bioethics

Opinion no. 47 of 9 March 2009 on ethical implications of the legislation concerning compassionate use and medical need programmes

Request for an opinion of 27 June 2007,
from Mr Marc Bogaert, Chairman of the Medical Ethics Committee of the AZ Sint-Lucas in Ghent.

CONTENT OF THE OPINION

The q**uestion put to committee**

In a letter dated 27 June 2007, the chairman of a medical ethics committee questioned the implementation of the recent legal provisions concerning the conditions under which medicinal products that have not obtained the marketing authorisation can be made available.

(Translation of an extract of the letter drafted in Dutch)

> "*This concerns*:
> - *compassionate use: authorisation to administer to a patient a medicinal product not licensed in Belgium;*
> - *medical need: use of a medicinal product which has been licensed in Belgium, but not for the indication concerned.*
>
> *In both these situations, the company responsible for the medicinal product submits a programme to the authorities. These programmes may only be authorised if the company plans to request eventually the licensing of the medicinal product (compassionate use) or the licensing of the pertinent indication (medical need).*
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> *As Chairman of a local ethics committee, I am faced with the fact that physicians quite frequently wish (particularly in a field such as oncology) to use - e.g. in a patient for whom all possibilities have been exhausted - a medicinal product for which there are relevant data in literature but which has not been licensed or, at least, not for this specific indication. If the company involved does not intend to request the licensing of the medicinal product, this poses a problem in the sense that the legal provisions do not authorise this product being made available through a "compassionate use" or "medical need" programme. The companies are aware of this and are faced with a dilemma: infringing the legal provisions or refusing potential help to the patient.*
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> *I would hence like to ask the Advisory Committee to examine this problem which has major ethical implications".*

1. The legal and statutory provisions

Industrialised countries have put in place procedures for evaluating the effectiveness and safety of medicinal products, prior to their marketing . This, e.g. concerns the procedures of the FDA (Food and Drug Administration) in the USA and of the EMEA (European Medicines Agency) in the European Union.
Without going into detail, we want to stress that the marketing authorisation is only issued after an in-depth examination of all the clinical, toxicological and pharmacological trials. This approach is formalised in the European Directives 2001/82/EC and 2001/83/EC.
This last Directive states in its article 6, paragraph 1:

> *"No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued [...]. ".*

The same obligation is found in Belgian legislation, in article 6.1 of the Law on medicinal products of March 25, 1964.

In 2004, a European Regulation no. 726/2004 was introduced which allows, in certain circumstances, exceptions to this general rule. Article 83.2 of this Regulation defines under what conditions access is made possible to medicinal products that do not have a marketing authorisation[1].

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

While transposing the European Regulation, the Belgian legislator provided for, in addition to compassionate use, the use of medicinal products in an indication other than that for which they received the marketing authorisation, under the name "medical need programme". It is important to note that these provisions enabling early access to medicinal products that do not yet have a marketing authorisation, are distinct from the rules which concern the medicinal products which are the subject of clinical trials such as defined by the Belgian Law of 7 May 2004 on experiments in humans.

The legal provisions such as summarised above do not concern compound preparations..

1.1. Compassionate use (CU)

Although, unlike a Directive, a European Regulation is mandatory in all its elements and is applicable in all Member States as of its publication in the Official Journal of the European Communities, the Belgian authorities have, however, transposed this Regulation into Belgian legislation by Article 6 *quater* of the Law of 25 March 1964 on medicinal products such as amended by the Law of 1 May 2006[2], which states in Article 1(2):

> *"2) The King may lay down the rules in order to make medicinal products available for human use in view of compassionate use within the meaning of Article 83 of the aforementioned European Regulation (EC) no. 726/2004. ".*

The application terms are detailed in Article 106 of the Royal Decree of 14 December 2006[3]:

> "*1. An application for carrying out a programme relating to making medicinal products available for compassionate use [...] shall be sent to the Minister or to his or her representative* (in practice, the AFMPS, the Belgian Medicines Agency), *and accompanied by the opinion of an ethics committee […] in which it emerges that the medicinal product fulfils the criteria in order to be able to be used in view of compassionate use. […]*

[1] It should be noted that medicinal products with an authorisation (or marketed) outside the European Union are assimilated with medicinal products with no European marketing authorisation and therefore fall under the provisions provided for compassionate use.

