# Early access to medicines in Europe:

# Compassionate use to become a reality

A EURORDIS Position

April 2017

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# EURORDIS Position on Compassionate Use

A compassionate use programme (CUP) is a possibility whereby patients receive a treatment at a stage where its efficacy is not yet demonstrated, and not everything is known on its toxicity, and the patient and his/her doctor have agreed on this option.

Compassionate use provides early access to promising new medicines.

Compassionate use programmes can save lives.

## *A position by EURORDIS*

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### About EURORDIS

EURORDIS-Rare Diseases Europe is a unique, non-profit alliance of over 700 rare disease patient organisations from more than 60 countries that work together to improve the lives of the 30 million people living with a rare disease in Europe.

By connecting patients, families and patient groups, as well as by bringing together all stakeholders and mobilising the rare disease community, EURORDIS strengthens the patient voice and shapes research, policies and patient services.

EURORDIS works across borders and diseases to improve the lives of people living with a rare disease.

The EURORDIS vision is better lives and cures for people living with a rare disease.

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# Executive summary

Considering that:

- Even in Europe, patients are discriminated against according to where they live, and huge inequalities prevail in terms of timely access to new medicines. This is the case after a medicine has been authorised but it is also the case before, at the stage when it is still an investigational product in clinical trials.

- Patients and their representatives no longer overlook products that are beginning first-in-men/preliminary studies, proof-of-concept trials, or confirmatory trials. Even before public registries of clinical trials existed, patients could explore scientific journals and understand when a new product development had started.
- The length of time needed to develop a medicine varies, but on average it takes five to seven years, usually followed by the regulatory process and its legal timeframe, followed finally by pricing and reimbursement negotiations.

**Investigational products may offer the best hope of treatment and relief to those without established effective options. Compassionate use is supported by ethical imperative to alleviate this unfairness.**

- Not all patients have the time to contemplate this relatively long process: their disease worsens, they gradually lose their body functions, and eventually die. In addition, at the same time as this inescapable deterioration is taking place, they can hear about "promising results" coming in the news, in real time. **No other situation can be a source of greater despair in a patient's life: dying and yet being aware a possible medicine is approaching the market.**

## Society has a response to this despair: compassionate use of a medicine.

- **A compassionate use programme is a possibility whereby patients receive a treatment at a stage where its efficacy is not yet demonstrated, and not everything is known on its toxicity, and the patient and his/her doctor have agreed on this option.**
- A compassionate use programme takes place prior to the authorisation of a medicine, with a higher degree of uncertainty on the efficacy and safety, and with no guarantee that the medicine will be actually authorised.
- However not all countries benefit from an efficient scheme for compassionate use, and **a time difference of more than three years** may exist in Europe between patients benefiting from a compassionate use treatment or not, depending on where they live.
- Each investigation of a new product raises hopes, but there a risk of false hope, and these hopes should be managed. Pre-authorisation access needs to be balanced with realistic expectations. Having a mechanism to gain early access is crucial, but the process must be guided by research and trial data to the greatest degree possible.
- Premature communication about "promising" results after a test on a single animal model or just a few patients is detrimental to all, as the views presented are not balanced. There is often too much hype and too little data.

EURORDIS is making proposals to remedy the situation.

# Policy proposals

EURORDIS proposes one of the following options:

1. **Promote the French ATU system** so that every Member State adopts it, as it is probably the most efficient compassionate use scheme; or

2. **Adopt European legislative measures** which would confer a greater role in the organisation of CUPs upon the EMA; and/or

3. **Apply the Directive on Patients' Rights in Cross-Border Healthcare** to include compassionate use as part of the care basket so that patients can benefit from these treatments wherever they live in the EU; and/or

4. **Apply Medicines Adaptive Pathways to Patients to all medicines**, where the EU regulator may authorise a medicine at an early stage for a limited group of patients who have a great need for the product, keeping in mind that post-authorisation confirmatory studies need to be conducted afterwards. This is in the spirit of the compassionate-use programme as defined by the EU legislation, but with a different regulatory angle. This can only work if payers are part of the initiative, as they will need to accept to pay for a medicine with high uncertainties in term of efficacy or safety at that point; and

**Inequalities in accessing compassionate use medicines were presented to the European Medicines Agency back in 1998. These inequalities undermine the success of the European legislation on pharmaceuticals.**

5. **Amend the EMA guidelines for compassionate use** so that the role of the EMA could be reinforced.

# Important aspects

## Group of patients or named patient basis?

### Group of patients or cohort

In the first case, a group of eligible patients who could benefit from compassionate use are selected (indication, population); after the programme has been authorised clinicians do not need to request an authorisation for each patient. The programme is then run and supervised by the developer using an approved protocol.

