Response to the Rare Disease Public Consultation

QUESTION 1: EU DEFINITION OF RARE DISEASES

Although possibly considered wide by North American standards (for example), the EU definition does satisfy a major aspect of "rare diseases"; i.e. the fact that pharmaceutical industry is reticent to develop specific drugs for diseases with low prevalence.

For some rare diseases, especially those for which underlying pathogenesis is unknown, definitions are still evolving; there is a trend towards regrouping entities which have common downstream pathways causing tissue and/or organ injury in order to develop coherent therapeutic and management strategies. We provide here one such example: since first described in 1975, hypereosinophilic syndrome (HES) has been defined as persistent hypereosinophilia (circulating levels greater than 1.5 G/L for more than 6 consecutive months) of unknown origin, responsible for end-organ damage. A series of related disorders characterised by eosinophil-mediated organ- or tissue-specific damage (e.g. eosinophilic fasciitis, eosinophilic gastroenteritis, eosinophilic pneumonia, episodic angioedema with eosinophilia, etc…) have been classified separately given their restricted and "predictable" clinical complications, in contrast to HES which can involve successively a number of different organs as disease progresses. However, in some cases, the passage of time reveals extension of the initially restricted spectrum of complications, and thus diagnosis changes from organ-specific disease (e.g. eosinophilic pneumonia) to typical HES. Also, for both types of presentations, although pathogenic mechanisms remain unknown in the large majority of cases, similar mechanisms have been identified in a few isolated cases (for example, abnormal T cells with a specific CD3-negative CD4-positive phenotype that produce eosinophil growth factors have been identified as the primitive cause of hypereosinophilia in some patients with HES and in some with episodic angioedema with eosinophilia). For these reasons, current efforts towards improving defining criteria for HES are extending these to eosinophil-mediated "organ-specific" disorders.

As a general rule, as pathogenic disease mechanisms unfold, there will be constant adaptation of defining criteria for rare diseases; in some cases, disease subsets will be more restricted (for example based on specific molecular/genetic abnormalities that can be targeted or substituted by highly tailored therapeutic strategies), and in others, larger disease entities are likely to emerge on the basis of similar "downstream" mechanisms implicated in end-organ damage, which could be targeted more largely for therapeutic purposes. In the latter situation, numbers of concerned patients falling into a larger "umbrella" diagnosis, will be higher than before, in hopes of improving overall management (as well as identifying pathogenic molecular cascades) of these closely related disorders.

We would favour maintaining the current EU definition, which does preserve the "orphan" status of these diseases and therapeutic developments, but leaves space for evolving definitions of rare diseases for which pathogenesis remains unknown.

QUESTION 2: CODING AND CLASSIFICATION

There is clearly a strong need for coding of rare diseases. However, we would suggest remaining very careful as far as classification is concerned.

Coding rare diseases is essential for approaching **prevalence** of these illnesses (on the basis of hospital discharges amongst other tools), which remain largely unknown. Also, coding will be

important for recognition of the existence of rare diseases, of their overall burden in terms of morbidity, mortality and cost, and of difficulties encountered in their management, by **public health authorities.** Direct implications of this include: 1/ adapting public health intervention in **financing in-hospital stays** for patients with rare diseases (i.e. in Belgium, the code corresponding to the major diagnosis is the main determinant for the length of financing a hospital stay for a given patient), to better reflect the difficulties encountered when dealing with them (i.e. the specificity and cost of diagnostic tests, related to their direct costs as well as those related to requirement of qualified personnel for their interpretation; time required for obtaining adequate treatment, often through compassionate use programs…), and 2/ **improving health insurance coverage** for patients who often require costly tests and treatment, frequent visits to out-patient clinics and hospitalisations, while often incapacitated by their illness in terms of financial autonomy. It is of note that these diseases don't "fit into" the typical forms that assess handicap, when patients apply for state-based financial support…

Classification of human diseases is an entirely different matter, and can be approached either from a *pathogenic* perspective, or from a "major concerned *medical sub-specialty*" perspective. Some rare diseases have well-documented underlying molecular defects affecting a specific cellular compartment, allowing for precise diagnosis (generally by using specific tests based on the identified molecular defect), and classification in terms of pathogenesis and medical sub-specialty.

