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Smarter Regulation of Drug Development: FDA Orphan Products and Fast Track Programmes

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This policy brief is one of a series describing Innogen's research on strategic innovation issues in life sciences, the governance and regulation of innovation and the resulting innovation trajectories determining which products are developed and which companies take the lead in developing them.

Advances in biomedical sciences are predicted to have enormous impact on the prevention, diagnosis, treatment and cure of disease and disability, for example pharmacogenomics, proteomics, nanotechnologies, micro-arrays, biomarkers, bio-informatics, synthetic biology, and tissue engineering. On the other hand, the R&D process is increasingly costly, unpredictable and inefficient, so that these advances will not automatically translate into improvements in health care.

The Innogen Centre research programme has identified radical revision of regulatory systems as the key to freeing up innovation in life sciences and this brief considers the role of two initiatives by the US Food and Drugs Administration in contributing to this outcome.

Radical revision of regulatory systems is the key to effective innovation in life sciences

Regulatory Background

The Orphan Drug Act (ODA) (1983) provided incentives for development of products to treat rare diseases:

1. Technical and administrative assistance with the identification and development of orphan products including specific protocol assistance concerning what studies the sponsor needs to complete, monitoring the review process and assisting in resolving specific issues.
2. Grants to cover clinical trial expenses, up to $200,000 per year for smaller Phase I, II or III studies, and up to $400,000 per year for Phase II or III studies.
3. User fees, such as registration fees paid to the FDA for review of a marketing application ($1,178,000), are automatically waived, recently expanded to include product ($65,030) and establishment fees ($392,700).
4. Tax credits for up to 50 per cent of clinical development costs, which can be carried forward for 15 years or backward for three years.
5. Orphan exclusivity prohibiting FDA from approving a marketing application for the same drug to treat the same condition for seven years from the date of approval of the first application, even in the absence of a patent.

Fast track designation facilitated the development of products for serious or life-threatening conditions, lowering the cost of bringing a product to market or allowing earlier access to patient markets through:

1. Regular consultations with the FDA, especially at critical junctures in drug development;
2. Written correspondence on the design of the principal trials and the adequacy of

Phase II or III development plans;

3. Opportunity for priority review of the application, a 'rolling review' of portions of a marketing application and accelerated approval; and
4. Dispute Resolution so that FDA determinations may be appealed at a level beyond the reviewing division/office.

The two programs overlap in that approximately 40% of fast track designated drugs in the early 2000s had orphan designations and over 30% of orphan and fast track products approved during 2004-2006 had both designations. Both initiatives are more concerned with problem-solving than policy bargaining and in many cases the impetus for designation originated with patient advocacy groups or FDA itself.

'What Works' in facilitating innovation in drug development

ODA

Before the ODA was passed, two or three drugs that might have been eligible as orphans were approved annually. Since then, some 1700 orphan designations have been granted, and approximately 300 orphan drugs approved, 10% with support from FDA grants. Of the orphan designations awarded from 1992-2006, 26% occurred during the first five years, 31% during the middle period, and 43% during the most recent five years.

Among the ODA incentives, the seven-year orphan product exclusivity works for large companies and SMEs, in both private and public sectors, and is considered the most important incentive. Tax credits are more valuable to large biotech and pharmaceutical firms, which have revenues that can be offset, while waivers of application fees are important for cash-strapped small companies. Orphan grants also provide seed funds which are valuable for sponsors working in the public sector.

ODA as exemplar for other countries

Similar approaches have been adopted in Japan, Australia, New Zealand, Singapore, Israel, S. Korea, Canada and the EU.

The FDA has disbursed some $246 million in orphan product grants, directly funding between one-quarter and one-third of designations and contributing to the R&D of 15% of approved orphan products, serving particularly more innovative product developers.

Of 72 grantees, who took part in a Tufts CSDD survey, 88% were affiliated with academic institutions, 6% with a non-profit research centre, and only 7% were corporate entities. For 70% of grantees, half or more of their program costs were covered by the grants. Orphan grants are essential for academic and non-profit researchers, who undertake much of the more challenging R&D. For 86% of grantees their programs had produced significant findings, and 22% of programs resulted in product approvals, a success rate that compares favourably with mainstream drug development. Novel outputs, such as new patents or use of novel surrogate endpoints, biological sampling techniques, statistical/analytic methods or software programs, were reported by 36% of orphan projects in 2002. The top rated disease groups included genetic diseases, neurological disorders, and infective diseases, areas that are considered by the biopharmaceutical research community to be among the most urgent and high-risk unmet medical needs.

Fast Track

By 2000 just over a 100 fast track designations had been granted and by 2006 this had increased to nearly 500.