This type of compassionate use is the one provided for in the EU Regulation; however, few Member States have adopted national rules to implement this type of programme.

### Named patient basis

However, on a named patient basis, clinicians need to request an authorisation for each patient. Typically, this is when the number of requests is expected to be low, as it is time consuming both for the clinician and for the regulatory authorities. No protocol is needed, and the product can be used to treat different conditions.

Most if not all Member States have a frame for compassionate use programmes on a named patient basis.

## Should compassionate use programmes be paid for?

A system where all CUPs should be free or paid for at the discretion of the company would be hardly sustainable.

One possibility could be to consider the financial situation of the company before accepting a paid for programme, and to agree on a payback if the product is finally not authorised, or at a lower price if it is not as valuable as initially estimated.

# Recommendations

## To patients' organisations

- Patients' organisations should be aware of the importance of compassionate use programmes
- Patients' organisations should be aware when the clinical development of a new product starts (or clinical trials for the repurposing of a known medicine), and engage in discussions with the developer at an early stage to agree on if and when a compassionate use programme could be relevant, and for which patients
- Patients' organisations and clinicians should consult each other about all practical aspects of the compassionate use programme.

## To industry

- Discuss the relevance and timing of compassionate use with patients' advocates and doctors early in the development of a medicine
- Define (inclusion) criteria for compassionate use with patients and clinicians;
- Put in place clear rules between compassionate-use and clinical trials.
- Explain the plans for the introduction of a CUP country by country
- Accept information on compassionate-use programmes cannot be considered as confidential
- Collect information from the compassionate-use programme, in particular toxicity data and special populations
- Plan an adequate supply of the product, and in case of an important increase in the number of requests consult with patients and doctors on how to slow down the programme. If tensions occur, the responsibility lies with the company who should not ask patients or doctors to make decisions

And avoid:

- Interrupting the programme in an abrupt manner, rather discuss the programme-end modalities with patients, doctors and regulators from the beginning
- Presenting the programme to clinicians as a gift to high inclusion rates in clinical trials

- Mixing compassionate-use programmes with humanitarian or financial support programmes.

## To Member States

- National authorities should improve the transparency of the compassionate use programmes they authorise, so that clinicians and patients are aware of which programmes are run in which countries and how to join them
- Member States should create a compassionate use programme Facilitation Group in order to exchange information and build upon common experiences to set up harmonised procedures and create a network which can facilitate future changes in the legislation
- Member States should respect article 83 of Regulation (EC) Nº 726/2004 and notify the EMA of compassionate-use programmes that they authorise.

## To European authorities

- The European Commission could compare different national schemes for compassionate-use programmes available in the EU
- The EMA could explore how to make better use of the European register of clinical trials to identify clinical trials whose purpose is to provide a medicine on a compassionate basis (typically open-label trials with no comparison arm).

# Introduction

## Compassionate use programmes can save lives

Back in 1988, people infected with the HIV virus advocated for earlier access to anti-HIV products, given the time needed for their development.

In the US, patients were marching to the F.D.A asking for accelerated evaluation of new medicines, and for a "parallel track" for all those who did not have a chance to enrol in clinical trials.

In France, discussions between patients' organisations and health authorities around the concept developed by French Doctors on "Octroi humanitaire/octroi compassionnel", namely humanitarian access and compassionate access had also started.

Very soon after these discussions, compassionate use authorisations were granted, both for anti-HIV products and for experimental treatments against the opportunistic diseases that can occur in HIV-infected individuals.

After the initial marketing authorisation of Retrovir® (zidovudine-AZT) in 1986 in the US and 1987 in European countries, other antiretroviral have systematically been the subject of an international compassionate use programme, see figure 1.

In particular, patients who exhausted all other treatments could almost continuously benefit from a new antiretroviral as subsequent developments were beginning.

In 1996, highly active antiretroviral became also available in compassionate use programmes. One example is in France, with the Temporary Use Authorisation scheme (A.T.U). Thanks to this scheme, 11,000 patients could be treated with

