

# Fast Track Options as a fundraising mechanism to support R&D into Neglected Diseases

Pharmaceutical R&D Policy Project  
London School of Economics

## Background

Incentives to promote neglected disease (ND) R&D must address a dual challenge. The first concern is how to channel more financial resources into ND R&D. The second is how to direct these resources in the most cost-efficient manner.

The current view is that the financing of R&D for neglected diseases should be provided by the public sector, while R&D itself is best carried out by the private pharmaceutical sector. In response to this model, most current policy proposals are aimed at mobilising substantial public finances to commercialise the neglected disease market, thereby allowing it to compete in company R&D priorities with traditional Western markets. These incentives generally aim to achieve a level of funding sufficient to motivate involvement by large multinational pharmaceutical firms (MNCs), which in practice means a neglected disease R&D incentive needs to match or exceed commercial peak sales of \$500 million plus per year.

Monies are either provided by developed country governments directly (Advance Purchase Commitments [APCs], tax breaks), or indirectly through higher healthcare expenditures (as proposed by Transferable IP Rights [TIPR]). The funding is channeled to companies via “push” and “pull” mechanisms that seek to create conditions similar to commercially driven projects, so as to attract companies’ interest. APCs, for example aim at commercialising the neglected disease market, while the TIPR proposal offers a sizeable market extension for an unrelated commercial drug in exchange.

By contrast, our research shows that in practice the majority of neglected disease drug development - around three-quarters of the 55 drug projects we have studied to date – is conducted *outside* this MNC commercial model. The main alternative models involve large companies working on a not-for-profit basis for charitable, public relations or strategic reasons; large and small companies working on a low-cost basis within PPPs; and small companies working alone or on a fully-paid basis with PPPs to exploit neglected disease markets that, although traditionally considered as non-commercial, are still attractive to them in relation to their smaller cost structures.

There are currently few and limited incentives aimed at these alternative models, even though they now represent the most productive pipeline for new neglected disease drugs. A fully effective public policy framework for neglected disease R&D would ideally select from a range of incentives, depending on which R&D model was being targeted. These categories of incentive are:

1. Large financial incentives targeted to companies whose motives are commercial, and generally designed to match MNC cost structures. These incentives, such as APCs or TIPR, are generally in the order of billions since they are designed to match competing Western commercial markets rather than the direct costs of neglected disease drug development;
2. Modest financial incentives aimed at supporting lower-cost R&D models, including industry partnerships (PPPs), and SMEs with more modest commercial aims. Funds needed to support R&D activity under these approaches are at least an order of magnitude smaller i.e. tens to hundreds of millions, rather than billions;
3. Non-financial incentives (mostly relevant to MNCs, whose motives for neglected disease involvement are unrelated to profit).

Current policy thinking tends to target Category 1 incentives. By contrast, our Neglected Disease Fast Track Option (FTO) proposal is focused on raising funds for Category 2. We have chosen this area for two reasons. Firstly, because, as noted above, analysis shows most current R&D efforts fall under categories 2 and 3 (45 out of 55 projects), which are the most productive source of new drugs for neglected diseases and the area of greatest industry engagement. Secondly, because there are few or no policies designed to support these two categories; and thirdly, because of these, only category 2 is commercially driven and therefore amenable to financial incentives. (Analysis of incentives for other categories is still in progress).

Before presenting the FTO proposal, we should make one final important observation. Our FTO proposal decouples neglected disease fundraising from neglected disease R&D. In other words, it is an R&D financing mechanism rather than an R&D incentive. The FTO concept is designed solely to raise funds for neglected disease R&D but does not automatically stipulate how these funds should be spent - although as discussed above, based on our research to date we suggest these are spent on category 2 projects. That said, we are concurrently analysing the cost-efficiency and health-efficiency of the various neglected disease R&D approaches set out above. Once this is completed, we would hope to provide policy-makers with both a fund-raising mechanism and a clearer idea of where and how those funds could most productively be spent, be this through MNCs, PPPs, biotechs or other alternatives. This paper will, however, not devote further time to this aspect.

## Neglected Disease Fast Track Option: the concept

We present a concept that we call “Neglected Disease Fast Track Option” (FTO), which is built on existing fast track registration as practiced in the US and potentially available under new EMEA regulations. Fast track reduces drug development AND regulatory approval times, allowing drugs to reach the market earlier. This time gain brings significant financial benefits to industry and could be leveraged to raise funds for ND R&D.

Our proposal would allow a company to purchase an option to fast track regulatory review for a commercial drug of its choice, for example a hypertension drug, rather than only for drugs for a serious or life-threatening disease, with the resulting funds being used to support R&D for neglected diseases (NDs). FTOs would build on FT's efficiency gains but would NOT include R&D shortcuts (see below).

In earlier publications we called this concept Transferable Fast Track (TFT). However we believe Neglected Disease Fast Track Option is a more accurate appellation as we propose companies purchase it, rather than obtain it in exchange for a licensed ND drug, as is the case with the transferable intellectual property rights proposal (TIPR).

Before going any further, we would like to acknowledge our debt to Henry Grabowski, who developed the concept of transferable priority review, which has since been elaborated into a proposal for priority review vouchers by Ridley et al. (PRVs) in exchange for R&D on neglected diseases. It was this work which catalysed our interest in the concept of efficiency gains to fuel R&D, although over time we have reached somewhat different conclusions. In particular, we believe FTOs may offer greater advantages than PRVs, as discussed below.

### What is fast track?

Fast track is a *formal* FDA package of measures to allow drugs for serious and life threatening diseases to reach the market earlier (see Table 1). In recent years, however, the FDA has extended the fast-track programme to non-life threatening diseases, including diabetes and obesity.

