Novartis Response to the Commission Consultation

"Rare Diseases: Europe's Challenge"

A Introduction

As a Swiss company operating globally out of Europe, Novartis employs more than 100,000 people, half of them in Europe. Novartis is committed to working with the institutions in the European Union to support policies and actions that improve healthcare.

Novartis pursues a balanced development portfolio of products in broad and specialized disease areas, including rare diseases. The Pharma Division of Novartis currently holds 22 EU designations for orphan medicinal products, including 2 marketed products. The Generic Division, Sandoz, is a global leader in delivering generic medicines to patients that include state-of-the-art biosimilars. Novartis is, therefore, in a unique position to present a cross-industry perspective.

Novartis' commitment to rare diseases is exemplified by its role as an active member of the joint task force on rare diseases and orphan medicinal products of the two associations EFPIA-EBE and EuropaBio. In addition, Novartis actively supports Eurordis' roundtable for companies engaged in the orphan drug field and holds one of the three industry seats at the COMP Working Group of Interested Parties.

Rare diseases pose a particular public health challenge to governments because the incidence of individual diseases is low. Only a few member states have established specific health policies in this area: France recently launched a national plan for rare diseases[1] and several member states have implemented national rare disease research programs. The lack of consistency across the EU in the way rare diseases are managed emphasises the need to make rare diseases a greater priority to keep them high on the political agenda of the community.

Rare diseases have traditionally been of ethical, but limited commercial interest to pharmaceutical companies on the basis that it would be impossible to recover research and development costs based on the small number of people for whom a treatment would be applicable. However, the introduction of the 'Orphan Drug Regulation'[2], facilitated the engagement of the pharmaceutical companies due to the provision of various incentives. Furthermore, investigation of rare diseases contributes to the wider field of drug development since they have the potential to provide models to elucidate disease pathways shared by rare and more common diseases.

Novartis is pleased to have the opportunity to respond to this public consultation addressing an issue of critical importance to drug development strategies for the future. We hope that its outcome will result in actions which ensure that there are opportunities for research into causal mechanisms of rare diseases and equitable access to diagnosis and care for all European citizens.

[1] French National Plan for Rare Diseases 2005 – 2008 "Ensuring equity in the access to diagnosis, treatment and provision of care"

[2] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

B Summary

- People affected by rare diseases should not experience worse healthcare simply because the illness from which they suffer is rare. Variations in access to effective treatment and care result in unacceptable health inequalities across Europe.

- Early and accurate diagnosis of rare diseases is critical and should be a priority for any EU activity. Classification and coding of rare diseases must be improved and harmonised and quality standards for all forms of diagnostic tests implemented.

- Accelerated access to orphan medicinal products which are approved by the EMEA based on their proven clinical benefit and established medical need is paramount for patients in need.

- The current EU definition of a rare disease remains appropriate and steps should be taken to ensure it is applied across Europe and potentially globally.

- Industry is an important stakeholder in this field and should be an equal partner of multi-stakeholder processes.

- Patients should be supported by ensuring easy access to information about their diseases, potential treatment and existing centres of expertise.

- A European Research Foundation for Rare Diseases should be established as a means of increasing focus on and improving coordination of research and development initiatives in the area of rare diseases.

C Answers to the Commission's Questions

Q1 Is the current EU definition (less than 5 per 10 000 persons in the European Union) of a rare disease satisfactory?

The current definition is satisfactory, and it is important that it is applied across Europe; the current variations which occur should be addressed.

Ideally there would be a globally harmonized definition of rare diseases. This would offer the advantage of providing a similar basis for research and development efforts. Such a global definition should follow the European model using a number of affected persons relative to the overall population. Other models, using an absolute number, are less flexible since they cannot adequately reflect changes in population size.

Novartis would encourage the European Commission to maintain a dialogue with the NIH Office of Rare Diseases in the US and regulatory bodies in Japan and Australia with the aim of harmonising the definition.

Q2 Do you agree that there is a pressing need to improve coding and classification in this area?