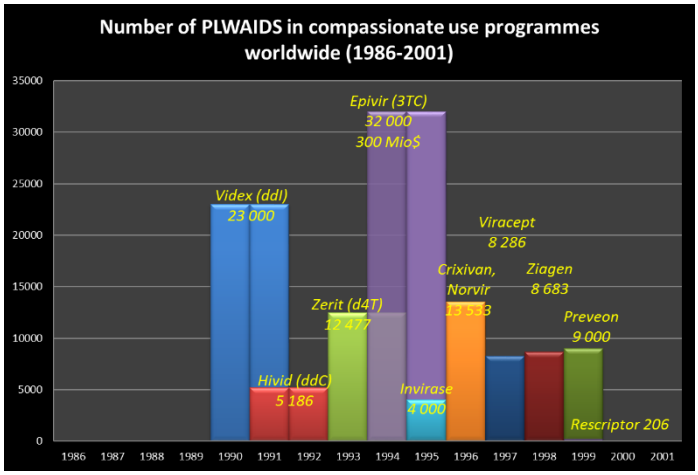


Figure 1

either indinavir or ritonavir from March 1996. When both products received marketing authorisation later in September and October 1996 respectively, the hospitalisation rate for 1,000 AIDS patients had already declined by 38% compared to early 1996. In mid-1997, hospitalisation rates for AIDS patients had dropped by 56%, and mortality by 14%.

This represented the prevention of an estimated 582 deaths, as 17,676 HIV individuals had reached the AIDS stage in 1996, with a 50% mortality risk at 6 months, of whom 11,000 could enter the compassionate use programmes.

This example illustrates the public health benefit of compassionate use programmes: in March 1996, ritonavir and indinavir had not been evaluated for marketing authorisation, a marketing authorisation had not even been submitted in the EU, and yet, based on presumed efficacy reported in a scientific conference in January 1996, regulatory agencies and developers agreed to the urgent initiation of the compassionate use programme .

This programme benefited the patients by reducing the immediate risk of death for 11,000 people in France, the developer of the programme. By collecting important safety information complementary to the evidence gained from clinical trials, and the health care system, the cost of the compassionate use programme was far less in comparison to the savings in terms of direct hospitalisation costs and lives saved.

However once again, in many other countries, patients had to wait sometimes an additional year after the marketing authorisation to benefit from these life-saving treatments: in the UK, the newly created National Institute for Clinical Excellence (NICE) was explaining that cost-effectiveness studies were necessary before the NHS could provide these treatments. In September 1996, patients organised a press conference to advocate for access to highly active antiretroviral therapies.

In Italy, some 1,000 patients could benefit from the French ATU by consulting doctors at the Hôpital de l'Archet in Nice, but other Italian patients had often to wait until 1997 to be treated.

# What is compassionate use and why is it much needed

- **A treatment, when there is none**: Compassionate use is a treatment. It is not an experiment with an investigational product. The intention is to treat the patient, hoping he/she can benefit from a positive effect.
- **Before the medicine is authorised**: This treatment is provided when the product is not yet authorised.
- **For patients who cannot wait for the end of development**: The idea is to treat patients who cannot afford to wait until a product's development is complete, regulators have agreed to authorise it and healthcare systems have agreed to cover it or to reimburse it.
- **It is a societal response to patients in desperate need of a last option before passing away or deteriorating severely.**

Patients with rare diseases are candidates for compassionate use programmes. Medicines that are designated as orphan by the Committee of Orphan Medicinal Products (COMP) at the European Medicines Agency are indicated for life-threatening or severely debilitating conditions, and in most cases, few treatment option exist.

It is difficult to know exactly how many different products for rare diseases are being developed at present. As of 11 July 2016, 997 phase III and 1,347 phase II clinical trials are in progress in the EU/EEA to explore the efficacy of medicines in rare diseases (European Register of Clinical Trials).

Another important figure is the number of orphan medicinal product designations: 1,654, of which 132 have already been translated into a marketing authorisation (this represents 122 different products), as of May 2016. Not all designated orphan medicinal products are the subject of clinical trials, and the precise number is not publicly disclosed (only the EMA could analyse the annual reports provided by the sponsors of the orphan designations that give information on their development status).

These R&D efforts generate huge expectations in the concerned patients' communities. From the

above-mentioned data, the precise number of different product/indication pairs cannot be estimated, but certainly a few hundred products are being investigated.

The US based association of Pharmaceutical Research and Manufacturers of America (PhRMA) regularly publishes reports and lists of medicines in development. In 2016 it estimated that there are more than 560 medicines in development for rare diseases (PhRMA, 2016).

# Legal definition of Compassionate Use Programmes in the EU (CUP)

Regulation (EC) Nº 726/2004 article 83.2 defines such programmes:

> **Running a Compassionate Use Programme (CUP) consists of making a medicinal product 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 product concerned either must be the subject of an application for a marketing authorisation or must be undergoing clinical trials.**

Again, the EU definition applies to programmes for groups or cohorts of patients, not to named patient basis programmes.