Fast track moves drugs to market earlier using a package of measures. Before going any further, we emphasise that our proposal would only include the first group of these measures,

as discussed below (efficiency gains), but WOULD NOT include the second group (R&D shortcuts). These collective fast-track measures are:

- Efficiencies in the regulatory process, including scientific advice to improve trial design and data collection, and reduced delays in reviewing regulatory submissions. Other benefits stemming from sponsor-Agency interactions include a more efficient development process and earlier termination of unsuccessful development plans, leading to resource, time and cost savings for both sponsors and the regulatory agency. Collectively, these measures reduce development time and cost, and speed up regulatory approval.
- Shortcuts in R&D processes, for example allowing companies to use unproven surrogate endpoints or smaller trials to establish efficacy and safety. These measures reduce development time in cases where a drug is felt to be urgently needed. These are not included in our proposal.

The US experience demonstrates the very significant benefits of a FT scheme. Analysis of real-life data from 1998 to 2003 shows that the FDA's FT programme delivered an impressive overall reduction in drug development time of **about 3 years** on average. This was due to an average cut in clinical development time for FT-designated drugs in the US of 2 to 2.5 years and a cut in approval time of about 1 year.<sup>1</sup>

**Table 1: Experience with the FDA's FT development programs between 1998 and 2003, and associated benefits**

Effect of FT	Benefits
<ul style="list-style-type: none"> <li>▪ <b>All FT sponsors had enhanced interactions with the FDA throughout the drug development process, starting at the pre-clinical stage.</b><sup>2</sup></li> </ul>	<p>Between 1987 and 1995<sup>3</sup>:</p> <ul style="list-style-type: none"> <li>▪ Average development time for approved NCEs for which there had been a pre-IND meeting was <b>27 months shorter</b> than for those without a pre-IND meeting.</li> <li>▪ The time gain for those that had an end-of-phase II meeting was <b>16 months shorter</b> than for those that had not had such a meeting.</li> </ul>
<ul style="list-style-type: none"> <li>▪ <b>The overwhelming majority received priority review (i.e. accelerated regulatory review of a marketing authorisation application).</b><sup>4</sup></li> </ul>	<p>Average approval time for drugs approved between 1998 and 2003<sup>5</sup>:</p> <ul style="list-style-type: none"> <li>▪ 19 months for Standard Reviews</li> <li>▪ 11 months for Priority drugs <u>outside the FT system</u>: an 8 month saving</li> <li>▪ 6 months for <u>Priority FT-designated</u> drugs: a <b>13 month saving</b></li> </ul> <p>Because the FDA already knows FT-designated drugs so well by the time a marketing authorisation application is filed, it approves them faster than other priority drugs.</p>
<ul style="list-style-type: none"> <li>▪ <b>About half benefited from Accelerated Approval (approval based on non established surrogate endpoints or smaller trials).</b><sup>6</sup></li> </ul>	<p>Accelerated Approval has been associated with development time gains ranging from 3 to 48 months<sup>7</sup>.</p>

<sup>1</sup> Impact Report Volume 5, Number 6, *FDA's Fast Track Initiative Cut Total Drug Development Time by 3 Years*, November/December 2003, Tufts Center for the Study of Drug Development

<sup>2</sup> *Fast Track product designation under the Food and Drug Administration Modernization Act: the Industry Experience*, Milne and Bergman, Drug Information Journal, Vol 35, pp. 71-83, 2001

<sup>3</sup> *Initiatives to speed new drug development and regulatory review: the impact of FDA-sponsor conferences*, DiMasi and Maniocchia, Drug Information Journal, Vol 31, pp. 771-788 (fig. 7), 1997

<sup>4</sup> Information based on CDER published data and lists

<sup>5</sup> Data provided by C. Milne in Aug 2004, Tufts Center for the Study of Drug Development, which was generated for the Impact Report Vol 5, No 6 (see footnote 1 above)

<sup>6</sup> Information based on CDER published data and lists

<sup>7</sup> *Faster access to drugs for serious or life-threatening illnesses through use of the accelerated approval regulation in the United States*, Cocchetto & Jones, Drug Information Journal, 1998

<ul style="list-style-type: none"> <li>▪ <b>Rolling submission programme (early submissions of parts of the application dossier)</b></li> </ul>	<p>The efficiency gains derived from the RS program are not clear, especially as RS allows early submissions of portions of an application but does not guarantee early review.</p>
<p><b>Total time saving</b></p>	<p><b>Nearly 3 years off standard drug development:</b></p> <ul style="list-style-type: none"> <li>▪ <b>2 to 2.5 years cut in clinical development time</b></li> <li>▪ <b>13 months cut in approval time</b></li> </ul>

As Table 1 shows, a significant part of this achievement stemmed from regulatory efficiencies, particularly associated with:

- a) Earlier and higher levels of sponsor-Agency interactions during the R&D process, which expedited a product's access to the market;
- b) Priority review, as part of a fast-track package;
- c) The efficiency gains of co-ordinating these components into an integrated fast-track package. We note, for example, the shorter regulatory approval time for priority drugs that were also fast-tracked (13 months time saving) over priority drugs that were not fast-tracked (8 months time saving)

Taken together, these efficiencies generate a substantial level of savings for industry.

At the moment, Europe does not have a formal fast-track package. However, recent changes to EC legislation<sup>8</sup> have given the EMEA all the components needed to implement a fast-track package in Europe, should they wish:

- Scientific advice and protocol assistance are already available to sponsors and access to these is expanding;
- EMEA has been given the mandate to increase early interactions with sponsors, and in a discussion paper the Agency published on the implementation of the new legislation, the Agency has confirmed its intent to extend opportunities for these as much as possible;<sup>9</sup>
- As noted above, the Agency has established a formal accelerated assessment procedure for the regulatory approval of marketing authorisation submissions, similar to priority review in the US;
- EMEA can now also grant conditional marketing authorisations, on criteria similar to those of the FDA's accelerated approval procedure (see Table 1 – although useful for accelerating approval of treatments for serious and life-threatening conditions, we recommend this component should not be included as part of fast track options).

It is important to note, however, that many of the efficiency gains the EU could derive from fast track will be lost unless these individual measures are packaged into a formal, integrated programme.