We agree that there is a need to improve coding and classification in particular in the area of rare diseases, because accurate coding and classification of rare diseases is important to ensure their reliable and timely diagnosis. More and accurate data will provide a greater understanding of the aetiology and natural history of these diseases and will benefit currently affected and at-risk individuals.

Coding and classification should not only improved but need also to be harmonised among the member states and even globally. This can be achieved by close collaboration between regulatory authorities of the EU and other regions as well as the World Health Organization (WHO). Such a collaboration can for instance help to identify therapeutic areas, where specific classification is still missing, such as for rare tumours. The fact that coding and classification of certain rare diseases are missing causes even sometimes difficulties for the designation of orphan medicinal products.

Changes to the coding/classification of diseases during the drug development process may adversely affect bringing a drug to market since existing data may not satisfy the regulatory process and new data may need to be created – with considerable difficulty - at a very late stage in the process. Therefore, suitable conditions for a transition should be defined.

Coding and classification does not only affect diseases, but also diagnostic assays, which need to be equally available and standardised, with the appropriate quality standards in place.

Q3 Can a European inventory of rare disease help your national/regional system to better deal with RD?

As a pharmaceutical company we wish to comment on the issue of a European inventory although the question as posed appears to apply to healthcare providers.

There are particular issues in rare diseases which impact on the care of people affected. There is often insufficient knowledge and experience about rare diseases among the medical profession, frequently leading to the lack of a formal diagnosis. An inventory of rare diseases will help improve both the understanding of the area and the diagnosis of affected individuals. A useful inventory implies that it is based on harmonised and standardised data fields and that it will regularly and systematically be maintained to ensure the database validity.

Orphanet has already established a searchable database of clinical symptoms and provides a valuable resource. Funding for Orphanet should be confirmed with additional resources provided to allow the dictionary of rare diseases to be translated into all EU languages and provided in a download-version (PDF) to make it accessible across all member states. Consideration should be given to Orphanet's possible role in developing and hosting an inventory. In addition, making more use of initiatives running in parallel in the EU, the linking of available databases, such as national cancer databases and the inventory of therapeutic needs for the paediatric population, should be envisaged.

Q4 Should the European Reference Networks privilege the transfer of knowledge? The mobility of patients? Both? How?

Novartis is in complete agreement that there is a need to improve the prevention of rare diseases and the diagnosis and care of those already affected. We recognise that this requires centres of excellence which concentrate knowledge and expertise about these diseases in one place. These centres should exchange knowledge among them and should establish national contact and advisory points for patients as well. (We would also make the point that this is no different to common diseases, where better outcomes are achieved when there is specialist expertise in managing the disease.)

We would wish to see consistency across Europe in the definition and balanced distribution of centres of excellence across Europe to facilitate access to medical expertise by all affected individuals. Patient mobility is essential to allow patients with rare disease to obtain the best possible medical care in a field where medical expertise is scarce. This requires agreements to be in place to ensure cross-border access to all health care.

We have already commented on the value of Orphanet and the need for continued financial support for the network (refer to Q3). Novartis believes that the focus should be on knowledge transfer, which takes into account delivery of high-quality information on diseases and available diagnostics and therapies to patients. To be of value for patients in different member states, it would be useful to have the resources produced by Orphanet available in all official European languages.

Q5 Should on-line and electronic tools be implemented in this area?

There is considerable scope for the use of modern technology to support activities in rare diseases. For healthcare professionals this includes detailed information on centres of excellence and reference networks, databases, and information. For patients and their informal carers, this will include information on the disease and treatments and access to support groups and acknowledged centres of excellence. For those struggling to obtain a diagnosis or access to expert care, electronic information can be a vital tool.

Such electronic tools should be readily accessible and understandable by lay people as well as ensuring data privacy and patient confidentiality. Therefore the involvement of patient organisations should be considered in developing electronic tools.

As already mentioned under Q3, we would like to stress that electronic tools require the definition and application of harmonised standards for the data fields and some quality assurance measures to allow high data quality and pan-European exchange of data as well as systematic maintenance to ensure their utility and accuracy.