For compassionate use programmes to be organised, different conditions need to be satisfied:

1. **Eligible patients**: A group of patients who could benefit from the programme[1] have to be defined/selected: indication of the CUP, inclusion and exclusion criteria
2. Available supply: The developer needs to make the product available for the CUP in addition to the supply needed for the trials
3. No interference with trials: National authorities need to agree on the programme and how to organise it, taking into account clinicians' request. Providing the investigational product for compassionate use should not interfere with the initiation, conduct, or completion of clinical trials to support marketing authorisation
4. A marketing authorisation likely to be obtained soon: A Marketing Authorisation Application should have been submitted, or clinical trials should be in progress (no prerequisite of having obtained a marketing authorisation in another jurisdiction than the EU). At this stage, efficacy can only be presumed.

[1] This does not apply to named-patients programmes

# Ethical considerations

## General principles

Few ethical recommendations exist on compassionate use. The French Comité Consultatif National d'Ethique published opinions of general interest (CCNE, 1997):

- **Equal access**: An indisputable ethical principle is the equal access to a compassionate product for all patients in need. Criteria such as the social position of a person, or his/her affiliation to a patients' organisation, or his/her shareholding in the company cannot serve as a reason to privilege him/her in accessing the product
- **Transparency**: clear operating procedures to ensure transparency in the programme are needed, both for the patients and the public in general. Some inconsistencies on the allocation of treatments were, rightly or wrongly, criticised (such as geographical inequality)
- **Clear definition of who the beneficiaries will be/who will benefit**: it should be based on scientific and medical criteria.

## Clinical trial participants

For clinical trial participants, ethical recommendations also exist regarding post-trial access to treatment. This applies both to participants who were receiving the experimental product, and to those who were taking the placebo or comparator.

The Helsinki Declaration as revised by the World Medical Association in 2008 states that "(33) *at the conclusion of the study, patients entered into the study are entitled to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*" (WMA, 2008).

And: (14) *The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits".*

# Differences between named patient basis and cohort programmes

### Named patient basis

Requested by a clinician

One request per patient, to be renewed

Full responsibility of the clinician

Safety and efficacy of the product are presumed

Compassionate situations often at a very early stage of the product development

No protocol

No data collection

No reporting

Many drugs, few patients

### Programme for a group

Requested by the company

One request for a group of patients, usually for 1 year

The clinician and the regulatory authority

Safety and efficacy are highly/greatly presumed

SPC, patient leaflet, labelling available

Follow up of patients and data collection according to a protocol

Company reports to the authority

Few drugs, many patients

Commitment to submit a marketing authorisation application

# Evidence needed to initiate a CUP

Regulation EC 141/2000 OMP states "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients". The information on efficacy/safety is part of the quality of our medicines and the more information patients and doctors have, the better the quality of the medicine. This is the reason why we need clear and complete data on benefit/risks, and as much information as possible should be generated before the marketing authorisation.

If generating a satisfactory level of evidence takes too long, the developer has the option of creating a compassionate use programme (CUP) for those who cannot afford waiting. The CUP inclusion criteria should mirror the exclusion criteria of clinical trials.

The greater the uncertainty, the more the patients can be disappointed or harmed.

Regarding the evidence on which a CUP can be authorised, different Member States require different evidence on the benefits. The French regulatory scheme for CUPs, called A.T.U (Temporary Use Authorisation) requires "efficacy and safety to be highly presumed, according to the scientific knowledge available[2]", which literally means "accepted without verification or proof". Harm or the absence of efficacy would of course prevent a CUP.

In Germany, efficacy needs to be also "assumed", and not fully established: "evidence and grounds for the assumption that the medicinal product is

[2] In French: « leur efficacité et leur sécurité d'emploi sont fortement présumées en l'état des connaissances scientifiques »

safe and effective for the envisaged (compassionate) use (Bfarm, 2010)".

The European Medicines Agency guidelines (EMA, 2007) explain:

> **In terms of efficacy, the assumptions for compassionate use may be based on mature, randomised phase III trials (e.g. in case of parallel assessment of compassionate use and application for marketing authorisation).**

However, acceptable assumptions may rely on promising early data observed in exploratory trials (e.g. uncontrolled phase II trials).

> **Full efficacy and safety evaluation can only take place at the time of the benefit/risk evaluation for a marketing authorisation application. For a compassionate use, real evidence cannot be requested, efficacy can only be presumed.**

# Product availability

For the initial phases of development, only small quantities of the compound are needed. When results come in (proof-of-concept studies), the developer decides whether to conduct confirmatory trials for which higher quantities are needed. At that time, often referred to as the Go/No Go decision, scaling up of the production is decided, which sometimes requires the construction of a new manufacturing site or bioreactor and/or the reorganisation of the manufacturing process. Arrangements for the scaling up of the production may be more or less difficult, but in any case they need to be validated by regulatory authorities (for commercial batches), and need to comply with Good Manufacturing Practices (ISPE, 2016). The time needed for this to be completed should never be under-estimated. There is often a time lag between the decision to launch large-scale production and the moment when new batches can be used on patients or clinical trial participants.