### **How would fast track options (FTO) work?**

Our proposal would allow a company to purchase fast track (FT) regulatory review for a commercial drug of its choice, for example a hypertension drug, rather than only for drugs for a serious or life-threatening disease, with the resulting funds being used to support R&D for neglected diseases (NDs).

We note that FT in the US has already been extended to some common non life-threatening diseases, so there is a precedent for fast-tracking a mainstream commercial drug.

<sup>8</sup> Commission Regulation (EC) No 726/2004 and Directive 2004/27/EC EMEA

<sup>9</sup> *Discussion Paper, The European Medicines Agency Road map to 2010: Preparing the Grounds for the Future*, EMEA, March 2004

The key point to note is that FTOs raise new funds by capturing the value to industry of efficiency and productivity gains in the R&D and regulatory process, which lead to shorter development times and earlier drug launch (see Figure 1 overleaf). The use of FTOs does not require additional public funding to cross-subsidise ND R&D.

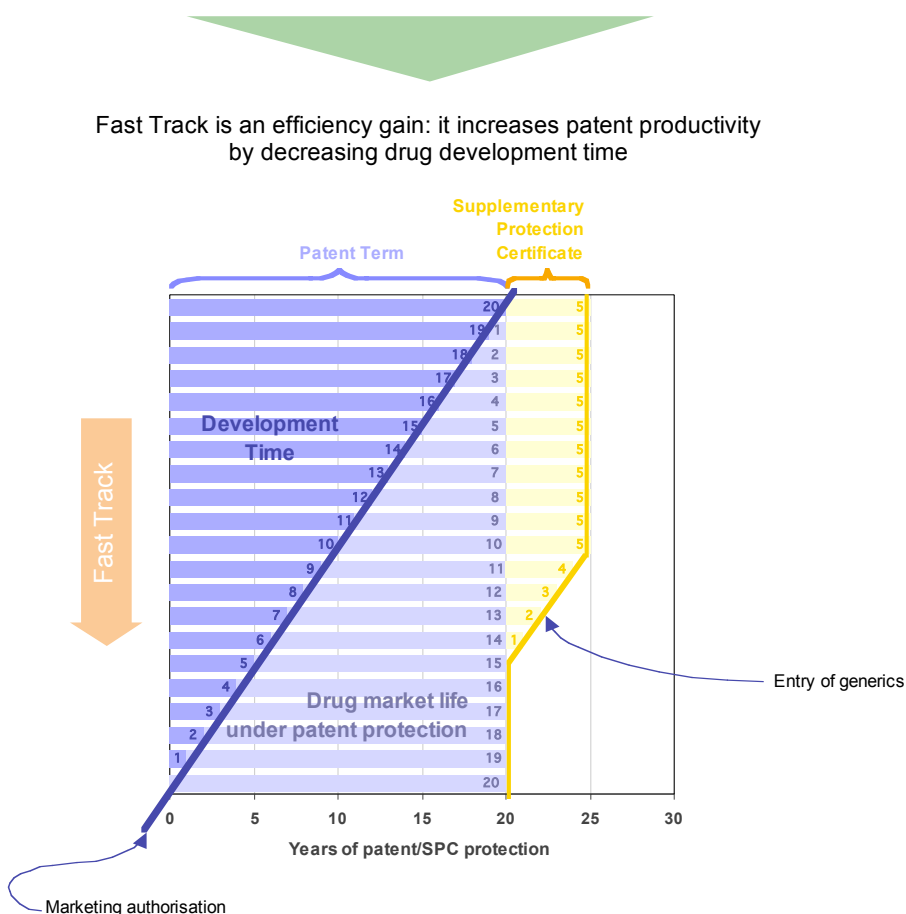
Under our proposal, FTOs would not allow R&D “shortcuts”, such as approval based on surrogate endpoints or smaller trials. Such measures would not be acceptable as it is likely industry will want to exercise the FTO it purchases for widely-used products aimed at non life-threatening conditions, where the risk-benefit equation is very different from that of serious and life-threatening drugs.

However, our FTO proposal would include all the benefits of FT derived from early and continuous interactions with the regulatory agency during development of the drug, and priority regulatory assessment of the submission. Even without R&D shortcuts, the statistics in Table 1 above indicate that potential time gains derived from an FTO could range from 6 months to 2.5 years, depending on how early in the development process a sponsor applied for fast track designation. These efficiency gains create substantial additional value for companies (see valuations in Appendix 2), some of which we are proposing to capture to finance R&D of drugs for neglected diseases, as discussed below.

Last, FTOs would not displace resources within the regulatory Agency at the expense of other drugs. We propose that part of the funds raised with FTOs be used to cover the cost of any additional staff needed.

**Figure 1**

FT does NOT increase patent term.



Supplementary Protection Certificates (SPC) are, in effect, patent extensions granted to compensate for loss of patent life due to regulatory delays throughout development and approval time (see Appendix 1 for further detail).

The second aspect of our proposal is the manner in which FTOs would be offered. A promising mechanism to optimize the price of FTOs may be through an auction mechanism, whereby the EMEA could auction one, or at most two, FTOs to industry every year. Competing firms would bid for the right to fast track a commercial drug, thereby reaching the market (and profits) before their competitors. The funding raised through this industry auction would be directly dedicated to neglected disease drug development (see separate paper for optimal use of ND funding). The raised funds could also be matched one-to-one by governments, thereby doubling the available funding for neglected disease drug development and encouraging industry participation.

Although other options to accurately capture the benefit of an FTO are still under consideration, we believe the auction mechanism is particularly efficient since it:

- Allows the price to be set competitively
- Reduces the risk of government setting the “wrong” price, since industry, who have the best knowledge of their cost structures and likely market, will bid competitively up to the appropriate level
- Is an accepted mechanism for industry (e.g. pollution rights)
- Does not require disclosure of commercial-in-confidence information on R&D costs

### **How does the FTO proposal compare to alternatives?**

We examine two current alternatives to FTOs: Priority Review Vouchers (PRVs), as mentioned above; and Transferable Intellectual Property Rights (TIPR).