Q6 What can be done to further improve access to quality testing for RD?

There is a well established EU-wide regulatory framework for clinical pathology testing for rare diseases provided by the Medical Devices Directive. Co-operation between centres of excellence exists, but this is currently on a voluntary basis. Consideration should be given to establishing a centrally funded framework on quality testing, which coordinated at EU level. The participation in this framework should be mandatory to all reference centres.
There is no similar quality programme applied to genetic testing; this should be rectified.

Q7 Do you see a major need in having an EU level assessment of potential population screening for RD?

Novartis would wish to see the Wilson and Jungner framework for evaluating screening tests, produced for the World Health Organization WHO in 1968 (see Appendix), applied to population testing for rare diseases before any decision is made.

Any population screening program would be implemented at a national level and the principle of subsidiarity would apply. There is clearly a need for sharing expertise across Europe on issues such as population screening.

Q8 Do you envisage the solution to the orphan drugs accessibility problem on a national scale or on an EU scale?

Combined efforts at both the national and EU level are needed to ensure patients with rare diseases have equal access to treatment and prevention.

Medicinal products, which have been designated as orphan medicinal products, are in the mandatory scope for registration via the centralised procedure. Centralised marketing authorisations approved by the EMEA are immediately valid in all Member States. These products do not create any disparity for access in the Member States.

Medicinal products, which have not been designated as orphan medicinal products, may be approved via the Mutual Recognition Procedure (MRP), which could lead to delays of access due to different time points of procedure completion at national level.

Another reason for market access delay seems to be the national procedures on pricing and reimbursement which cause post-market authorisation delays .

In order to get more systematic information on access delays, we believe there could be value in a two yearly reporting by the Commission to the Council on access issues for orphan drugs with recommendations for any necessary legislative modifications in order to guarantee equal access to orphan drugs throughout the EU. This reporting should be based on a broad consultation with physicians, patients, industry and other relevant stakeholders. To ensure a balanced view the Working Group of Interested Parties at the COMP should support this process.

Novartis would wish to see the transparency directive applied in relation to access to orphan drugs and some appropriate actions for non-compliant member states.

Possible solutions for addressing the access problem include:

- In line with the intention to accelerate the regulatory assessment and approval of orphan drugs through the centralized procedure, products designated as OMPs should automatically qualify for accelerated pricing and reimbursement assessment;
- Fast track assessments for pricing and reimbursement of OMPs should be complemented by mechanisms for ensuring fast implementation of positive P&R recommendations;
- Considering a two step reimbursement process with an obligation to deliver proof of a predefined set of data a certain number of years after launch, since the limited clinical data in rare diseases makes health technology assessment difficult. This approach could be linked to the rarity of the disease;

We encourage exploring additional incentives at national or European level to strengthen research into rare diseases and development of orphan medicinal products, and Member State familiarity with these products (for example, the granting of priority review of marketing authorisation applications).

Q9 Should the EU have an orphan drug regulation on medical devices and diagnostics?

We would preface our comments by acknowledging that currently Novartis does not have any medical devices or diagnostics for rare diseases. Nevertheless, we take the view that in light of the importance of accurate diagnosis for patients with rare diseases, there is a case for orphan regulation on medical devices and diagnostics. The regulation on orphan medicinal products implemented in 2000 was very successful in stimulating the delivery of more innovative products to patients suffering from rare diseases.

We are not aware of any particular issues in relation to medical devices but we would propose that the regulations in this area should replicate those applied to orphan medicinal products.

Q10 What kind of specialised social and educational services for RD patients and their families should be recommended at EU level and at national level?

The impact of rare diseases is huge both on the patient and their informal carers. Because the diseases in question are rare, they are particularly isolating: there may be no other affected families nearby. Furthermore, the challenges faced with rare diseases may be both physical and mental and may require adjustment to both the educational setting and the home and society overall. For this reason, social and education support services are crucial.