[2] Law of 1 May 2006 revising the pharmaceutical legislation, published in the Belgian Official Gazette on 16 May 2006, whose Art. 11 amends Art. *quater*, 1, 2 and 3 of the Law on medicinal products of 25 March 1964.

[3] The Royal Decree of 14 December 2006 concerning medicinal products for human and veterinary use, published in the Belgian Official Gazette of 22 December 2006.

[…]

The application for carrying out the programme describes, inter alia, the criteria according to which the patient(s) can be included in the programme, the indication for which the medicinal product shall be made available, the period during which the programme shall take place, the breakdown of the transport and administration costs, as well as how the unused medicinal products shall be dealt with. The applicant also draws up a standard informed consent document which shall be submitted by the physician to the patients entering the programme.[…]

[…]

3.[…]
The medicinal product which is the subject of such a programme may not be sold to the patients included in this programme [...]. ".

Article 107 of the same Royal Decree of 14 December 2006 defines the procedure to be followed to include a patient in such a compassionate use (CU) programme.

"2. The physician sends a written request per patient to the programme coordinator (in practice, the pharmaceutical company).

In this request he or she declares:

- *that he or she is aware of being personally responsible for the use of a (yet) unauthorised medicinal product;*
- *that the disease for which the medicinal product shall be used is either a chronic disease, or a seriously debilitating disease, or a life-threatening disease, and that the disease cannot be treated satisfactorily using a medicinal product marketed in Belgium and which is authorised for treating this disease; the physician gives a description of the disease;*
- *that he or she shall clearly and fully inform the patient concerned or his or her representative, pursuant to the Law of 22 August 2002 on patients' rights, of all the terms and conditions of the programme;*
- *that he or she shall ask as soon as possible, and at the latest before the start of the treatment using the medicinal product concerned [...], for the written consent of the patient or of his or her representative [...], to participate in this programme [...].*

3. The programme coordinator shall check the conformity of each individual request [...], with the programme [...], He informs the physician of his decision as soon as possible [...]. In case of refusal, the reasons are explained.

It keeps [...] a copy of the documents [...] for 10 years [...]. ".

Whereas the legislator requires the opinion of a medical ethics committee with "full approval"[4] prior to the submission of a request to carry out a programme, the intervention of an ethics committee when a patient is included in the said programme, is not required.

[4] The notion "medical ethics committee" coincides with the definition of "ethics committee" given in Art. 2.4 of the Belgian Law of 7 May 2004 on human experiments. Only the medical ethics committees which have "full recognition " are authorised to issue the single opinion on an experiment protocol (for the period from 1 April 2009 until 31 March 2012, there are 38 ethics committees). If Article 106 of the Royal Decree of 14 December 2006

1.2. Medical need programmes (MNP)

In addition to the rules established in order to make medicinal products for human use available in view of compassionate use, such as provided for at European level, the Belgian law of 1 May 2006 also provides for "Medical Need Programmes" allowing the use of a medicinal product already licensed but used in an indication other than those indicated in the marketing authorisation: this provision, which is not included in the European Regulation, extends the access possibilities.

> *Article 6 quater, 1, 3, second paragraph:*
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> *In "Medical need programmes" a medicinal product for human use can be made available in order to meet the medical needs of patients suffering from a chronic disease, from a seriously debilitating disease or a life-threatening disease, and who cannot be treated satisfactorily using a medicinal product which is on the market and which is authorised for the treatment of this disease. The medicinal product for human use concerned must have been the subject of a marketing authorisation, but the indication for the treatment of this disease is however not authorised or the medicinal product for human use is not yet on the market with this authorised indication. ".*

The Bill of 23 December 2005 submitted for the opinion of the Council of State[5] included four situations where it was possible to authorise a medical need programme "*for the medicinal product for human use concerning the treatment of the disease in question […]*

- *if an application for a marketing authorisation is being examined for this medicinal product, or*
- *if the marketing authorisation for this indication is granted, but that the medicinal product for human use has not yet been put on the market with this indication, or*
- *if the related clinical trials are in progress, or*
- *if there are, in the literature, physiopathological or relevant data available concerning the use of this medicinal product for human use for the treatment of the disease in question. ".*

The last eventuality, which made reference only to data in literature, has been deleted from the final version of the law further to the opinion of the Council of State. This situation was deemed too wide and difficult to define.[6]

The Committee notes the analogy between these medical need programmes and the widespread use of licensed drugs in indications or in populations of patients other than those indicated in the marketing authorisation (off label use), or even of the use of unlicensed medicinal substances or galenic forms.