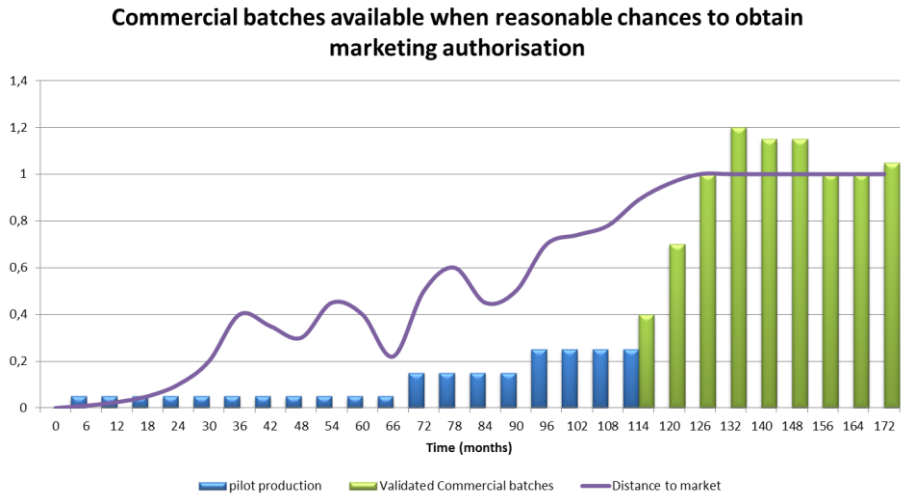


**Figure 2: Product supply increases in a discontinuous manner, firstly prioritising clinical trials, then preparing for the market launch. The line represents the probability that the product reaches the market, with ups and downs depending on various events all along the development.**

# EURORDIS views on CUPs within the context of the European Legislation[3]

- A CUP use programme should be largely inclusive (reason why it is preferred to named-patient basis programmes)
- The CUP inclusion criteria should mirror the exclusion criteria of the clinical trials
- A positive benefit/risk ratio should be presumed, not fully demonstrated
- Equity:
  - Members of patients' organisations should not be given an (unfair) advantage/advantaged compared to non-members (no advantage for the best informed)
  - If extremely limited supply: random draw to enrol patients

# Usefulness of CUPs

In a workshop organised by EURORDIS on 21 November 2011 (Eurordis Round Table of Companies, 2011), 82 participants from industry, the European Medicines Agency and Members States reviewed the societal benefits of compassionate use, beyond facilitating access to new medicines.

The advantages are:

1. For clinicians, an opportunity to learn to use new medicines in patients other than the ones enrolled in clinical trials (usually with comorbidities, or different ages, or concomitant therapies)
2. For the developer of the medicine, an opportunity to build networking with specialists other than the clinical trial investigators and to shorten the delay on market access;
3. For the regulators, better knowledge about the medicine (when data from the compassionate use programme is collected and evaluated).

[3] Again, these provisions do not apply to named-patient basis compassionate use

# Recommendations

## Recommendations to industry

Patient advocates who are working on the design and organisation of CUPs can recommend the industry to:

a) Discuss the relevance and timing of a compassionate use with patients' advocates and doctors early in the development of a medicine
b) Define inclusion criteria for the compassionate use with patients' representatives and clinicians
c) Explain the plans for the initiation of a CUP country by country
d) Accept information on compassionate-use programmes cannot be considered as confidential
e) Collect information from the compassionate-use programme, in particular toxicity data and special populations
f) Update the programme according to demand and avoid excluding patients, for example on grounds that they are considered potentially unreliable
g) Involve and coordinate different departments within the company: medical affairs, clinical development, regulatory, pharmacovigilance, finance and supply chain
h) Produce clear guidelines for the safe use and administration of the product
i) Plan an adequate supply of the product, and in case of an important increase in the number of requests consult with patients' representatives and doctors on how to slow down the programme. If tensions occur, the responsibility lies with the company and a company should not ask patients or doctors to make decisions
j) Allocate adequate resources to establish and run the programme, including processes for handling and vetting requests, mechanisms to review eligibility of patients and reporting of adverse events
k) Industry should continue dialogue with European and national authorities on how to improve the situation and on setting up clear rules between compassionate-use and development programmes.