Positive impacts of fast track designation are:

1. Fast track products have shorter median approval times than other applications assigned Priority Review, with the following effects: (i) earlier access to cash returns; (ii) cuts in development costs; (iii) allowing a sponsor to gain first mover advantage, i.e., engender brand loyalty resulting in higher and longer market share; and (iv) earlier launch, and thus longer effective patent life or period of market exclusivity protection.
2. There is a positive impact from the 'meeting effect'. Between 1987-1995 average development time was 27 months shorter if sponsors had pre-investigational new drug

designation (IND) meetings, and 16 months shorter if they had an end-of-phase II (EOP II) meeting. From 2002-2004, 52% of sponsors that had an EOP II meeting achieved approval upon first cycle review, but only 29% of those that did not have EOP II meetings were successful on first cycle. Nearly 90% of fast track designees believed FDA interaction would be the primary benefit from participation: 81% of fast track product sponsors have meetings at critical development junctures, but only 57% of priority non-fast track product sponsors. The FDA also recognise that one of the best things that FDA can do to improve quality and predictability of the review process is to meet regularly with sponsors

3. Fast track designation also fosters innovation through an 'investment effect', acting as an indicator that a product should be given priority review status, requiring FDA to take first action within 6 months of accepting a marketing approval application compared to 10 months for standard review, potentially getting the product to market more quickly. A more subtle impact on shareholder value may stem from the perception among investors that designation is associated overall with lower financial risk. A first-day return in stock valuation bump-up of 18% has been seen following a designation announcement, especially for small and micro cap companies. There has also been a statistically significant change in stock prices after fast track designation (p-value of .04), and the difference in the percent change of stock prices after fast track designation was also significant (p-value of .03).

Fast track designation fosters innovation

Both programmes

Both programs contribute significantly to breakthrough innovation: 72% of fast track products, are new molecular entities (NMEs) or significant biologics (SBs); for orphan products the figure is 50%. In 2004-2006, 60% of all new priority approvals went through these programs (56% of priority NMEs and 66% of priority SBs). Overall, half of new product approvals each year are standard review, but among fast track or orphan designated approvals, just under 10% are standard review status.

Both programmes seem effective in nurturing the more innovative segment of the industry. Small biotechnology companies, without the intercession of special regulatory programs, are less effective at getting their products through the approval process, attributed to a lack of regulatory experience – those with no prior FDA approvals were found to have half the first cycle approval rate of large US-based companies. The US and Japanese orphan product programs were both credited with helping to get fledgling biotechnology sectors off the ground in the 1990s.

Stakeholder involvement in drug development

Both programmes contribute to breakthrough innovation

The ODA was crafted in response to patient advocacy and a government investigation in the early 2000s found that it is meeting public stakeholder needs. The innovation community (industry and academic) have also said that, while they question some individual product decisions, they generally supported the orphan products program. Likewise, a majority of respondents to a survey of orphan grantees, primarily academic investigators, noted that both the application and reporting processes for FDA grants were very manageable and acknowledged the importance of organized advocacy to support their efforts.

Patient advocacy groups were also instrumental in securing passage of the fast track legislation which has considerable buy-in from other stakeholders - increased regulatory and sponsor attention throughout the development and review process may contribute to the timely identification and resolution of regulatory issues. For sponsors, the program helped to distribute their workload and to get a head-start on the additional time required to address issues arising from parts of the approval dossier that sponsors were allowed to submit early under the program. Timely FDA feedback also helped sponsors to plan product development programs.

Patient advocacy groups are contributing to inducing pharmaceutical companies to make information about fast track trials available on the c*linicaltrials.gov* website and the program has also helped advocacy lobbies to get expedited review and tentative approval of specific applications.

Safety Issues

A review of 1998-2005 NME and SB approvals looked at the percent that had acquired Black Box warnings, indicating an elevated safety risk, and found that orphans are no more risky than non-orphans (26% of both orphans and non-orphans had Black Boxes). On the other hand, for fast track, 34% of NME and SB approvals had acquired Black Box warnings (25% for non-fast track). There were no permanent withdrawals for safety reasons of NMEs and SBs approved with orphan or fast track designation, but 5 such withdrawals for products without orphan or fast track designation. For products with fast track or orphan designation, 5.8% had been discontinued or withdrawn and later returned to the market for limited distribution, compared to 8.2% without fast track or orphan designation. In aggregate, considering the more serious nature of the relevant diseases, for which there are often few or no therapeutic alternatives, and hence the greater benefits accruing to treatment, products from these designation programs could be considered to have a more favourable risk/benefit balance than non-designated drugs.

Policy makers can build on experience of ODA and Fast Track to engineer systemic change in regulatory systems

Broader Applicability

The ODA and Fast Track are examples of specific regulatory programs that have been demonstrated to deliver the expected benefits across some areas of pharmaceutical innovation, combining industry incentives, more appropriate government intervention, and stakeholder inclusiveness.

Policy makers could usefully build on this success to engineer the more systemic and proactive approach to pharmaceutical innovation and regulation needed to create a sustainable and competitive biopharmaceutical industry - '21st Century regulation for 21st Century science'.

NOTES

This policy brief is one of a series dealing with Appropriate Governance of Life Sciences – see http://www.genomicsnetwork.ac.uk/innogen/publications/innogenpolicybriefs/title,20871,en.html

Data contributing to this policy brief are referenced in full in:

Milne, C-P and Tait, J. (2009) Evolution along the Government-Governance Continuum: impacts on medicines innovation in the United States. In eds. C. Lyall, T. Papaioannou and J. Smith, *Limits to Governance: challenges of policy making for the new life sciences*. Aldershot: Ashgate Publishing Limited, pp 107-132.

Milne, C-P and Tait, J. (2009, in press) Evolution along the Government-Governance Continuum: FDA's Orphan Products and Fast Track Programs as Exemplars of "What Works" for Innovation and Regulation. *Food and Drug Law.*

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