

ECONOMIC EVALUATION AND FINANCING OF ORPHAN DRUGS

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and on a posterior article by some of the participants at the workshop:

DRUMMOND, M. F. ; WILSON, D. A. ; KANAVOS, P. ; UBEL, P. ; ROVIRA, J. Assessing the economic challenges posed by orphan drugs. *International Journal of Technology Assessment in Health Care*, 2007, vol. 23, núm. 1, p. 36-42.

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OBJECTIVES

The objectives of this presentation are

- (i) to discuss whether the standard methods of HTA are adequate for assisting decisions concerning orphan drugs
- (ii) whether the present arrangements for funding R&D and utilization of orphan drugs as appropriate, and
- (iii) to outline a research agenda.

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Content

- Promoting innovation in rare diseases
- Access and reimbursement
- HTA and orphan drugs
- A research agenda
 - Assessing the societal value of orphan drugs
 - Funding the development and use of orphan drugs
- Conclusions

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PROMOTING R&D IN RARE DISEASES

- Patients with rare diseases have historically been under-served by commercial drug development.
- Many countries or regions address this disparity by means of specific legislation for drugs to treat rare diseases (orphan drugs).
- **OD legislation has successfully encouraged the development of drugs**
- Legislation focus on incentives to foster and reward innovation including grants and tax credits for research and clinical development, reduced fees for approval applications, guarantees of market exclusivity and the promise of fast-track assessments (**supply side/push measures**).

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PROMOTING R&D IN RARE DISEASES

- In the 8 to 10 years preceding the **USA Orphan Drug Act**, **only 10** treatments for rare diseases had been approved by the FDA and brought to market (Haffner 2006).
- In the **24 years since the Orphan Drug Act** was passed in the USA **282 drugs** and biologic products came to market under the legislation.
- **After the first 5 years** (April 2000 – April 2005) of the **orphan legislation in the EU 22 orphan medicines** were authorized from for the treatment of 20 different life-threatening or chronically debilitating rare diseases
- More than 1 million people having the potential to benefit from treatment.

(Report from the Commission of the European Communities 2006)

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ACCESS AND REIMBURSEMENT

- However, **genuine success** in terms of patients with rare diseases realizing increased life expectancy and/or quality of life are **less obvious**.
- Decisions regarding access and reimbursement are taken at national, state, regional and provider levels.
- Several studies have documented the variability and constraints in access to available treatments for orphan diseases.
- **In only 9/25 EU countries were all 10 then approved orphan drugs (ODs) marketed and in only 1/25 countries were all 10 ODs on a national reimbursement list** (noting drugs on these lists are automatically reimbursed).

(Alcimed, 2005)

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ACCESS AND REIMBURSEMENT

- In the UK a survey of orphan disease associations and support groups **in the UK** indicated that, **out of 62 orphan conditions, some form of treatment was available for 38 (69.1%)**. Where a treatment was available, **34.2% of them were provided unconditionally by the National Health Service (NHS)**. In a further 31.6% of cases the treatment was provided selectively by different health authorities. **In the remaining 34.2% of cases no treatment was provided.** (Kanavos and Saka, 2005)
- A survey compared access in Europe to care between countries and between different rare diseases. (EURORDIS 2005).
- **In only 1 of the 26 European countries studied, was there access (in December 2004) to all 12 orphan medicinal products** authorized before December 2003. **In only 34% of the countries (9/26) was there availability for half the products (6/12).**

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HTA AND ORPHAN DRUGS

- **Increasing use of HTA, including economic evaluation**, to assist in decisions concerning P&R of drugs and other health technologies.
- **Concerns about whether HTA based decisions adequately reflect societal preferences for the treatment of serious and/or life threatening rare diseases.**
Underlying **principle of equity** in access to treatment: patients suffering from rare conditions should be entitled to the **same opportunity of receiving treatment** as other patients with more frequently occurring disorders.
- But, how should “same opportunity” be interpreted in practice?