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provides that a request for carrying out a programme for making available medicinal products for compassionate use must be accompanied by the opinion of an ethics committee, this ethics committee must be understood as one having "full recognition ". Neither the compassionate use programmes nor the medical need programmes fall within the remit of the law on human experiments of 7 May 2004.

[5] *Parl.* doc., House of Representatives, 2005-2006, 51-2189/001, p. 74.

[6] Idem, p. 107, 23.3. See also Gobert M., "Usage compassionnel et programmes médicaux d'urgence: le cadre légal créé par la nouvelle loi du 1er mai 2006 portant révision de la législation pharmaceutique et par son arrêté royal d'exécution du 14 décembre 2006 ", *Revue de droit de la santé,* 2007-2008, p.7.

2. The "off label" use outside recognised indications

The prescription of a medicinal product with a marketing authorisation and available on the market, in other indicators or in populations of patients not indicated in this MA, is effectively a widespread practice. Admittedly, the medical need programme is intended more specifically for chronic diseases and the practice of "off label use" more usually, but not exclusively, for everyday diseases. In the USA, 21% of all prescriptions are not for the indications recognised by the FDA and for 73% of them there is little if any scientific grounds for this. This proportion is particularly high for some pharmaceutical categories: 74% for anti-epileptic drugs, 60% for anti-psychotic drugs and 41% for antibiotics (Stafford 2008[7]).

The use of a medicinal product which has a marketing authorisation in an unrecognised indication, relies most often on an expected pharmacological effect. Sometimes it is justified by an analysis of the physiopathological mechanisms, for example, the extension to patients suffering from chronic obstructive pulmonary disease of treatments whose effectiveness has been proven in asthmatic patients.
This practice certainly has advantages. It authorises the practitioner to make use of his or her right to therapeutic freedom. It enables innovation in clinical practice, specifically when recognised treatments have failed. It sometimes enables the cost of the treatment to be reduced. The use of antibodies against VEGF (Vascular Endothelial Growth Factor) in the treatment of macular degeneration in the USA is an example of this. The treatment using Ranibizumab, a product recognised in this indication, costs €1,435 per intra-ocular injection. Bevacizumab, another antibody used against VGEF licensed only in the intravenous treatment of some cancers (for example metastatic colorectal cancer),[8] is sometimes used in the treatment of macular degeneration using intra-ocular injections because it is up to 50 times cheaper. However, no randomised study has proved its effectiveness in this indication[9].

Off-label use concerns not only the use in other disease states but also the administration of other doses and/of different methods of administration (such as in the example of Bevacizumab mentioned above), to other samples of the population and in never evaluated associations.
Off label use is frequent in certain populations, particularly in children, pregnant women and the elderly. Few medicinal products have been studied in detail in baby's and very often appropriate dosage presentations are not available. A recent study carried out in a paediatrics university department in Belgium, noted that 50% of all medicinal product prescriptions were done outside the conditions stipulated in the marketing authorisation and that 17% of the products prescribed were not licensed in Belgium, at least in the galenic form used. Of the patients studied, 74 received at least one medicinal product outside the marketing authorisation conditions during their stay in hospital. The highest rate was observed in the neonatal and paediatric intensive care units.[10] Given the small number of patients, split into different age groups (premature babies, newborn babies, children, adolescents), the pharmaceutical industry shows little interest for the evaluation of medicinal products in the paediatric populations and the marketing of adapted presentations, and fears the major costs of this. This is particularly the case given that, up until now, the absence of recognised paediatric indications does not seem to limit the use in this specific population of medicinal products evaluated only on adults. This

[7] Stafford R.S. "Regulating Off Label Drug use. Rethinking the Role of the FDA", *N. Engl. J. Med.*, (2008)358; pp.1427-1429.
[8] Colorectal cancer = cancer of the colon and of the rectum.
[9] *Folia Pharmotherapeutica*, 2007, 34(12), pp. 106-107.
[10] Annicq A., Robeyst A., Segers N. *et al.*, "Unlicensed en off-label gebruik van medicatie bij kinderen", *Tijdschrift voor Geneeskunde,* 2008, 64, pp. 677-682.