However, in many cases, the situation is less straight-forward, namely when underlying **pathogenic mechanisms** are **unknown**. Many orphan diseases remain **clinically** rather than pathogenically **defined syndromes** for which specific diagnostic tests don't exist; in some cases, an orphan disease will be diagnosed after having excluded other pathologies with more straight-forward presentations and diagnostic tools ("diagnosis of exclusion"). Clinically defined rare diseases tend to regroup entities with similar disease expression (better termed "rare syndromes") although pathogenic investigation may later reveal several different underlying molecular mechanisms, which retrospectively explain some degree of clinical heterogeneity within these syndromes (e.g. HES, now at least partially split into disease variants on the basis of pathogenesis). On the other hand, several distinct clinical diseases may share common pathways, and although the primary defect is unknown, it may prove worthwhile to regroup them for investigating downstream pathogenic mechanisms that could be targeted by similar therapeutic approaches (e.g. choice of regrouping so-called ANCA-associated vasculitides, which may include patients with Wegener's disease, microscopic polyarteritis, Churg-Strauss disease, rather than considering each disease entity separately on the basis of empirical diagnostic criteria, whether or nor serum ANCA antibodies are present…).

Another important consideration is that many rare diseases are "**systemic**", either because they are mediated by soluble or cellular factors that are widely distributed, or because a molecular defect has arisen in a pluri-potent cell. Given the wide spectrum of clinical complications, classification according to medical sub-specialty is not feasible, and if pathogenesis is unknown (which is the case of large majority of auto-immune diseases or vasculitides for example), classification on the basis of underlying disease mechanisms is not possible either. The orphan disease our center is actively investigating represents one such example: hypereosinophilic syndrome (HES) is characterized by multiple clinical complications due to infiltration of various tissues and organs by eosinophils (e.g. lungs, heart, digestive system, central and peripheral nervous system, skin, liver, etc…), which cause damage in their environment through release of toxic molecules. Clinically, this is a systemic disease which can't easily be classified into a medical sub-specialty. Recent advances in pathogenesis further underscore this difficulty, in that a small subgroup of patients presents a

clear-cut myeloproliferative haematological disorder characterized by clonal eosinophil expansion secondary to a molecular defect (partial chromosomal deletion resulting in expression of a fusion tyrosine kinase), whereas in another subgroup, hypereosinophilia develops as a result of over-production of the eosinophil growth factor interleukin-5 by T lymphocytes, a mechanism similar to that encountered in allergic disorders. Finally, for the majority of patients with HES, pathogenesis remains unknown, and among these, clinical and biological features may be strongly reminiscent either of a primitive myeloproliferative disorder (i.e. a haematological disorder), or of an immuno-allergic disorder. Another example is systemic sclerosis, a clinically defined rare "auto-immune" disorder regrouping patients with skin (as well as visceral connective tissue) thickening due to excess collagen deposition (this clinical observation is what determines diagnosis); patients that satisfy the diagnostic criteria have extremely variable clinical presentations and biological alterations, and there is no doubt that several pathogenically distinct disease entities co-exist under this "umbrella".

When elaborating RFAs for funding of clinical research dedicated to rare diseases, we strongly feel it is important to keep the potentially systemic nature of diseases in mind, as well as the fact that for the numerous disorders for which pathogenesis is unknown, it is likely that future investigations will reveal heterogeneity of molecular mechanisms ultimately resulting in disease expression, which will further remodel disease classification.

QUESTION 3: EUROPEAN INVENTORY OF RARE DISEASES

Creating a European inventory of rare diseases would facilitate their recognition by public health authorities and health insurers. This is also an important step in creating a platform for easy access to information on clinical presentation, diagnostic tests, optimal management, clinical trials, etc… for both patients and physicians. However, as underlined in the response to question 2, classification by medical specialty, mechanism, or etiology is not straight-forward for a large number of these disorders.

QUESTION 4: EUROPEAN NETWORKS PRIVILEGE TRANSFER OF KNOWLEDGE OR OF PATIENTS?

Both approaches are already used "informally" for rare diseases, but clearly transfer of knowledge is more frequent across borders of MS for a number of reasons, including cost of travel, limited mobility of patients with some degree of handicap related to their diseases, doubtful health insurance coverage in states other than one's own, …

Transfer of **knowledge** is critical for optimal patient care; long-distance case presentations can help non-expert physicians (often already highly qualified specialists) manage their patient locally. Practically, communication is often based on identification of experts through specialised medical literature dedicated to a given rare disease by a physician, followed by e-mail exchanges on the case through which the "expert" guides the diagnosis and management of the patient. Less frequently, it is the patient him(her)self who manages to identify the expert, and seeks information by presenting his(her) case; this happens more often with patients with a higher socio-economic status. Providing a wider range of patients (and less qualified physicians such as general practioners) with a web-based platform through which they can easily identify experts for their particular disease would partially help overcome this form of inequality.

