

ROLE OF SOCIETY IN MANAGING RARE DISEASES

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Introduction

Western civilization has developed a strong notion of equity in seeking to treat diseases, even rare diseases which by definition afflict only small defined populations.

The following 4 quotes underlie the philosophical basis and provide legislative and economic justification for the development of diagnostic and therapeutics:

1. *"Patients suffering from **rare conditions** should be entitled to the **same quality** of treatment as other patients."¹*
2. *"Some promising **drugs will not be developed** and it is in the public interest to provide such changes and incentives for the development of orphan drugs."²*
3. *"It is my opinion that those who first called this **disease 'sacred'** were the sort of people we now call **witch doctors, faith healers, quacks and charlatans**"³*
4. *"What escapes our vision we must grasp by **mental sight**, and the physician, being unable to see the nature of the disease nor to be told of it, must have recourse to **reasoning from the symptoms** from which he is presented."⁴*



In this paper, I highlight some legislative mechanisms which have been developed in the European Union, United States of America and Australia to enable the introduction of medicines to treat patients with rare diseases and the underlying philosophical foundation enshrined in Western civilisation's heritage.

Rare diseases

It is widely estimated that there are between 5,000 and 8,000 distinct rare diseases, affecting 6% to 8% of population.

The greater majority of rare diseases appear during adult life, although some diseases commence at child birth.

The predominant cause is genetic, though foreign agents such as viruses are found to play an emerging more significant role.⁵

Cost to develop medicines

It is widely acknowledged that the cost of developing medicines in almost US 1.2 billion.⁶ The combination of high risk and reward (which is being reduced) and reduced productivity has lead Europe and the United States of America to develop defense mechanisms to ensure treatment for rare diseases does not become an early casualty.

In addition, the level of regulatory scrutiny placed on developing large population medicines and also the cost effectiveness of niche (orphan) drugs is the key indicator used in these 3 jurisdictions when deciding on the funding of medicines. The inherent dilemma with orphan drugs is that:

- they are expensive to produce
- benefit only small number of patients
- trials occur on statistically insignificant patient numbers
- trial design poor due to small patient pool

Given this reality, should the cost-effectiveness of orphan drugs be treated differently from other drugs and interventions?

Orphan Drugs

Orphan drugs are drugs which treat defined populations (typically small) and designated as such pursuant to legislative authority.

Commercial drivers for developing orphan drugs have been created (and I believe are far from a mature state) and have resulted in the marketing of over 300 medicines to treat rare diseases in the last 2 decades. There is also a strong emerging trend, based on the number of orphan designations, which demonstrates that in the coming decades the number of orphan drugs will increase substantially.

The next portion of this report will comment on the legislative mechanisms in the European Union, the United State of America and Australia to facilitate the commercialisation of orphan drugs.

The European Union

On 16 December 1999, Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products was enacted.

The criteria for designating orphan status is described in Article 3, is as follows:

Criteria for designation

1. *A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:*

(a) *that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than **five in 10 thousand persons** in the Community when the application is made, or*

*that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that **without incentives it is unlikely** that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;*

and

(b) *that there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.*

Article 4 creates the administrative committee, the COMP (Committee of Orphan Medicinal Products) and Article 5 provides for the Community Register for Orphan Medicinal products.⁷

Tied in with this authority is the European Union's Seventh Framework Programme for Research and Technological Development (FP7, 2007-2013) that aims to boost specific fields of research.⁸

The incentives provided to developers of orphan drugs are:

- *protocol assistance*
- *10-year marketing exclusivity*
- *fee reductions or exemptions*
- *R&D into rare diseases*

Since 1 January 2007, orphan medicinal products are eligible for the following level of fee reductions:

- *100% reduction for **protocol assistance***
- *100% reduction for **pre-authorisation inspections***

- 50% reduction for *new applications for marketing authorisation*
- 50% reduction for *post-authorisation activities*, including annual fees

The funds made available by the Community for fee exemptions for orphan medicinal products amount to €6,000,000 in 2007.

At present, there are 459 orphan drug designations by COMP-EMA for more than 200 diseases and 35 orphan drugs authorised for the European market.⁹

An example of a recent marketed orphan drug is 04/01/2007 DIACOMIT Stiripentol (INN) Treatment of severe myoclonic epilepsy in infancy, by French company Biocodex.

An example of a recent orphan designation is PI-88 for the treatment of pancreatic cancer, by Australian company Progen.