situation has led the European Union to take measures aiming to encourage the pharmaceutical industry to carry out drug studies on children in certain conditions.
If the prescribers should have to wait for the official recognition of indications in these different situations, numerous studies would be necessary and the new treatments, sometimes vital, would only be available to specific populations after long periods of time. Still today , many children do not have access to essential treatments due to a lack of medicinal products that are dosed or formulated for paediatric use.
The disadvantages of off label use of medicinal products with a marketing authorisation are mainly that proof of their effectiveness is not established for this use and, on the other hand, that the side effects for some population categories are, to a large extent, unknown. This is particularly the case in young children and the very elderly whose metabolic systems are different , or even in pregnant women in regard to the specific risks for the foetus.
This practice also involves financial aspects : some of these medicinal products are very expensive and their reimbursement is only granted in certain situations and depends on the prior agreement of the medical advisor of the patient's sickness fund , or of the Belgian Special Solidarity Fund.
Another disadvantage lies in the fact that the widespread practice of this "off label" use could dissuade the pharmaceutical industry from undertaking the appropriate studies to validate the use of these medicinal products in new indications, other doses, or even in specific populations. In this respect, the current interest for studies carried out in paediatrics represents progress..

3. Ethical discussion

3.1. Introduction

The procedures for evaluating the effectiveness and the side effects of medicinal products prior to their marketing present undeniable advantages. They provide guarantees as to the efficacy and safety of the molecules studied. However, absolute safety does not exist as the clinical trials are generally carried out on a small number of patients fulfilling specific criteria in terms of age and absence of associated disease states . Some exceptional side effects, but which may put the life of patients in danger, are only detected by spontaneous notifications made by physicians or pharmacists or even by studies carried out on a large number of unselected patients, representative of the population for which the molecule is designed. However, such studies are most often carried out after marketing of the drugs.The evaluation procedures also have disadvantages. They are expensive and require a lot of time: several years pass between the start of the procedure and the marketing authorisation. The delay in availability of innovative molecules for the treatment of diseases for which the available treatment means are insufficient is questioned. The associations of patients suffering from cancer or HIV (human immunodeficiency virus) infection have stressed on several occasions the importance of this problem, emphasising that patients likely to benefit from the medicinal product are likely to die before it is made available.
The described procedures - i.e. the compassionate use (CU) programme and the medical need programme (MNP) - endeavour to provide a response to this situation and allow the use of medicinal products which have not yet obtained the marketing authorisation (CU), or which do not have the authorisation or are not yet on the market for the indication in question (MNP). Their application does however raise a certain number of ethical questions which concern the patients, the prescribing doctor, the pharmaceutical industry, but also the ethics committees. These questions are similar for the compassionate use programmes and for the medical need programmes. In the following text, these will only be treated separately when necessary.

3.2. The patient

The members of the Committee can understand the impatience of the patient suffering from a chronic disease, who has exhausted all available options and who is desperately seeking access to something, to anything, which is likely to slow down the development of the disease, or even simply to give him or her a bit of hope: "They have not tried everything".
It is the doctor's responsibility to inform the patient about the inevitable tension between speed and knowledge of safety/effectiveness. Confirming the effectiveness and the safety of a medicinal product takes time. Now time is what the patient no longer has in a situation where his or her life is in danger.[11]

In the Royal Decrees, the definition of diseases which justify the use of compassionate use programmes and medical need programmes is not explicit. These diseases must be life-threatening, seriously debilitating and cannot be treated satisfactorily using a medicinal product available on the market. Medicinal products which potentially provide significant advantages over existing treatments, either in terms of effectiveness or in terms of tolerance enter within this framework. This notion of innovative medicinal product may be difficult to establish since the CU programme caters for medicinal products being developed, and for which the experience gained is limited.
At this stage in the development of a medicinal product, the risk-benefit ratio is difficult to evaluate. The patient must be clearly informed of this situation. He or she must therefore know the elements which justify the use of a molecule not yet available on the market (CU), or of a medicinal product that has obtained the marketing authorisation but not in the indication in question (MNP). Once again, it should be recalled that many molecules that are developed will never be introduced into clinical practice, either due to lack of effectiveness or due to the major side effects detected during the development. Now, the Royal Decree of 14 December 2006 provides for extended availability. If the decision not to market the drug is taken by the company, the programme will probably be stopped. What will happen in this case to the patients still treated - and perhaps successfully so - by the medicinal product in question? One may regret that the comments in the media on the results of preliminary studies is not always sufficiently qualified and gives patients unjustified hope. The researchers bear some of the responsibility in this situation. Their reports in the media sometimes suggest treatment solutions which are only still hypothetical .