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HTA AND ORPHAN DRUGS

- HTA usually involves an assessment of the incremental cost-effectiveness of the new therapy compared with the existing treatments for the disease in question. UK threshold around £20,000-£30,000 per quality-adjusted life-year (QALY) gained (Rawlins and Culyer, 2004) (Devlin and Parkin, 2004).
- The **incremental cost per QALY of OD is usually very high**, being in excess of ‘standard’ cost-effectiveness thresholds.
- Because of the **small number of persons** suffering from rare diseases, it is often difficult to enroll sufficient patients into a standard RCT =>**limited clinical evidence for orphan drugs**, as compared with those for more common diseases.

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HTA AND ORPHAN DRUGS

- In short, **if standard HTA procedures were to be applied to orphan drugs virtually none of them would be 'cost-effective'**.
- However, modest budget impact (between 0.7% and 1% of national medicine budgets) (Alcimed, 2005)
- Why are supply side incentives to develop OD set up, if they will later be judged by reimbursement criteria on which they are doomed to fail?
- What price rarity? McCabe et al (2005) argue that standard procedures should be applied to all health technologies equally and pose the question

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C/E THRESHOLDS AND BEYOND

- There is more to decision-making than the strict application of cost-effectiveness thresholds (Rawlins and Culyer, 2004)
- Other factors may include (i) the **seriousness** of the health condition (ii) the **availability of other therapies** to treat the disease in question and (iii) the **cost to the patient** if the drug is not listed for public reimbursement, George et al (2001).
- Most orphan drugs exhibit many of the characteristics of these exceptions that funding committees already make: a) they represent the **only therapeutic options** for patients suffering from the diseases in question and b) the **cost of therapy** would be **far beyond the financial means** of most patients if no public subsidy were available c) In 40% of the diseases for which orphan drugs have been approved in the EU there were **previously no satisfactory treatment options** authorized (EC Commission Report).

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NICE REPORT ON SOCIAL VALUE JUDGMENTS (April 2005).

- It found that cost-utility analysis was a necessary, but insufficient, basis for decisions.
- However, NICE needed explicit reasons to recommend interventions with incremental costs per QALY above its normal threshold.
- Rejected reasons: age, social roles (for example, working or not), income, social class, gender, sexual orientation, ethnicity or self-inflicted illness.
- Uncertain position on the Rule of Rescue
- Potentially acceptable: innovations that provide significant improvements in health for previously untreated conditions.

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BEYOND ICER THRESHOLDS

- Departures from the strict cost-effectiveness criteria are **also observed in other fields**.
- Society is prepared to invest vast amounts of resources in rescuing **mountaineers** who encounter difficulties, or those who are **missing at sea**.
- On the other hand, society appears to be reluctant to adopt some policies that will save large number of lives, or would be much more cost-effective, such as road safety measures (Drummond and Shannon, 1986).
- Relevance of **other factors**, beyond cost-effectiveness, in societal decision-making is found in empirical research into individuals' trade-offs between efficiency and **equity** in healthcare provision. (Nord, 1993; Ubel and Loewenstein, 1996).

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A RESEARCH AGENDA

Two main themes:

- (i) assessing the societal value of orphan drugs and
- (ii) funding the development and use of orphan drugs.

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ASSESSING THE SOCIETAL VALUE OF ORPHAN DRUGS (1)

- To what extent does any **deviation depend on the characteristics of the disease and the technology** being assessed? Where do orphan drugs fall on this spectrum?
- In assessing the incremental cost per QALY of orphan drugs, **in what ways does rarity impact?**
- Compared with drugs for more common diseases, **does rarity impact mainly on the incremental costs**, because the costs of development are being recouped through sales of the drug to fewer patients worldwide?
- Alternatively, **does rarity impact on the incremental QALYs**, because the nature of the diseases being treated makes it difficult to demonstrate a large increase in QALYs with any degree of certainty?