Under the PRV concept, companies who create and license a drug for neglected diseases would be rewarded with a voucher offering FDA priority review status for another (commercial) drug. The voucher would be tradable.

We believe FTOs offer a number of advantages over PRVs, as outlined below:

1. By definition, the time savings to be gained from a PRV are smaller than those of an FTO. A PRV expedites regulatory review of the finished drug dossier but does not reap efficiencies during the R&D process, while an FTO covers both. In the US, the expedited “priority” review of drugs for which a PRV would be of interest (i.e. drugs otherwise not eligible for fast-track or priority review) would yield only an 8-month time saving on standard review (see Table 1 above). In the EU the time gains would be limited to an average of only 6 months<sup>10</sup> over standard review. An FTO yields significantly larger efficiency gains, potentially saving 1-2.5 years off total time to market.
2. A company will assess the value of a PRV at the time it decides whether or not to invest resources in neglected disease R&D. The value of the PRV to the sponsor must therefore be discounted at the industry cost of capital for the duration of the neglected disease R&D carried out - perhaps 10 years – since the PRV is granted only in exchange for a finished ND drug. Accounting for this cost of capital and for the risk that the ND drug might fail and not trigger a PRV significantly reduces the pull effect of the incentive. Unlike a PRV, when a company buys an FTO it can choose to use it for any drug at any stage of development, as the time of use of the FTO is not linked to any ND R&D outcome. As a result the time and risk-discounted FTO benefits are more than threefold greater than for a PRV (see Appendixes 2 and 3).
3. PRVs would be granted to companies in exchange for creating and licensing a drug that treats neglected diseases. FTOs, on the other hand, aims to raise revenue for neglected disease R&D but are de-linked from the ND R&D process. This provides greater flexibility in terms of funding different R&D models (see above).

<sup>10</sup> Between 2000 and 2003, 5 products were granted marketing authorisation using the accelerated assessment procedure, leading to an average approval process of 9 months – compared to 15 months for other drugs

4. PRV is only applicable to drugs that would not already receive priority review i.e. “standard” drugs, defined by the FDA as drugs that cannot demonstrate significant benefit over existing drugs in terms of efficacy, safety, compliance or extension to a new patient sub-population, although they may offer other benefits. This represents around three-quarters of new drugs approved in the US.<sup>11</sup> By contrast, an FTO is available to any drug that would not already be fast-tracked – this is around 90% of drugs in the US, including both standard and priority drugs.

A second commonly discussed alternative to FTOs as a fundraising mechanism for ND is Transferable Intellectual Property Rights. This is the proposal to reward companies who conduct R&D into neglected diseases with extended patent rights on a commercial drug of their choice. The relative benefits of TIPR and FTOs in the EU context are set out in Table 2.

**Table 2: Impact of FTO and TIPR in EU**

	<i>FTO</i>	<i>TIPR</i>
1	No additional public financing is required Creates new R&D funding through efficiency gains Costs associated with selling FTO minimal and covered by funds raised	Substantial new public funding required (billions) – see point 3 below
2	Health benefit, as brings new drugs to EU patients more quickly  (If these are “priority” drugs, the EU health benefit is even greater.)	No European public health benefit.
3	EU health budget pays only for the European public health benefit (i.e. payment for earlier new drugs for EU patients)	EU health budgets fully cross-subsidise developing country R&D and industry cost-structures, but without health benefit to themselves
4	Benefits of the funding generated are shared between industry and the public sector (see point 5 p. 8)	No new funding generated.
5	Increases productive patent life, but <u>does not extend</u> the term of the patent.	Increases productive patent life by <u>extending</u> the term of the patent by the term of the TIPR, e.g. 1-6 years <sup>12</sup> .  Patent extensions are politically sensitive.
6	Provides earlier access to generic equivalents in around two-thirds of eligible cases (see section on Benefits to industry for details on this)  Does not delay entry of generics in about 1/3 of eligible cases	Delays access to generic equivalents by 1-6 years in all cases (see point 5 above)
7	Number of FTOs is controlled by the Government (ideally no more than 1-2 per year)	No upper limit in terms of number of TIPR's, therefore no limit on potential public expenditure
8	No open-ended scope for future lobbying to extend the term of FTO: automatic “natural” limit on benefit of FTO since it is based on efficiency gains	Under current proposals, no upper limit on term of TIPR.  TIPR's term could be increased to 8 years, 10 years etc. (much as has happened with copyright term following lobbying from the likes of Disney), thereby increasing cost of TIPR to EU

<sup>11</sup> <http://www.nihcm.org/innovations.pdf>, p.12

<sup>12</sup> *Developing the Idea of Transferable Intellectual Property Rights (TIPR) To Incentivise R&D in Drugs and Vaccines for Neglected Diseases*, OHE, Towse, March 2004

		governments.
9	Would require EMEA to co-ordinate their existing mechanisms into a formal package.  May require an additional auction mechanism (if this option is chosen).	Simple to implement as several IP extension mechanisms already exist (e.g. SPCs; data exclusivity)
10	Funding can be spent on any R&D model, depending on which is most efficient (this will be discussed at length in a later paper).	Under current proposals, funding is provided to industry to conduct R&D and cover associated costs of the industry model.

The advantages of the FTO approach are further discussed below.