Novartis agrees that resources should be provided to support such activities. We believe that the actual requirements should be defined by affected individuals, their informal carers and the health professionals looking after them. We applaud the work done by patient organizations in general – and Eurordis in particular - in elaborating the support needs of patients and their informal carers and believe that the organization has a central role to play in ensuring that any EU action is appropriate.

The private sector can offer a significant contribution to delivering educational services to the rare disease community, because a pharmaceutical company developing a treatment will have expert knowledge about the given disease.

Q11 What model of governance and of funding scheme would be appropriate for registries, databases and biobanks?

Novartis believes that biobanks, registries and databases are all essential for the development of innovative treatment approaches in rare diseases.

As a company developing new treatments, timely identification of individual patients affected by rare diseases is essential in order to carry out clinical trials. A major challenge with rare diseases is identifying enough patients to complete a clinical development program. Early-onset clinical trials have the potential to bring new, not fully tested treatment options to patients who have no alternatives available. They can also reduce the time which is needed to bring innovative therapies to the patient community as a whole.

Shortening the process of identifying study participants is also an important factor in the decision matrix of every private company and a very real incentive to pursue the development of orphan medicinal products. This can greatly be facilitated by access to registries of affected individuals (e.g. via 3rd parties or a European Research Foundation for Rare Diseases in order to respect data privacy rules). Registries also provide a mechanism for maintaining comprehensive records on a large number of affected people. Although some rare diseases have been well studied and their natural history is established, EPPOSI (European Platform for Patient Organisations, Science and Industry) estimates that around 5 or 6 new diseases are described each month, reinforcing the need to collect information on affected individuals to elucidate the manifestation of the disease.

Scientists in private companies must – like their colleagues in academia - be able to access biological materials on which to test molecules in development. To do this efficiently they must have access to a ready source of samples: it is time consuming and expensive and unnecessarily invasive for patients if scientists have to start by searching for affected individuals every time there is a new concept to prove. Biobanks provide this resource and although there must be checks and controls in place to ensure that materials are used appropriately – including guarantees for confidentiality of patient data - they offer the only opportunity to progress development of new chemical entities in a timely fashion.

Informed consent is a central issue and must be given due regarding in the development of registries, databases and biobanks. This is particularly relevant where consent may be given for use of patient materials which is as yet unspecified. A number of ethics guidelines for the use of human tissue have been developed and these should be adhered to. There may be a central role for the EU to ensure that high standards for informed consent are applied across Europe.

Funding for registries, databases and biobanks must be sustainable. They cannot depend on the political inclinations of public bodies for funding, and they must not depend solely on industry funding. It is inappropriate for data and samples to be 'owned' by individual institutions – whether it is academia or pharmaceutical companies - and withheld from other legitimate researchers. At the same time it is inappropriate for effort to be duplicated unnecessarily and we see value in the pooling of expertise in a single body which would have responsibilities for registries, databases and biobanks. As described later, a European Research Foundation for Rare Diseases would provide an appropriate host for these functions.

Q12 How do you see the role of partners (industry and charities) in an EU action on rare diseases? What model would be the most appropriate?

Novartis believes that industry and charities have a vital role to play in the development of an EU action on rare diseases, because they are united in ensuring that patients have access to early diagnosis and effective treatment. Building awareness of symptoms and treatments of rare diseases among patients and physicians is a critical first step in ensuring diagnosis and effective treatment. Eurordis has made a major contribution to awareness of rare diseases and has developed a model for industry and charities to work together through its roundtable for companies engaged in the orphan drug field.

In all multi-stakeholder efforts industry should be included as a respected partner with a broad variety of expertise, products and services – like information on diseases and treatment

options – to offer. Whenever complex issues are addressed - such as the development and validation of biomarkers – broad stakeholder involvement should be through well-defined consortia. Specific public-private partnerships to tackle several questions on rare diseases (similar to the Innovative Medicines Initiative) may facilitate research, development of and also easier and faster access to new effective and safe medicines in Europe.

Q13 Do you agree with the idea of having action plans? If yes, should it be at national or regional level in your country?

