The EUROPEAN COMMISSION
DG Health and Consumer Protection
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Thank you for giving us the opportunity to join the debate on "Rare Diseases" through your public consultation.

We would like to contribute on the definition of rare diseases with particular regard to rare tumours, and on the issues related to this definition. We have assembled a group of experts in this domain to work on the RARECARE project for the surveillance of rare cancers in Europe. RARECARE is funded by the European Commission.

The current definition of a "rare" disease is based on prevalence: a disease with fewer than 50 persons currently affected per 100,000 population. This definition is used for rare diseases in general in Europe and is considered valid for rare tumours. In the USA, the corresponding threshold for "rare" tumours is 75 per 100,000.

Prevalence has shortcomings as a measure of rarity for tumours, although we acknowledge its appropriateness for non-neoplastic diseases. Many of these are chronic conditions, so prevalence, which reflects the total number of cases at any given time in a population truly renders the burden that a disease poses at a population level. On the contrary, tumours are subacute diseases in which everything tends to happen once. By and large in the natural history of a tumour, there will be one potentially eradicating surgery, one local radiation therapy, one first-line chemotherapy, one terminal phase, etc., and each of these will take place in definite time intervals. Incidence, which reflects the yearly number of new cases occurring in a population might thus be a better indicator to describe the burden posed by a tumour. We may view this issue under the main perspectives which make rare tumours a problem. From the perspective of clinical research, it is the small number of cases with a given clinical presentation at a certain time which limits the number of eligible patients for clinical trials (e.g. the annual number of cases undergoing surgery for localised disease, etc.). From the perspective of clinical decision-making, it is the limited number of cases with a given clinical presentation which affects the expertise which a physician or a cancer centre can accumulate in a reasonable time-span (e.g. the annual number of patients eligible for surgery, etc.). That is why we would prefer to advocate incidence as the criterion on which to determine "rare" disease status, at least for malignant disease.

The prevalence of a disease depends on two time-dependent characteristics which are completely independent of one another: incidence and survival. With the prevalence threshold adopted as a definition by Europe, some commonly-occurring diseases for which the survival is very poor, such as most cancers of the stomach, pancreas, oesophagus, head and neck, liver and brain, and the leukaemias, will nevertheless be defined as rare on the basis that the proportion of the general population at any one time who are survivors of that disease is very low. By contrast, some neoplasms that occur very infrequently ("rare" in the sense of incidence) but which have very good survival, such as cancers of the testis and thyroid, and Hodgkin's disease, will be defined as common on the basis of prevalence, because although they occur infrequently, most people who develop the disease survive for long periods. Since it is rarely possible for a cancer survivor to be declared as cured, most cancer patients who survive are considered to remain prevalent cases. If we consider prevalence as the "pool" of survivors who have had the disease at any time in the past, then prevalence can be markedly affected by recent trends in either incidence or survival. By contrast, the incidence of tumours tends to change in a more predictable manner. It is more closely connected both to the cause of the disease and it is a direct measure of the public health burden imposed by the need for first-line treatment of patients diagnosed with the

disease each year.
For what it is worth, incidence (rather than prevalence) is also one of the numerical criteria used by the pharmaceutical industry to determine priorities for research into drug development. That takes on a particular significance in the light of the EU's new Innovative Medicines Initiative to spend one billion euros over the next seven years in developing new drugs.

The RARECARE project has among its aims to provide an operational definition of "rare cancers", and a list of cancers that meet this definition. We are working on this and we will provide both the definition and list by the end of May. For all the rare tumours identified, important indicators of burden of the disease like incidence, prevalence, survival and mortality will be estimated and provided as major results of the project. We hope these results will convince the European commission to adopt a different definition for rare tumours.

Yours sincerely
The RARECARE project leader* and partners.

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