## Benefits to EU patients

Beyond raising money for ND R&D, FTOs potentially have a number of public health benefits:

- FTOs will expose regulatory inefficiencies, leading in the long term to shorter regulatory delays for ALL drugs. We note that in the long term, this benefit will decrease the value of FTOs (i.e. the time gain derived from an FTO will be reduced). But in the meantime, FTOs could potentially raise more than double the total annual budget of all drug PPPs,<sup>13</sup> who now account for around three-quarters of all ND R&D projects. (See below for a valuation of FTOs);
- It brings new drugs to EU patients more quickly (an EMEA objective);
- Early involvement of regulatory authorities in drug development will allow greater public scrutiny of clinical trials, trial results and drug development dossiers;
- Intensive advice from regulatory authorities during development of clinical trial protocols should improve the quality of these trials from the public perspective. In a post-Vioxx context, fast track can provide an opportunity for more scrutiny throughout the development process than with a standard approval process.
- Health benefits to EU patients can be maximised by limiting the FTO to “priority” drugs (defined by the regulatory authorities as drugs offering a clear benefit over existing therapies). This would, however, restrict competition for the FTO and reduce its value, thereby reducing the funding available for developing country drug development. By contrast, allowing companies to apply for an FTO on any drug would not deliver as large a health benefit to EU consumers (since a standard drug might be fast tracked rather than a “priority” drug), but it would increase competition and therefore maximise the benefit to developing country drug development. This is a choice for policy-makers to weigh up.

## No requirement for public resources to fund R&D

The FTO proposal requires no additional public funds, either for its implementation or for the core purpose of funding neglected disease R&D, since it is entirely funded from efficiency gains in the R&D and regulatory process.

While implementation costs do exist, we expect these would be recovered from the finance raised through the FTO auction. These sums would, in any case, be relatively small, including:

- The cost to EMEA to administer the FTOs (which may require a small number of additional staff to coordinate the programme), and;

<sup>13</sup> Average total R&D budgets between 2000 and 2004 were around \$60 million per annum, although this would be expected to increase as more projects enter the clinical trial stage. (Based on annual budgets of MMV, GATB, Institute of One World Health, DNDI, and TDR).

- The potential cost of administering the auction (if this were the chosen mechanism to sell the FTOs).

We note that European governments would be purchasing the fast-tracked drug one or two years earlier than they would have otherwise (if it had not been fast-tracked), however this additional outlay is for purchase of the additional health benefit derived from earlier access to the therapy, with no cross-subsidy of the ND R&D process. For around two-thirds of eligible drugs, the additional cost will also be offset by more rapid access to generic versions, whose market entry will also move forward.

From a theoretical point of view, it is true that health budget expenditures would be lower if the fast-tracked drug (and indeed all drugs) could be delayed in the regulatory process. The ultimate aim of health budgets, however, is to deliver positive health outcomes to EU patients in a cost efficient manner, not to minimize expenditures. The argument above tends to be predicated on whether one believes that most industry-developed drugs are “me-too” drugs of little health benefit or, alternatively, whether most new drugs offer at least some health benefit. As noted above, restricting FTO eligibility to “priority” drugs would, in any case, make this argument irrelevant since all parties would agree that earlier access to the fast-tracked “priority” drug was of clear public health benefit.

## Benefits to industry

With time gains of potentially up to two years, an FTO could bring numerous benefits to a company:

1. Fast track gives a product sponsor earlier access to cash returns:
2. FT cuts R&D costs by shortening the duration and increasing the efficiency of the drug development process. It avoids unnecessary waste of time and resources spent by industry on irrelevant outputs or inadequately prepared submissions.
3. FT allows companies to gain first mover advantage. The pharmaceutical market is characterised by high brand loyalty / high consumer switching costs. First mover advantage provided by market entry before competitors, results in higher and longer lasting market share.
4. FT increases the certainty of outcome because it enhances early and continuous dialogue between firms and the regulatory agency. EMEA’s records show that the provision of scientific advice is strongly correlated with a higher likelihood of positive outcome<sup>14</sup>. Also, FT enables sponsor and Agency to uncover potentially irresolvable problems early on. This may lead sponsors to terminate development programmes early instead of wasting effort and expenses on completing trials for a drug that will not get approval.
5. Purchase of FT can deliver possible PR benefits for companies. There is often negative publicity associated with measures such as TIPR, which can be seen by the public as “giving money to rich drug companies”. The purchase of FTOs by companies, on the other hand, shows industry *funding* neglected disease R&D while at the same time purchasing something of commercial interest – thereby allowing the benefits of the efficiency gain to be shared between the public and private sectors.
6. The purchase of an FTO allows companies who are not involved in neglected disease R&D, and do not wish to be, to nevertheless contribute funds to NDs. Alternative incentives under discussion (e.g. APCs) would require each company to develop neglected disease R&D capacity if they are to receive the benefit, irrespective of their area of comparative advantage and even if they lacked in-house experience or inclination. FTOs, on the other hand, provide a mechanism open to all companies to contribute to neglected disease R&D.

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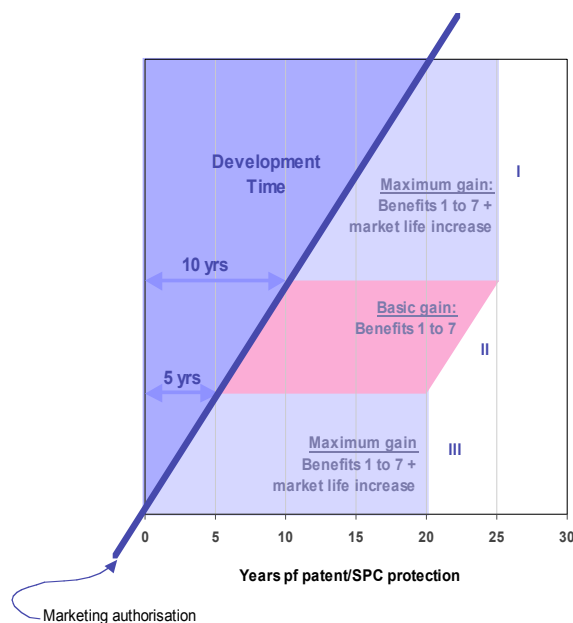
<sup>14</sup> EMEA Annual Report 2003, p.22

7. The positive impact of FT on shareholder value is highest for small firms that have fewer drugs in their pipeline and for which FT is associated with lower financial risk. IMMTECH is a case in point. On receipt of fast track designation from the FDA in April 2004 for one of its drugs, this pharmaceutical SME saw its share price rise by 10%.
8. Depending on where a drug is on the chart on Figure 1, (i.e. length of R&D time and whether or not the chosen drug has an SPC), an FTO may also increase the length of the market protection of the product thereby delivering additional years of sales. (See Appendix 1 for more detail.)