And avoid:

l) Stockpiling supply to prepare market access which is to the detriment of the number of patients who can be enrolled in the compassionate-use programme. Available supply should be prioritised to complete the clinical trials and the largest compassionate use programme
m) Interrupting the programme in an abrupt manner in the eventuality of a negative CHMP opinion on the marketing authorisation, instead discuss the programme-end modalities with patients' representatives, doctors and regulators in the first place
n) Interrupting the programme when a positive opinion is obtained, but rather continue providing the product to patients who were enrolled earlier until the price and reimbursement decision and

in some case inclusions can be closed during that phase

o) Presenting the programme to clinicians as a gift to high inclusion rates in clinical trials

p) Mixing compassionate-use programmes with humanitarian or financial support programmes.

## When supply is limited and cannot satisfy the demand

When there is a very limited supply of the compassionate use medicine, ethics committees have already published their opinion: in the 90s, in the context of HIV/AIDS, when the demand exceeded the supply, with only 250 treatment doses available for 20,000 patients in France in February/March 1996, the National AIDS Council's advice was to select patients via a random process. "Since patients will be selected randomly by computer, there will be no conscious or unconscious emotional preference or pressure. Drawing lots will relieve doctors of the responsibility of choice and preserve patients' trust in their attending physicians. Lots will be drawn each time supplementary drug doses are made available, with the aim of including all eligible patients."

The National Ethics Council (CCNE) had a similar opinion: "A draw at local level could be organised as an ultimate possibility, in cases where the rational elements of decision does not suffice to reach a decision".

None of these opinions explained who should organise the draw. Local hospitals? National authorities? The sponsor of the clinical trials/ developer of the product? The clinical research organisation?

The view of prominent patients' advocates is that the pharmaceutical company that is responsible for the communication on "promising results" in its press releases or at scientific conferences is therefore responsible for monitoring the consequences of this communication, including the impact of the requests for compassionate use; society should accept no body other than the company to operate the random process of selecting new patients to be enrolled in the CUP.

## Should the company set up its own ethics committee?

Some companies appoint an ad hoc ethics committee that reviews requests and decides which patients can enter the programme. This approach is raising major issues:

- Transparency: members of these ethics committees are appointed by the company, but the arrangements are unknown. The criteria they use are unclear: if the programme has been authorised by regulatory authorities, then why set up this committee? Clinicians should be in a position to enrol their patients without the intervention of a third party.
  For named patient basis programmes, where regulators have not defined the eligible population, the company should be very clear on how many patients can be treated and how the company should interpret its responsibilities: if there is enough of the product for all patients, then no triage is needed, or if there isn't enough product then the more ethical approach is a random selection of

patients, under the strict control of the company.

- Medical criteria are not the solution: when a clinician really wants to enrol a patient in a programme, he or she will make sure the documents are filed in in a way that corresponds to the programme inclusion criteria
- The company ad hoc ethics committee usually receive requests as they come in, and patients are enrolled on a first come first served basis, which always favours the best informed
- And above all, the creation of these committees can be a way for the company to displace their responsibilities onto others, with an appearance of a concern for ethics, but in fact with no guarantee of a fair and equitable procedure.

# Recommendations to European & national authorities

- National authorities should consult patients' organisations and clinicians when deciding on the criteria and conditions for the compassionate use programmes on their territories
- Similarly, when asked for an opinion on a compassionate use programme, the CHMP should consult with patients' representatives and clinicians. This could be best done within the PRIME initiative (EMA, 2016)
- The European Commission could compare different national schemes for compassionate-use programmes available in the EU
- The EMA could explore how to make better use of the European register of clinical trials to identify clinical trials whose purpose is to provide a medicine on a compassionate basis (typically open-label trials with no comparison arm)
- National authorities should improve the transparency of the compassionate use programmes they authorise, so that clinicians and patients are aware of which programmes are run in which countries and how to join them
- Member States should create a compassionate use programme Facilitation Group in order to exchange information and build upon common experiences to set up harmonised procedures and create a network which can facilitate future changes in legislation
- Member States should respect article 83 of Regulation (EC) Nº 726/2004 and notify the EMA of compassionate-use programmes that they authorise. EURORDIS recognises the need for explanation by Member States as interpretations may differ on the definition of compassionate use, depending on whether it addresses named patient programmes or cohorts. However, Regulation (EC) No 726/2004 is very clear as Article 83.2 states that "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".