In some instances, modern therapeutic compounds that are still under development (e.g. being evaluated in the setting of a clinical trial) are not delivered in all MS, and in such cases,

patient mobility should be facilitated. Indeed, the physicians who are principal investigators for clinical trials in rare diseases evaluating novel and promising molecules have in-depth knowledge of the disease, and the molecule under investigation, and generally work in academic centers which in a sense allows more time for acquisition of such knowledge; it would be imprudent to conduct the study in a centrifuge manner, as the more "peripheral" physician is less likely to have such knowledge. Patients living in MS that are not evaluating a given compound for their disease should be able to travel easily, and benefit from adequate health insurance coverage when doing so.

Finally, a global action at the European level for identification of **Centers of Reference** for rare diseases should be undertaken (for example by issuing a RFA). Currently, several MS have been more active in this field than others (for example, France); such decisions should not be left to MS' initiatives, but rather should be situated at the European level to harmonize quality of rare disease management at the European level. This is important for justification of patient mobility, and in the other direction for transfer of knowledge (i.e. identifying most appropriate center for requesting information).

QUESTION 5: ON-LINE AND ELECTRONIC TOOLS

Yes, clearly electronic tools should be implemented. This is already a precious source of information for patients and care-givers, as well as physicians, and should be further implemented. The number of tools should be limited so that the quality of provided information remains excellent (peer-reviewed up-dates on diseases, including clinical presentation, pathogenesis, diagnosis, management, prognosis, on-going clinical trials, etc…).

There is already a high-quality **general website** for rare diseases in Europe, with the Orphanet website. However, there is no homogenous attempt to create **disease-specific web-sites**, which would provide patients, families and physicians with more specific and detailed information related to their illness. Creation of a new website and its subsequent management are time-consuming and require know-how, explaining the paucity of quality websites for individual rare diseases. Efforts in this direction should be made, both at national and EU levels. One solution would be to centralise such efforts, by entrusting websites for rare diseases to a small group of web-designers; centers of reference would implement the designers with the information (and the way it should be organised) that should be made available to different users.

That being said, physicians and patients will access these sites only when a precise diagnosis is made; this is a **pro-active** means of obtaining information. There is still much room for improvement in **making the overall community of physicians aware** of clinical presentations that should raise suspicion of a given rare disease (i.e. education of practioners). Large-scale delivery of very brief and practical **fliers** on rare diseases is an interesting **centrifuge** approach that appears feasible.

QUESTION 6: AVAILABILITY OF DIAGNOSTIC TESTS

Transfer of patient material is indeed critical for optimal management, as diagnostic tests are often non-routine and available in only a limited number of centers. This is generally ensured by express mail delivery either of fresh blood (within 1 day) or frozen specimens (within 5 days on dry ice); the costs being handled either by the physician caring for the patient, or by the team which is consulted for its expertise. There are also considerable costs related to performing the test itself, which is generally not reimbursed by social security

systems within MS. The problem of specific diagnostic tests is closely related to the concept of **centers of reference**; a more systematic approach to designating such centers and would help resolve some of the difficulties related to sample shipment and handling. Part of the financial support to such centers could be specifically allocated to sample handling for diagnostic purposes.

QUESTION 7: EU LEVEL ASSESSMENT OF POPULATION SCREENING

We would suggest that this initiative be left to experts for each rare disease; if a panel of experts for a given disease find that population screening is feasible given the development of a reliable diagnostic test that is not harmful, and that it is worthwhile, it is up to them to approach EU authorities in that regard.

QUESTION 8: ACCESS TO ORPHAN DRUGS

Access to orphan drugs is an issue that should be regulated at the EU scale, to overcome existing heterogeneity among and within MS. Currently, there are significant and unacceptable inequalities in delivery of orphan drugs. (see response to question 4)

However it is important to keep in mind that in-depth knowledge on such drugs and the rare diseases that may benefit from their administration is not wide-spread; delivery should be entrusted to highly qualified centers (issue of centers of reference).