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ASSESSING THE SOCIETAL VALUE OF ORPHAN DRUGS (2)

- **To address uncertainty of effectiveness, explore risk-sharing schemes**, where final level of reimbursement of drugs is determined based on evidence of long-term clinical effect. This approach was followed for beta interferon in the treatment of multiple sclerosis in the UK, but has yet to be evaluated. (Department of Health, 2002a, 2002b)
- **Do current processes for assessing and appraising drugs need to be adapted** to make them suitable for orphan drugs? In particular, are standard evidence requirements in line with what can be realistically delivered? Also, can all the elements of societal value be adequately reflected in existing decision-making procedures or does this need to be done more explicit?

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FUNDING THE DEVELOPMENT AND USE OF ORPHAN DRUGS (1)

- Innovation in pharmaceuticals is rewarded by a mixture of direct funding of R & D to pharmaceutical companies and public research centers and by the temporary monopoly price associated with patents. These two sources of funding are usually not coordinated.
- However, **the rationale for coordinating these two sources of funding is obvious in the case of orphan drugs**: It does not make much sense for the public system to fund or subsidize R & D on orphan drugs and later not reimburse the resulting innovations: waste of R & D resources and discouragement of future R & D
- Health insurers can and should not be expected to fund, at any price, all effective orphan drugs that the industry voluntarily decided to develop and bring to the market.

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FUNDING THE DEVELOPMENT AND USE OF ORPHAN DRUGS (2)

- Given that the need to recoup development costs under the present IP system results in high prices, is there a better way for society to provide the necessary financial incentives? Prizes, APC, auctions of patents?
- Funding of OD should preferably be nationally and centrally controlled in order to maintain equity and consistency, avoiding so-called post-code prescribing, and to avoid unacceptable levels of financial risks falling on providers with small budgets.

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CONCLUSIONES (1)

- Todos los AVAC no deben tener necesariamente la misma valoración, pues es obvio que la evaluación económica no siempre capta todos los factores relevantes, pero...
- No es obvio si y cómo la “rareza” debe afectar la valoración.
- La “rareza” depende de cómo se definan las enfermedades.
- El auge de la farmacogenética y la medicina individualizada puede llevar a que un número creciente de enfermedades raras y tratamientos huérfanos.
- Los factores “especiales”, incluyendo la rareza, deberían ser objeto de consenso social y posterior incorporación explícita en los criterios de evaluación.
- Las decisiones de reembolso y fijación de precio deberían ser justificadas y transparentes.
- Criterios explícitos y transparencia en su aplicación darían señales claras y reducirían la incertidumbre a los potenciales innovadores.

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CONCLUSIONES (2)

- La innovación en medicamentos se promueve mediante tres mecanismos:
 - 1) subvenciones a la I&D
 - 2) condiciones de exclusividad
 - 3) financiación subvencionada de medicamentos a precios monopólicos
- Las empresas reciben subvenciones y exclusividad para desarrollar medicamentos huérfanos, que luego no son financiados por su elevado precio, lo que supone un despilfarro de recursos en I&D y una frustración para innovadores y pacientes.
- Para abordar estas disfunciones el sector público debería utilizar los tres mecanismos como una estrategia única, coordinada, que supusiese un incentivo eficiente, suficiente para lograr simultáneamente la innovación y el consumo necesarios.

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CONCLUSIONES (3)

- El sistema actual de incentivos a la innovación biomédica está siendo cuestionado por diversas razones. La comisión IGWG de la OMS elaboró un informe, en base al cual la AMS 2008 aprobó una resolución para desarrollar un plan de acción que buscase alternativas al actual sistema de incentivos a la innovación para enfermedades que afectan predominantemente a países pobres.
- Alguna de las propuestas formuladas podrían ser útiles en el caso de las enfermedades raras:
 1. Separación del mercado de innovaciones del mercado de productos
 2. Fondos de premios para promover la innovación
 3. Tratado internacional para la financiación de la I&D

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Mensaje final

Necesidad de desarrollar y probar métodos innovadores para promover la innovación biomédica, en general, y en enfermedades raras, en particular.

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