Therefore, named patient programmes are not addressed by the Regulation and EURORDIS does not see the need for further explanation here. The minimum patients would expect is that:

a. Member States comply with Article 83.3 and notify the EMA of their programmes, as they are ethically and legally obliged to do
b. Member States and the EMA create a public catalogue of the compassionate programmes they authorise, in the appropriate European languages

# Recommendations to patients' organisations & healthcare professionals

a) Patients' organisations should be aware of the importance of compassionate use programmes
b) Patients' organisations should be aware when the clinical development of a new product starts (or clinical trials for a repurposing of a known medicine), and engage in discussions with the developer at an early stage to agree on if and when a compassionate use programme could be relevant, and for which patients
c) Patients' organisations and clinicians should consult each other about all practical aspects of the compassionate use programme: inclusion criteria, number of eligible patients, rules to ensure fair access to the programme (information, clinical sites where the programme is run…), follow-up (collection of data on safety, efficacy…) etc.

> **But despite all the efforts to accelerate the process, both on the company side and on the regulatory side, when the compassionate use programme starts, there are always patients for whom it will be too late.**

# Specific situations in rare diseases

## Gene therapy

Gene therapy trials typically enrol few patients (around 50 in average, EUDRACT). For the benefit/risk evaluation, gene therapy products (belonging to the Advanced Therapy Medicinal Products) do not benefit from a large set of patient data, and yet uncertainties on safety are a major concern for these products before they can be authorised.

At the end of early trials, when promising results are shown, patients can legitimately request access on a compassionate use basis. But as gene therapy is a one-time shot (maybe to be renewed after a certain number of years, 5, 1, 20, to be determined case by case by post-marketing monitoring), the developer cannot afford to offer the gene therapy product on a compassionate basis, as the market would vanish by the time the product is authorised.

For gene therapy products, Member State encourages the conduct of clinical trials with high quality data collection. Therefore, proposals are:

- To enrol larger numbers of subjects in gene therapy trials
- If a compassionate use programme is to be launched: the developer could receive payment if and when the product is authorised and deemed of therapeutic value

# Free or paid for CUPs?

Compassionate use programmes can be free of charge (when the company offers the treatment at no cost), or paid for. In addition to the treatment, other costs are to be budgeted (prescription visits, exams, sometimes hospitalisation with/without surgery or injection…).

## If for free

Some might consider running a CUP for free as a marketing strategy, equivalent to a promotional campaign to "invade" the market prior to the marketing authorisation (NLD): this would represent unfair competition and would cause market distortion.

For small enterprises, the cost of running a CUP could limit its size, or even the capacity to start one, if the company could not generate revenues from it.

## If paid for

Some may argue this is against the spirit of the European Pharmaceutical Regulation and Transparency Directive according to which a medicine cannot be commercialised if not authorised.

On the other hand, the possibility to generate revenues is an attractive factor for developers to decide a compassionate use programme. Historically, CUPs always started earlier, sometimes much earlier, in countries where the developer could charge, to the benefit of the patients.

## If for free in some and paid for in others

The current practice varies largely by country, introducing inequities in accessing a treatment on a compassionate basis, as patients living in countries where a charge for the product can be demanded will always access the product earlier compared to products where the company cannot charge, or even needs to pay (e.g. fees to ethics committees).

A simple rule such as 1) or 2) below would not represent an efficient solution:

1. In all Member States all CUP should be free of charge
2. In all Member States all CUP should be paid for

Solution number 1 would be detrimental to the attractiveness of CUPs in Europe: industry could simply refuse to start them (levelling CUPs downwards) and solution 2 could represent a high financial burden, making it complex for all Member States.

## Possible solutions: criteria depending on the financial condition of the company, and risk sharing agreement

- Paid-for CUPs could be restricted to CUPs run by small and medium size enterprises only (as defined by EMA) that might have objective financial difficulties in running them
- Exceptions for SMEs that pay high dividends to share-holders or whose financial situation indicates the company has the financial resources to bear the cost of a CUP: could not charge for, or only "minimally"

- If other products exist for the condition: given the uncertainties of the efficacy/safety of a medicine used on a compassionate basis, its cost could be limited to half the average cost of other products (including off-label use) based on the defined daily dose (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2009), and after the marketing authorisation, if the market price is lower than the price for the ATU, then the marketing authorisation holder could reimburse the difference
- If there are no other treatments available for price referencing, then the company could charge for the treatment. If the product is finally not authorised, then the company could reimburse part of the expenses
- Even when the programme is for free, there is a huge incentive for the company to initiate a compassionate use programme quite early, which may represent a more powerful incentive than the revenues it can generate. By implementing the programme the company installs its product on the market and when a price is finally agreed upon and the reimbursement decided, revenues then come in very rapidly as time is not wasted as a result of the time needed to place the product on the market (work with hospital pharmacists, negotiate with distributors, visit the prescribers etc.), everything is already in place and sales start more or less immediately.
- And if the product is finally not as valuable as initially thought, a pay-back system for the difference between the compassionate use price and the market price once authorised could be created, with a minimum and a cap.