Whether benefit 8 applies will significantly affect the value of an FTO to industry. Therefore, we have quantified the value of the option to industry for both categories (see Fig.2), that is:

- Drugs eligible for the “Basic” FTO gain, which provides benefits 1 to 7 but no increase in market life (see figure 5 in Appendix 2 for illustration);
- Drugs eligible for the “Maximum” FTO gain, which provides benefits 1 to 7 plus an increase in market life (see figure 4 in Appendix 2 for illustration).

**Figure 2**  
**Basic versus Maximum gain of FTO**



To determine the relative size of each group, a quantitative analysis of new drug approvals in the UK over the past 10 years was performed. Data on new drugs registered in the UK between 1994 and 2003, obtained from the UK Medicine and Healthcare products Regulatory Agency (MHRA), were cross-referenced with SPC data from the UK Patent Office for that same period. A detailed assessment based on yearly numbers of New Chemical Entities, yearly number of SPCs granted to new drugs, and length of granted SPCs, showed that in the UK, about 2/3 of NCEs approved during this time would have been eligible for the basic gain and 1/3 for the maximum gain.

The cumulated benefits of an FTO to industry, whether basic or maximum, are considerable. We have quantified these, as shown below, to assess FTOs' potential as a fund-raiser for NDs.

## A high value for industry, translating into millions raised for ND R&D

Depending on its portfolio and risk profile, a company could choose to use an FTO for any drug at any stage of development. The extent of FTO benefits will vary accordingly:

- A firm could opt for the complete fast track package for a drug at an early phase of development. By doing this, it runs a higher risk that the drug is not going to reach the market, but will potentially achieve a 2 to 2.5 year time gain if the drug gets approved. This risk is partly offset by a lower cost of failure and a higher likelihood of regulatory approval (see point 4 on p.8)
- Alternatively, it could choose to get only accelerated regulatory assessment for a drug close to registration (cf. Ridley et al's Priority Review proposal). The outcome would then be more certain but the gains could be limited to six months earlier market access in the EU, or eight months in the US. This is nevertheless not insignificant on a blockbuster drug.
- Of course, all options between these two extremes are possible (and potentially more likely) scenarios.

In order to quantify the benefits of an FTO, we have estimated the net gain in present value of revenues at time of decision to purchase an FTO, taking account of:

- Industry cost of capital, at which future earnings must be discounted
- Benefits of earlier returns;
- Risk of failure, to reflect the risk of purchasing an FTO for a drug that is still in development - risk/attrition rates are based on standard averages. We note however that currently many approved new drugs are follow-on drugs<sup>15</sup>, which typically have a lower attrition rate. Our risk discounting for the FTO is therefore likely to be overly conservative;
- Longer patent/SPC protected market life, when applicable.

First mover advantage and R&D savings are not included in our conservative baseline estimates, since we have sought to provide governments and industry with a "hard" figure, avoiding inclusion of guesstimates. We therefore expect the true benefits would be larger than the figures below.

We applied our model to the example of Prozac, whose shape and length of market life are typical of 1<sup>st</sup> decile drugs and for which 17 years of sales data are available (see Appendix 2).

Table 3 below summarises the financial benefits to a company purchasing an FTO today for a drug with an expected return profile similar to that of Prozac:

- First, if that drug were two years away from approval, leading to an expected one-year time saving with the FTO;
- Second, if the drug were five years away from approval, leading to an expected two-year time saving with the FTO.

<sup>15</sup> Incremental R&D Creates Safer, More Effective Drugs & Fosters Competition, Tufts CSDD Impact Report, Volume 6, Number 6 • November/December 2004

**Table 3: The impact of an FTO using Prozac as an example (2004 US Dollars)**

	Launch 1 Year early			Launch 2 Years early		
	NPV gain estimated at time of launch*	NPV gain estimated <u>at time of purchase</u> (2 years before launch)		NPV gain estimated at time of launch*	NPV gain estimated <u>at time of purchase</u> (5 years before launch)	
		On a successful drug	Discounting for risk		On a successful drug	Discounting for risk
<b>Basic gain</b>	+\$357m	+\$290m	<b><u>+\$275m</u></b>	+\$753m	+\$447m	+\$306m
<b>Maximum gain</b>	+\$610m	+\$495m	+\$470m	+\$1,282m	<b><u>+\$761m</u></b>	<b><u>+\$521m</u></b>

This table includes estimates of NPV gains using two different models: first, time of launch as base year; and second, time of purchase of the FTO as base year. We believe that the latter calculation more accurately reflects the way companies will value an FTO. However, we have included the former to allow comparison with other incentives, the benefits of which are generally calculated using launch year as baseline (PRVs/TIPR).

Overall therefore, a conservative estimate of the financial value of an FTO to industry would be between one-quarter and one-half a billion dollars on a first decile drug, without the additional advantages of first-mover and R&D cost savings.

In reality, the outcome of an FTO is an all or nothing situation. If a company picks a drug that does reach the market, a 2-year gain will yield benefits of \$1/2 billion to \$3/4 billion. If a company, on the other hand, picks a drug that is unsuccessful, the loss is the auction price minus the savings from earlier failure and R&D efficiencies.

We note that TIPR carries a similar risk element. Millions of dollars may be invested developing a neglected disease drug that may ultimately fail, leading to a failure to secure a TIPR. In fact, the risk element associated with TIPR for a company that is moving back into the field of ND drug development is likely to be higher than that associated with TFT, for which companies could be expected to pick drugs with a low risk of failure.