QUESTION 10: SOCIAL AND EDUCATIONAL SERVICES FOR RD PATIENTS AND FAMILIES

Access to compassionate use programs is essential for optimal management of rare diseases, and the current evolution in this respect has been extremely pejorative for such patients; access to expensive molecules through compassionate use programs has actually become more difficult in the past 2 years. It is unconceivable that while progress is being made in understanding pathogenic mechanisms, access to treatment is decreasing (this is clearly the case in Belgium). The approach to **compassionate use programs** does indeed require close interactions between MS and the EU. The possibility of providing support to patients and industry for delivery of therapeutic compounds that are not reimbursed differs among MS (for example, in Belgium, the situation is evolving towards quasi-systematic rejection by pharmaceutical industry of requests for compounds on a compassionate basis; whereas in France, such compounds are delivered provided a board of adequately selected specialists deems there is sufficient rationale to administer such a molecule in a given clinical situation); intervention at the level of the **EU** is necessary to homogenise access to compassionate use programs.

Educational services such as **help-lines** are extremely useful for rare disease patients and their families, and a national approach is preferable for reasons of “proximity” (more reassuring, less intimidating), language, provision of very practical information on what is available locally in terms of appliances, medical assistance, social services, etc… Organisation and action should be national efforts, adapted to the MS population, with logistical support from the EU.

QUESTION 11: MODEL OF GOVERNANCE AND FUNDING FOR REGISTRIES, DATABASES AND BIOBANKS

In the field of rare diseases, merging of patient data from multiple centers is critical in order to overcome the inevitable referral bias and to have a representative overview of disease presentation and natural disease course. This is a critical first step for optimal biomarker assessment and assessment of response to therapy. Although careful elaboration of multi-disciplinary consortia for creation of rare disease clinical research centers may allow for data collection on a more representative patient cohort, optimal management of databases is in itself a very time-consuming endeavour that requires hiring and training of dedicated personnel (data managers) in each of these CRC. Fragmented efforts across Europe by each rare disease consortium could advantageously be replaced by creation of a centralised European data coordinating center for rare diseases, wherein professionals in data management would elaborate and manage databases, websites (see response to question 5) etc… in close collaboration with all concerned clinical research centers. European funding for rare diseases could contribute to mounting and managing a **centralised data coordinating center**.

In North America, the ORD launched a RFA on rare diseases in 2003; resources were allocated in part to support for a limited number of Rare Diseases Clinical Research Centers, and in part to creation of a unique Data and Technology Coordinating Center (DTCC) which is based in one State. The DTCC combines experts in data base management and computational science, and provides a coordinated clinical data management system for collection, storage, and analysis of data emerging from the research centers; it also manages a web-based resource site on rare diseases for physicians, patients, and research scientists.

QUESTION 12: ROLE OF PARTNERS IN EU ACTION ON RARE DISEASES

The contribution of industry to activities related to rare diseases depends on the nature of these actions. There is little room (and interest) for industry in fundamental research on rare diseases, although these efforts may eventually lead identification of pathogenic pathways that could be targeted by therapy. Biomarker development and assessment remains in our eyes an academic endeavour, preferably in the setting of multi-national consortia for reasons developed in the present EU document (recruitment of a sufficient patient cohort to draw representative conclusions on the value of a given biomarker etc…). Industry should have little to do with this, during development in any case. The same holds true for development of patient registries and databases. **Charity** may contribute to such actions, generally in the form of punctual funding with well-defined resources, to address a very specific question, which can be tested in a well-defined patient cohort.

Investigator-based clinical trials on rare diseases, supported by **industry**, are a means through which physicians can make expensive compounds available to their patients. For example, if there is rationale for evaluating an existing molecule as a treatment option for a rare disease despite the fact that it is not reimbursed in this setting, industry can agree to provide the molecule free of charge to investigators if they set up a meaningful clinical protocol. Patients (through their health insurance) and investigators handle costs related to testing, visits, etc… and industry handles costs related to delivery of the molecule. Thus, for clinical trials, participation of industry should be encouraged, provided physicians and academic centers offer the rationale, patient care, follow-up, and reporting in medical literature.

QUESTION 14: EUROPEAN AGENCY ON RARE DISEASES

Yes; the rationale is very well developed in the text issued for the present public consultation.