The United States of America

The country's reason for developing orphan drug legislation is best described by the following statements from Congress:

The Congress finds that---

- *adequate drugs for many of such diseases and conditions have not been developed*
- *because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss;*
- *there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs; and*
- *it is in the public interest to provide such changes and incentives for the development of orphan drugs.*¹⁰

The mechanisms are found in the *Orphan Drug Act* 1983, which is administered by the Office of Orphan Product Development, created within the FDA. The prevalence threshold is as follows:

1. *Affects < 200 000 individuals in the USA*
2. *Affects > 200 000 individuals in the USA without it being possible to cover the cost of development and distribution by sales on national territory*

The incentive for the drug developers are as follows:

- *Pharmaceutical, biological, medical devices, dietary of diet products*
- *50% tax credit* on clinical trials undertaken in the USA
- *reduction* of waiting period and registration fee
- exempt from FDA *user fees* and can apply for exemption of annual fees
- *market exclusivity* – 7 years after marketing approval is granted
- *assistance* by the FDA defining trials to be undertaken to register the new drug

The results of the legislation may be assessed as follows:

- 1730 total Orphan designations
- 309 Orphan Designations that have received marketing approval
- 61 Orphan Designations 2007
- 11 Orphan Designations in 2007 that have received Marketing Approval

An example of a recent marketed orphan drug is Doxorubicin liposome injection (for use in combination with bortezomib for the treatment of patients with multiple myeloma who have not previously received bortezomib and have at least one prior therapy), by US company Johnson & Johnson Pharmaceutical.

An example of a recent orphan designation is Cetuximab (Erbix) for the treatment of pancreatic cancer, by US company ImClone Systems Inc.

Australia

Australia does not have a formal orphan drug management system. It has developed a very simple orphan designation process and thereafter review and treatment of registration and reimbursement applications are not differentiated from non orphan drugs.

The Therapeutic Goods Administration manages the orphan designation process and works closely with the US FDA. An orphan designation enables a subsequent registration review to be fee free.

The *Therapeutic Goods Regulations* 1990, Regulation 16H states:

- (1) *A medicine, vaccine or in vivo diagnostic agent is an orphan drug if it complies with this regulation.*

- (2) *It:*
- (a) *must be intended to treat, prevent or diagnose a rare disease; or*
 - (b) *must not be commercially viable to supply to treat, prevent or diagnose another disease or condition.*
- (3) *It is not an orphan drug if any of the following persons or bodies has refused to approve it for use for the disease for a reason related to the medicine's safety:*
- (a) *the Secretary;*
 - (b) *the Food and Drug Administration of the United States of America;*
 - (c) *the Medicines Control Agency of the United Kingdom;*
 - (d) *the Bureau of Pharmaceutical Assessment of Canada;*
 - (e) *the Medical Products Agency of Sweden;*
 - (f) *the Medicines Evaluation Board of the Netherlands;*
 - (g) *the European Agency for the Evaluation of Medicinal Products.*

The definition for "rare disease" means a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time.

There exists another process, termed the Life Savings Drug Program ('LSDP') which is very difficult to receive and is based on the Federal government finding funding on an individual basis.

The orphan drug Aldurazyme (that treats a mucopolysaccharidosis type 1 (MPS1), an extremely rare enzyme deficiency disorder which affects many body functions. There are 8 to 12 people that will be treated in the first few years of funding, having allocated AU \$16.4 million over four years.

The only other drugs which have received such discretionary funding are

- Cerezyme is used for the treatment of Gaucher disease
- Fabrazyme and Replagal for Fabry disease
- AU \$30.8 million was provided in 2005-06

The results of the legislation may be assessed as follows:

- 131 Orphan designations

- 14 Orphan Designations in 2007

An example of a recent marketed orphan drug is Adefovir dipivoxil, to be used in monotherapy or in combination with other therapies, for prevention of recurrence of HBV infection in liver transplant recipients, by US company Gilead Sciences Pty Ltd. An example of a recent orphan designation is COMBIVIR for the treatment of HIV infected children < 12 yrs of age, by UK Company, GSK.

Hippocrates

I believe that Hippocrates, in his recorded writings, demonstrate his life's practice and critical observation of rare diseases and has developed a 2 step mechanism, as follows:

- to differentiate the rationale to develop scientific and evidence based steps; and
- to apply his new reasoning to all diseases, irrespective of previous social stigma

I believe this conceptual leap in rationale has lead to the Western philosophy of constant innovation to find a solution, irrespective of the advocacy of 'sacred disease' status of the mass population of the day.

Conclusion

The treatment of rare diseases has become a central idea of Western civilization and the relationship between healer and patient.

I believe there is still substantial evolution needed in the European Union, United States of America and Australia to enshrine a mechanism, which are equitable and commercially viable to enable the development of innovation, which will inevitably challenge the 'healer' to look beyond the diseases that can be managed by sight, to those classified by Hippocrates as 'internal diseases' and heal the afflicted patients.

NOTES

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1. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 Recital.
2. The Orphan Drug Act (as amended). <http://www.fda.gov/orphan/oda.htm>
3. Hippocratic Writings. Medicine – The Sacred Disease. Translated by J. Chadwick and W.N. Mann. Penguin Books, 1986. page 237.
4. Hippocratic Writings. Medicine – Tradition in Medicine. The Sacred Disease. Translated by J. Chadwick and W.N. Mann. Penguin Books, 1986. page 145.
5. European Medicines Agency media release entitled “Orphan drugs and rare diseases at a glance” dated 3 July 2007.
6. The Tufts Center for the Study of Drug Development Impact Report, November /December 2006.
7. <http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm>
8. http://ec.europa.eu/research/fp7/index_en.cfm
9. <http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm>
10. The Orphan Drug Act (as amended). <http://www.fda.gov/orphan/oda.htm>