The initial stages of evaluating a molecule are carried out on healthy volunteers (phase I) or on patients selected for age and state of health criteria (phases II and III). It is e.g. usual to exclude from these protocols patients presenting an alteration of hepatic or renal functions. In the studies concerning patients suffering from cancer, it is usual to recruit only subjects who are still capable of a certain autonomy and with a life expectancy of at least six months. On the basis of these studies, one cannot predict the response in terms of effectiveness or side effects in a patient suffering from advanced cancer who has exhausted all treatment possibilities and whose life expectancy is limited if no new treatment becomes available. What is true for a molecule being developed is also true, albeit to a lesser extent, for a medicinal product that has obtained the marketing authorisation but not in the indication concerned or the population envisaged.
The physicians involved in the treatment of patients suffering from cancer, HIV, or degenerative neurological diseases, say that sometimes they are put under totally unjustified pressure from individual patients or patient associations informed by the media or by the

[11] Mayer M., "Listen to *all* the voices : an advocate's perspective on early access to investigational therapies", *Clinical Trials*, 2006, 3, pp. 149-153.

internet of the possibilities offered by a laboratory observation or by the initial results on a small group of subjects. This pressure has sometimes led the authorities to speed up the marketing authorisation procedure.
The programmes for access to the medicinal products being developed or which have not yet obtained the marketing authorisation cater above all for groups of patients characterised by a specific disease. It is rare that they provide a response to the situation of an individual patient faced with a critical situation in an often complex situation and who hopes for a solution in the use of a new medicinal product which is not yet on the market. Before the European and Belgian legal provisions concerning such programmes, the company concerned usually accepted supplying the medicinal drug for compassionate use for a specific patient, who does not always respond to the criteria defined in these early access programmes. The duty to respect the legal provisions and to submit a programme has made such specific interventions difficult or even impossible. A positive response to individual requests is however particularly useful in order to enable early access with good safety conditions to sometimes very expensive medicinal products.

It will be the responsibility of the informed patient or his or her representative to sign a consent form. It seems useful to ask also for the agreement to transmit after anonymisation the data which will be collected and which concern the tolerance of the molecule used within the framework of such a programme: one may thus enhance knowledge on the medicinal product in question, as is the case with the data collected in clinical trials.

3.3. The physician

The responsibility of the prescription of a medicinal product is incumbent always on the physician , but even more so when the product prescribed has not obtained the marketing authorisation or is not used for a recognised indication. If in these situations, an undesirable effect should occur, difficulties could arise at the medico-legal level.[12]

Where the physician has an ethical duty to keep up to date with the progress of knowledge in order to assure his or her patient is given the best treatment, he or she must also demonstrate a critical mind and the duty to select, from the discoveries presented as innovative and promising, the one which will be useful for his or her patient. Inappropriate treatment would not be acceptable ethically and would be an act of therapeutic persistence . The duty to help the patient as much as possible does not justify doing just anything.
The doctor subjected to unjustified demands must inform the patient in detail of the reasons which justify his or her attitude.

The evaluation of the interest of the molecule and of its disadvantages is sometimes difficult at this stage. The information available is generally limited. Admittedly, given the severity of the diseases concerned, these patients are most often treated by specifically qualified physicians who are up to date with the latest scientific developments in their domain.

It is the physician who asks the company concerned to include the patient in the programme. It is the physician who makes the request, who details the patient's characteristics, who obtains

[12] On this point, see Delforge C., "La responsabilité civile du médecin au regard de la prescription de médicaments", *R.G.D.C.*, 2003, pp. 369-383, *adde* Gobert M., "Publicité et information relatives aux médicaments: les limites de ces deux notions au travers de la pratique dans tous ses aspects", *Revue de droit de la santé*, 2008-2009, pp. 187-203.

his or her consent and who finally prescribes the medicinal product and monitors its administration.
In such a context, the doctor must check that his or her liability insurance policy or the hospital's insurance policy covers the risk related to the use of a medicinal product which has not yet obtained a marketing authorisation.

3.4. The pharmaceutical industry

It is the company which has developed the medicinal product which submits the application to the competent authority to start the programme.. The company must, however, favour the participation in controlled studies and therefore restrict access to the programmes for patients who do not fulfil the criteria for being included in these studies.
The law does not oblige the company to respond favourably to a request for a programme or to a request to have a patient included in an authorised programme. The company's refusal may be motivated by different reasons. Either the underlying arguments of the request are insufficient to justify the setting up of the programme, or the commercial future of the molecule remains uncertain and the company does not wish to bear the expenses related to these programmes, particularly the free distribution of the medicinal products concerned. The law in fact provides that these medicinal products cannot be sold.