The auctioning of one to two FTOs each year could therefore raise hundreds of millions per year, particularly if matched by government funds. It is expected that the competitive auction mechanism may drive companies to purchase FTOs for a price as close to these values as possible. But even at half or two-third of these values, and even after taking into account the fact that a small portion of this money would be directed to EMEA to cover administrative costs, the overall result would be a substantial and reliable stream of funding for neglected disease drug development. This in addition to the commercial, efficiency and health gains for industry, the public sector and patients respectively, as listed above.

## **Implementing Neglected Disease FTOs: a politically and legislatively feasible option**

FTOs offer a number of advantages over other approaches. Unlike Transferable IP rights, FTOs are not likely to be politically sensitive since, as discussed earlier, it neither extends patent life, delays generic entry nor requires additional public funding. FTOs also avoid the political and public downsides associated with transferable patent extension or other cash incentive to industry since industry will be seen as providing, rather than receiving, cash to support ND R&D (while purchasing something of interest).

Unlike other incentives, which leave the current system untouched and simply add on additional public payments, the benefits of FTOs to both industry and the public are derived entirely from efficiency gains in the regulatory process. This approach fits comfortably with the direction of industry and government thinking, with both being supportive of more efficient regulatory approval (a very different matter from regulatory or safety shortcuts). For instance, the IFPMA noted in October 2004 that: "It is in the interest of governments and patients to

make the regulatory process as swift and effective as possible, without compromising safety and quality standards.”<sup>16</sup> FTOs open the way to reaching this objective for all drugs in the long run.

Finally, the implementation of FTOs should be rather straightforward from a legislative point-of-view since, as discussed earlier, the fast track components are already available in the new EMEA legislation. What remains to be done is to package them into a formal scheme.

## The way forward

The next steps involve finalising the details and determining the attractiveness to industry, governments and health groups of such an incentive. We would therefore welcome the feedback of CIPIH participants and others on:

1. **The economic and business model:**  
An accurate valuation of the cash value of an FTO is important for both the government vendor and potential industry bidders. *We would therefore welcome feedback on further modelling first-mover advantage and R&D efficiencies.*
2. **Capturing the benefits:**  
Options for extracting the cash value of benefits for R&D in neglected diseases need to be further assessed. *We would therefore welcome feedback on other potential mechanisms as well as the practicalities of managing an auction mechanism: Could EMEA include this role in its mandate? Or would it require a special body?*
3. **Maximising outcomes for/with stakeholders:**  
Discussion with stakeholders (big and small) to ensure any FTO solution is attractive and politically feasible (industry, regulatory bodies, governments, R&D groups) are vital, since incentives only work if they are attractive to industry and provide a good public health outcome. *We would therefore welcome your views on the attractiveness and feasibility of an FTO. Other issues of interest to us are a) safeguards to ensure administrative efficiencies do not become potentially dangerous shortcuts – are they needed? If so, what could they be? And b) Your views on whether the efficiency gains should go entirely to fund new tools for neglected diseases or whether they should be shared with Western consumers through price reductions, or through restriction of FTO eligibility to “priority drugs” of interest to the West.*
4. **Ensuring optimal use of the resulting funds for neglected disease drug development:**  
This issue is addressed in a separate document, which is the result of extensive analysis of neglected disease drug development projects.

Contact: Pharmaceutical R&D Policy Project, LSE  
Email: [a.l.ropars@lse.ac.uk](mailto:a.l.ropars@lse.ac.uk) or [m.moran@lse.ac.uk](mailto:m.moran@lse.ac.uk)

<sup>16</sup> *The Pharmaceutical Innovation Platform: Sustaining Better Health for Patients Worldwide*; IFPMA, Oct. 2004; p.55

## Appendix 1

### How SPCs affect the impact of an FTO

In Europe, Supplementary Protection Certificates may be granted to compensate for loss of patent lifetime due to delays resulting from the medicinal product regulatory approval process. The term of the SPC is calculated as follows:

**Term of SPC = date of marketing authorisation *minus* date of filing patent application *minus* 5 years**

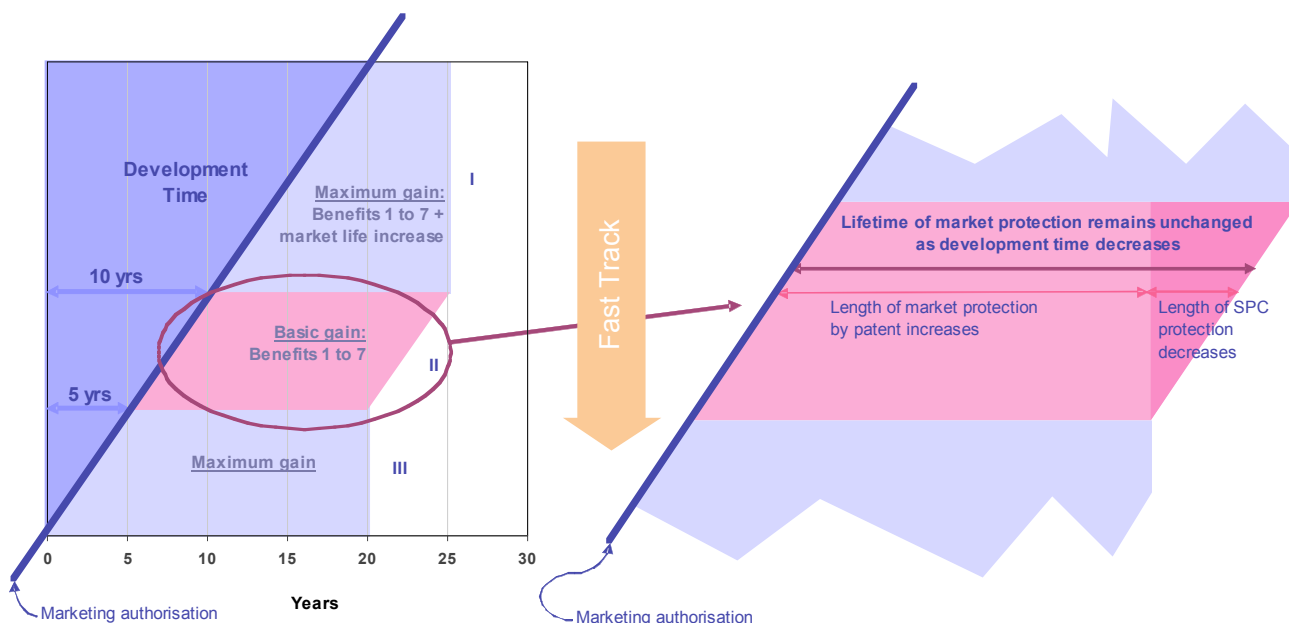
The relevant marketing authorisation date is the first marketing authorisation in the EC (or Norway, Iceland, Liechtenstein or Switzerland). The term of the SPC is capped at 5 years.<sup>17</sup>