# The Right-to-Try laws in the USA

EURORDIS shares the opinion that "Right-to-try" laws may in fact reduce patient autonomy (Neveloff-Dubler, 2016). "Right-to-try is a sham," she said, "It's an empty promise which delivers nothing, and patients who want to try a substance that's in the middle of a phase I trial have no basis on which to choose that [substance] and the company has no basis on which to grant it," she said. One of the core ethical principles of compassionate use must be a scientifically valid basis for believing a treatment will benefit a patient, and "right-to-try" circumvents some of the protections that ensure that validity.

# Way forward

Solutions to abolish these disparities are simple to theorise but little progress has been observed in the last ten years. Possible actions for next steps to make progress are:

1. **Promote the French ATU,** probably the most efficient compassionate use scheme so that every Member State adopts it; or

2. **Adopt an EU Regulation** which would confer a greater role in the organisation of CUPs upon the EMA; and/or

3. **Apply the Directive on Patients' Rights in Cross-Border Healthcare** to include compassionate use as part of the care basket so that patients can benefit from these treatments wherever they live in the EU, and/or

4. **Apply the Medicines Adaptive Pathways to Patients** to more medicines, where the EU regulator may authorise a medicine at an early stage for a limited group of patients who have a great need for the product, keeping in mind that post-authorisation confirmatory studies need to be conducted afterwards. This is in the spirit of the compassionate-use programme as defined by the EU legislation, but with a different regulatory angle. This can only work if payers are part of the initiative, as they will need to accept to pay for a medicine that is highly uncertain at that point; and

5. **Amend the EMA guidelines** on compassionate use.
In its Communication on Rare Diseases (European Commission, 2008), the European Commission proposed the EMA to review its guidelines on compassionate use programmes with the objective of ensuring "*A better system for the provision of medicines to rare diseases patients before approval and/or reimbursement (so-called compassionate use) of new drugs".* However, the Commission has not yet invited the EMA to revise their existing guidelines.

Many aspects need to be improved:

- There are important differences between Member States' policies (authorisation of the CUP, documentation required, assessment time, validity, follow-up, reporting…)
- Liability risks need to be clarified
- Transparency of the programmes need to be improved so that clinicians and patients receive timely information
- Interference with the marketing authorisation procedure and whether or not the data collected in a programme can be part of the dossier submitted to regulatory authorities
- Supply and logistics, information and language
- Pressure on supply under compassionate use
- Free of charge or paid for programmes

The role of the EMA could be reinforced with or without legal changes to the pharmaceutical legislation:

Article 83.4 of Regulation (EC) No 726/2004 states:

"When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted."

In its guidelines (EMA, 2007), the EMA acknowledges that the conditions for distribution are not defined in the pharmaceutical legislation. It therefore interprets them as whether or not the medicinal product is subject to medical prescription, or whether it is subject to special or restricted medical prescription. It excludes the possibility to address conditions for distribution, the strategy for supplying the medicinal product in the Member States (e.g. quantity of product, choice of MS).

This is very unfortunate, as this self-restricted role leaves many issues related to compassionate use programmes unaddressed, with loopholes and unregulated aspects.

There is a distribution of roles between Member States who implement the compassionate use programmes in their territories, and the EMA. With the current distribution of roles, and given the self-restricted role EMA has, the following aspects are not regulated, neither at the national nor at the European level:

- Anticipation of the programme during early scientific advice, and discussion with the developer on the relevance and feasibility of a compassionate use before clinical trials start, and the respective inclusion/exclusion criteria for the clinical trials and the compassionate use programme
- Estimates on how many patients could benefit from the compassionate use in the EU
- Criteria to progressively increase the number of patients when more product becomes available
- Paring back measures when the demand for compassionate use exceeds the available supply, and measures to ensure a fair and equitable distribution of available stock among Member States

# Conclusion

Unfortunately, even if the best compassionate use scheme is adopted everywhere, there will always be patients who will reach an irreversible stage of their disease or who may pass away the day before the compassionate programme is authorised and implemented.

For these patients, who are aware that a new product is being developed somewhere and who are willing to take a higher risk with a not-fully tested product, society does not currently propose any solution. In such situations, some argue there is no role for regulators to intervene: it is up to the patient and the doctor to decide.

This debate is quite similar to the debate on end-of-life and euthanasia, when the decision can lie with the patient and his/her doctor who are not required to fill in a form for a named-patient decision. Some refer to this stage as ultra-compassionate use, which is again dependent on the availability of the supply for compassionate use.

Read the annexes to this position paper, including a glossary of terms related to compassionate use, as well as information on how to find a CUP in your country.

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