Basing the use of an innovative treatment only on data from the literature can pose major ethical problems if, and this will frequently be the case, the product is never authorised in the targeted therapeutic indication. It is however to this specific aspect that the question which is the basis of this opinion refers . We can understand the distress of a patient faced with an irreversible situation who has exhausted all available treatment possibilities, and the doctor's wish to offer this patient all the treatment possibilities, even the slightest ones. It is probably this search for a last hope which explains why certain patients use alternatives without the slightest scientific grounds, such as for example, the magnetic bracelets offered for treating leukaemia in children.

To initiate a compassionate use programme or a medical need programme, the company, potentially in collaboration with the expert physician behind the request, has to collect the necessary information to enable a medical ethics committee with full approval such as defined in the Belgian Law of 7 May 2004 to hand down an opinion on the interest and the justifications of the request.

As regards the introduction of patients into an existing programme, the company can refuse the benefit of access to the medicinal product to some patients if they do not meet the defined criteria but also for other reasons, e.g. when not enough product is available . In the initial phases of the clinical trials only a limited amount of the product is available. For some medicinal products based on molecular biology techniques, the production at this stage may not have reached an industrial scale due to the major investment necessary, which the company may hesitate in investing before knowing the future of the molecule. The literature cites the recent example of cetuximab, a monoclonal antibody used against the epidermal growth factor receptor (EGFR). After the publication of the initial results proving its effectiveness in some patients suffering from colon cancer with metastases or skin cancer of the head or the neck, the manufacturing company ImClone received some 8,500 requests for providing the medicinal product for compassionate use. Initially, it tried to cope with the situation by applying the "first come, first served" rule. It was quickly forced to stop the compassionate use programme which risked compromising the commercial development of the product. The company then put pressure on the FDA to speed up the marketing procedure and it simultaneously increased its

production capacity so as to respond to the numerous requests, including for compassionate programmes for the use of cetuximab in other indications.

The refusal to initiate a programme or to accept certain patients in it may also point to the fear that the use of a new molecule in patients suffering from advanced diseases, could lead to an excess of side effects or to treatment failures, and sogive the medicinal product or the company a negative image. Such an initial impression may be difficult to correct and may have major consequences when introducing the product on the market.

The physicians faced with such situations which make use of CU and MNP programmes impossible, encounter an ethical conflict. How to obtain these medicinal products in favour of patients suffering from chronic diseases whose have exhausted all available treatment possibilities, or are even unable to afford the cost of it on the one hand, and not to infringe the legal provisions on the other? Obtaining the medicinal product through indirect routes, for example via the internet, carries the risk of obtaining products whose quality may not be guaranteed. Begging the manufacturing company for samples, which are always limited, carries the risk of acting illegally and also making the company illegal, but also of not being able to continue the treatment in patients who would have benefited from being introduced into the programme.

In order to guarantee that these problems have maximum effectiveness in the interest of the patients who can benefit from them, it would be useful for the compassionate use and medical need programmes approved by the AFMPS (Belgian Medicines Agency) to be listed in a database that is accessible to prescribers . It is however not desirable that the existence of such a reference list should constitute publicity for the abusive recourse to this unrecognised use or for a new indication.
Likewise, it would be regrettable that experience gained from using the medicinal products within the framework of these programmes is not collected. The legal provisions should be adapted and should make it mandatory for an anonymised report, for example on a quarterly basis, of the response of patients to treatment administered in the programme outside the recognised indications. This would imply a procedure which would enable reporting to the AFMPS for what type of problems the medicinal product is administered, whilst respecting the confidentiality of personal data, and enabling the data to be collected concerning their response to the treatment and their tolerance, and also the interest and indeed the risks of the programme initiated to be evaluated.