We have seen value in action plans in other therapeutic areas. We would wish to ensure that action plans or other strategic approaches to the management of rare diseases should be developed with proper consultation of all stakeholders. Such action plans should be at national level to reflect subsidiarity. There may be value in providing central guidance on the components and standards of a national action plan and follow-up of achievements on an EU level.

Q14 Do you consider it necessary to establish a new European Agency on RD and to launch a feasibility study in 2009?

Novartis does not see the need for a new agency: we believe that the existing structures have the knowledge, experience and expertise to progress any actions agreed as a result of this consultation.

Novartis does, however, see potential value in the development of a European Research Foundation for Rare Diseases. The aims of a European Research Foundation for Rare Diseases should include:

- Pooling of the wide-spread central funding efforts of the European Union for rare diseases to allow more rational and aligned budget decisions
- Initiation and support of cutting edge biological research to discover the causes of the diseases, find and improve methods of prevention and develop more effective diagnostic approaches and new treatments
- Initiation and support for the set-up and maintenance of pan-European patient registries, natural disease databases and networks of excellence
- Support and advice for Member States in the set-up and implementation of national action plans on rare diseases
- Regular organization of international conferences, workshops and congresses on rare diseases
- Consultative status to the European institutions, including high-level scientific and policy support in international harmonization efforts

The European Research Foundation for Rare Diseases would have a range of diverse teams, with the scientists investigating all aspects of the disease process, from understanding the genetic changes to the range of phenotypes which might arise from these changes and the different treatment strategies that are needed.

We believe that such a research foundation is best achieved by a governance structure that includes all interested stakeholders, including people affected by rare diseases.

We would suggest that the Commission uses the opportunity of a conference on rare diseases in September 2008 in Paris to dedicate a multi-stakeholder workshop on this topic. If deemed

useful, Novartis would be happy to support such a workshop by bringing our international expertise to an organizing committee.

The proposal for a European Research Foundation for Rare Diseases may copy aspects of the approach taken in the US:
In the US the National Institutes of Health created in 2003 the Rare Diseases Clinical Research Network (RDCRN) to increase collaboration and critical resources related to diagnosing and treating rare diseases. The network consists of ten consortia along with a Data and Technology Coordinating Centre with funding of $7.1 million. The RDCRN is funded by a range of government organisations; there is no public acknowledgement of private funding.

The RDCRN is coordinated primarily by the National Institutes of Health's Office of Rare Diseases and the National Centre for Research Resources. The first clinical studies were launched in 2006 in the US and in several other countries including Canada, the UK and Japan. Included are interventional trials to test new therapies or drugs, as well as longitudinal or natural history studies that will provide information about the characteristics of rare diseases and their progression over time. The data produced will be made publicly available with appropriate safeguards for patient confidentiality.

The RDCRN will investigate a variety of diseases, but not all rare diseases. The consortia are organised around themes, such as the Bone Marrow Failure Disease Consortium and the Rare Genetic Steroid Disorders Consortium. Each consortium in the network includes active participation by the relevant patient advocacy groups. In addition, the Coalition of Patient Advocacy Groups (CPAG) was created to represent the more than 30 patient advocacy groups involved in the network.

However, the Novartis proposal for a European Research Foundation for Rare Diseases goes further than the RDCRN as it is not focused on clinical research alone, but on all aspects of R&D for rare diseases and is a multi-stakeholder approach.

Appendix: **Wilson and Jungner criteria for screening**

- Knowledge of disease:
  - The condition should be important
  - There must be a recognisable latent or early symptomatic stage
  - Natural course of condition, including development from latent to declared disease, should be adequately understood
- Knowledge of test:
  - Suitable test or examination
  - Test acceptable to population
  - Case finding should be continuous (not just a "once and for all" project)
- Treatment for disease:
  - Accepted treatment for patients with recognised disease
  - Facilities for diagnosis and treatment available
  - Agreed policy concerning whom to treat as patients
- Cost considerations:
  - Costs of case finding (including diagnosis and treatment of patients diagnosed) economically balanced in relation to possible expenditures on medical care as whole