3.5 The medical ethics committee

The legislator has reserved a major mission for the medical ethics committees in these CU and MNP programmes enabling early access to innovative medicinal products. The evaluation of the programmes is indeed reserved for the medical ethics committees recognised by the Belgian Law of 7 May 2004 to give the sole opinion in terms of clinical trials. Restricting this role to committees with "full recognition " does actually seem justified as the missions devolved upon them within the framework of these programmes requires expertise and easy access to scientific competencies.
Indeed, the ethics committee must first of all check that the medicinal product meets the criteria for the use in compassionate use or in a medical need programme.
The committee must also evaluate the documents designed to inform the patient or his or her representative and obtain his or her consent. Its role on this point is particularly important when the request concerns underage or incompetent patients.

In the opinion of the Advisory Committee, the committee must also evaluate the scientific arguments which have motivated the initiation of a programme. Some members of the Advisory Committee wonder whether an ethics committee has enough diversified expertise to evaluate the merits of the different programmes concerning new and sometimes highly innovative molecules. Others underscore that within the framework of the Belgian Law of 7 May 2004 on human experiments, the evaluation of the merits and the design of the protocol is part of the missions of the ethics committee authorised to give the "single opinion". The evaluation of the interest and the risk-benefit ratio of the new molecules of which the clinical experience remains limited, requires, however, specific competencies enabling *in vitro* and animal studies to be analysed critically. The ethics committee must avoid refusing *a priori* ideas which could seem too original. It should be recalled that numerous treatment innovations rely on their first use in conditions which today seem disputable, such as the first transplantations, or not relying on any physiopathological basis such as the use of betablockers in cardiac failure.

The legal texts do not mention the intervention of an medical ethics committee (with or without "full approval") when an individual patient is to be included into an existing programme. It is the responsibility of the company that has initiated the programme to check, on the basis of the report drafted by the applicant doctor, that the patient meets the criteria defined when the programme was created. Even if this procedure is not stipulated in the Royal Decree, the Advisory Committee recommends that this request is, furthermore, subject to the prior opinion of the ethics committee of the institution where the patient is treated . Indeed this institution, more than the pharmaceutical company, has the competence to judge the merits of the request and, where appropriate, the possibility of hearing the physician and collecting the necessary additional data. It is also its responsibility to ensure that the data transmitted respects the privacy of the patient. Its opinion may also be important with regards the doctor's coverage in terms of his or her liability insurance.
The Advisory Committee is aware of the difficulty of this evaluation and more specifically of that of handing down a negative opinion, with the consequences one might imagine for a patient already informed of the possible treatment. A conflict may actually arise, for example, if a medical ethics committee hands down a favourable opinion concerning the inclusion of a patient in a programme, but that the pharmaceutical company decides not to include the patient, e.g. because the programme has been ended for commercial reasons.

Finally, the Advisory Committee stresses the obligation that the report sent to the company respects the utmost confidentiality of the patient and the data covered by medical privilege.

4. The limitations of the recent legal provisions and the recommendations of the Committee

During the second half of the 20th century, the therapeutic arsenal increased remarkably in the Western world. This development occurred in terms of quantity, effectiveness and also quality. Hence, it was deemed necessary to establish rules concerning the evaluation of the medicinal product before being placed on the market.
Studies take time, and these time frames are sometimes unacceptable, e.g. by physicians who treat chronic diseases such as cancer, HIV infection or degenerative neurological diseases. Some patients who have exhausted the available medicinal product possibilities when they exist, will die before the new treatments are available to them.

The compassionate use programmes and the medical need programmes enable the early provision of a medicinal product designed for treating chronic diseases (mentioned in Article. 3.1 and 3.2 of the European Regulation no. 726/2004), to patients suffering from a debilitating, chronic or serious or even a life-threatening disease as these patients cannot be treated satisfactorily by an authorised medicinal product. These programmes are however limited on the one hand to medicinal products which are the subject of an undergoing application for a marketing authorisation, or undergoing clinical trials, or on the other hand, to medicinal products which have the marketing authorisation for another indication or which are not available on the Belgian market.

The conditions defined for initiating these programmes do, however, seem too restrictive. The use of molecules for which there are, in the literature, physiopathological data or other relevant information, as is considered as a fourth criterion in the initial text of the Bill[13], is often invoked by physicians in favour of patients who have exhausted all treatment possibilities. This seems particularly important for patients suffering from rare diseases. In this case, in fact, clinical studies are particularly long and the industry hesitates marketing a drug for which the market seems restricted. The data obtained during studies on animals or *in vitro* tissues and, furthermore, the data resulting from the first administration in human beings, may be widely covered in the media, and encourage in patients and physicians questions and hopes to which it is difficult, today, to respond. The legislator has, rightly, not felt it appropriate to include the fourth criterion[14]. As has been said above (1.2.) this criterion has been deemed too wide by the Council of State, and likely to create ethical problems such as a premature end to the provision of the medicinal product if the company decides not to market it or if the authority rejects the company's application for a marketing authorisation. This criterion would, however, have authorised possibilities of treating rare diseases or exceptional situations for which the studies are difficult to carry out. **The Advisory Committee thinks** that the possibility of extending the initiative possibilities of the prescriber should be considered, while avoiding arbitrary decisions . Amendments of the legal text should however put down strict criteria , both from the legal and from the ethical point of view , to ensure the safety of the patient and to ensure that a too liberal use of these facilities does not interfere with the initiation of controlled studies and delay the marketing procedures. **The Advisory Committee emphasises** that in this way, the interest of the patient remains the primordial concern. Use of a treatment whose effectiveness has not been proven, or at least is not probable, may entail for the patient more disadvantages than advantages, and may constitute a situation of therapeutic persistence . The ethics committees of hospitals where patients are treated have a supervisory role to play in this domain.

Apart from the legal framework of the compassionate use programmes and medical need programmes, **the Advisory Committee notes** the high frequency of use of medicinal products outside the criteria defined in the marketing authorisation. This use may comprise unrecognised indications, different doses or even, most often, populations of patients for whom the indication has not been studied. This "off label" or "unlicensed use" practice is particularly frequent in paediatrics and even more in neonatology. It goes without saying that the off-label use for this group of patients often concerns medicinal products licensed for the same indications in adults, but for which there are no controlled studies for this age group. Sometimes these are indications or doses which are specific for this group of patients. There may be physiological arguments

[13] "*if, in literature, there is physiopathological or relevant data available concerning the use of this medicinal product for human use for the treatment of the disease in question*", criterion included in the version of the Bill of 23 December 2005 cited supra footnote page no.5.
[14] Idem.

for use in this age group. Obviously, controlled studies for this population have to be encouraged as much as possible. However, given the number of medicinal products that have been used off-label for a long time in patients of this age group, as well as the situations for which they have to be administered, it is not realistic for this to be done in a short period. Whilst awaiting the controlled studies, a temporary alternative could consist of formalising what is prescribed by having experts in the field draft guidelines which could be applied (inter)nationally.

The Committee invites the authorities to encourage pharmacological research in these areas, so as to limit this off-label use which comprises a high risk of side effects and lack of efficacy.. Hence, the patient must be given objective information concerning not only the reasons of the physician to propose using this new medicinal product , but also the particularities and the limitations of medical need programmes (CU, MNP). Duly informed, the patient or his or her representative must express his or her consent in writing. A medical ethics committee with "full approval" must give an opinion concerning the documents given to the patient. This committee is also responsible for checking whether if the medicinal product meets the criteria stipulated by the European Regulation and the Belgian legislation concerning its use in the CU and MNP programmes for the treatment of the disease in question. **In the opinion of the Advisory Committee**, the ethics committee has to evaluate whether , in the limits of the data available, the medicinal product concerned offers sufficient interest and a risk-benefit ratio which justifies the initiation of a programme. When exercising this responsibility, it must have the necessary competencies, or, as is most often the case, make use of experts in the domain concerned. It must also avoid abusive use of these procedures which could constitute an obstacle to the carrying out of controlled studies and, in this way, delay the marketing.

Apart from what is stipulated in the legal texts, the **Advisory Committee recommends** that the introduction of an individual patient in the programmes is also the subject of an opinion from the ethics committee (with or without "full approval") of the hospital where the patient is treated. This committee must check that the patient meets the characteristics defined when the programme is initiated. From this point of view, its competence is greater than that of the company to which the Royal Decree entrusts this mission. Further, being closer to the place where the patient is treated, it has the possibility of requesting additional information, without lengthening the time frames.

The **Advisory Committee expects** the medical ethics committees to evaluate carefully the interest for the patient in making use of new medicinal products of this type. As the expected benefit of medicinal products presented as innovative cannot always be checked, the ethics committee has a role to play in order to avoid this "last hope" treatment becoming therapeutic persistence

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The opinion was prepared by the select commission 2005-3 consisting of:

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The working documents of the select commission 2005-3 - questions, personal contributions of the members, minutes of the meetings, documents consulted - are stored as Annexes 2005-3 at the Committee's documentation centre, where they may be consulted and copied.