In the case of an FTO, the approval process would go through EMEA so the date of first marketing authorisation would be that of the EMEA's approval.

Where the eligibility criteria are met, a Supplementary Protection Certificate may be granted to extend the life of market protection by up to five years. However, unlike a patent, the SPC protection only extends to the product which has received marketing authorization.

Therefore, depending on the length of productive patent life (itself dependent on R&D time) and on eligibility for an SPC, an FTO would bring different benefits:

**Figure 3: Relationship between fast track, patents and SPCs**



- If the time between filing the patent application and obtaining marketing approval is between 5 and 10 years (group II in figure 3 above), **although there will not be any absolute increase in the lifetime of market protection, more of this lifetime will be spent protected by the patent rather than the SPC**, which may be an advantage for the

<sup>17</sup> See for further information on SPCs the UK Patent Office Guide for SPC Applicants which explains the SPC system - <http://www.patent.gov.uk/patent/info/spctext.pdf>

patent/SPC holder as the protection given by the patent is broader than the protection given by the SPC. For instance, a drug that took 9 years to develop (or rather that took 9 years to move between filing the patent application and obtaining regulatory approval) would have a total market protection lifetime of 15 years – 11 years remaining of the patent lifetime and an SPC of 4 years. If, as a result of the FTO, that drug only took 8 years to develop, although the total market protection lifetime would still be 15 years (i.e. 12 years of the patent lifetime and 3 years of SPC) an extra year of this would be under patent protection rather than SPC protection.

- If the time between filing the patent application and obtaining marketing approval is either less than 5 years, or more than 10 years (groups I and III in figure 3 above), then **there will be an absolute increase in the lifetime of market protection**. For instance, again referring to Figure 1, a drug that took 12 years to develop (or rather that took 12 years to move between filing the patent application and obtaining regulatory approval) would have a total market protection lifetime of 13 years (i.e. 8 years remaining of the patent lifetime and an SPC of 5 years). If, as a result of the FTO, that drug only took 11 years to develop, the total market protection lifetime would increase from 13 years to 14 years – 9 years of patent lifetime and an SPC of 5 years.
- If, for any reason, a drug were only patent protected and no SPC had been granted, then the FTO would **always** bring an absolute increase in the lifetime of market protection.

## Appendix 2

### FTO gain: the example of Prozac

We assume that drug companies will purchase an FTO for one of their anticipated top revenue earners i.e. a first decile drug in terms of sales.

If the company developing such a 1<sup>st</sup> decile drug (Drug X) decided to purchase an FTO, its expected financial gain, calculated at the time of purchase, would depend on:

1. Whether or not the gain from the FTO will be “Basic” or “Maximum”;
2. How early in the development process the company makes the decision. This has an impact on (a) the expected number of years gained with the FTO, and (b) the present value of future earnings. We note that in their paper on Priority Review Vouchers (PRV) - which are a form of fast-tracked regulatory approval but not fast-tracked R&D - Ridley et al.<sup>18</sup> calculate NPV gain using the original launch date as base year. By contrast, we have chosen to estimate the value of an FTO to a company using the time of purchase of the FTO as a base year. This means discounting the value of the NPV gain by the number of years between time of purchase and expected time of launch to account for industry’s cost of capital. Although this approach provides a significantly lower figure than under the Ridley et al. model, we believe it more closely reflects standard industry valuation practice. Similarly, our valuation of PRVs uses as base year the time at which a company decides whether or not to invest resources in neglected disease R&D, based on expected returns derived from a PRV. This decision point may be up to 10 years before the PRV is granted, as it is proposed PRVs are awarded in exchange for finished ND drugs (at the end of the R&D process) – see Appendix 3 for calculations.
3. The risk that the drug will not reach the market.

We assume that a company willing to purchase an FTO today:

- Could launch Drug X two years early with the FTO if the drug were about to enter, or were in early, phase III with a launch expected in 5 years without the FTO. Based on standard attrition rates, the probability this drug will reach the market is 68.5%<sup>19</sup>;
- Could launch Drug X one year early with the FTO, if the drug were in late phase III (i.e. shortly prior to regulatory submission) with a launch expected in 2 years without the FTO. Because the company is likely to choose a drug with a low risk of approval failure, we estimate the probability this drug will reach the market to be 95%.

Based on these assumptions, the valuation of the various FTO gains is as follows:

#### **Basic FTO gain**

Basic gain can be expressed as follows:

$$NPV = s/(1+r)^z \times NPV_0 \times ((1+r)^y - 1)$$

Where:

- r = real discount rate
- NPV<sub>0</sub> = NPV of net earnings at launch date (base case)
- y = number of years gained through the FTO (1 or 2 years)
- z = number of years between time of decision to purchase the FTO and expected launch date without FTO
- s = likelihood the drug will reach the market

<sup>18</sup> Developing drugs for developing countries, Ridley D, Grabowski H, Moe J, December 2004

<sup>19</sup> The price of innovation: new estimates of drug development costs, DiMasi, Hansen, Grabowski, J Health Econ 2002

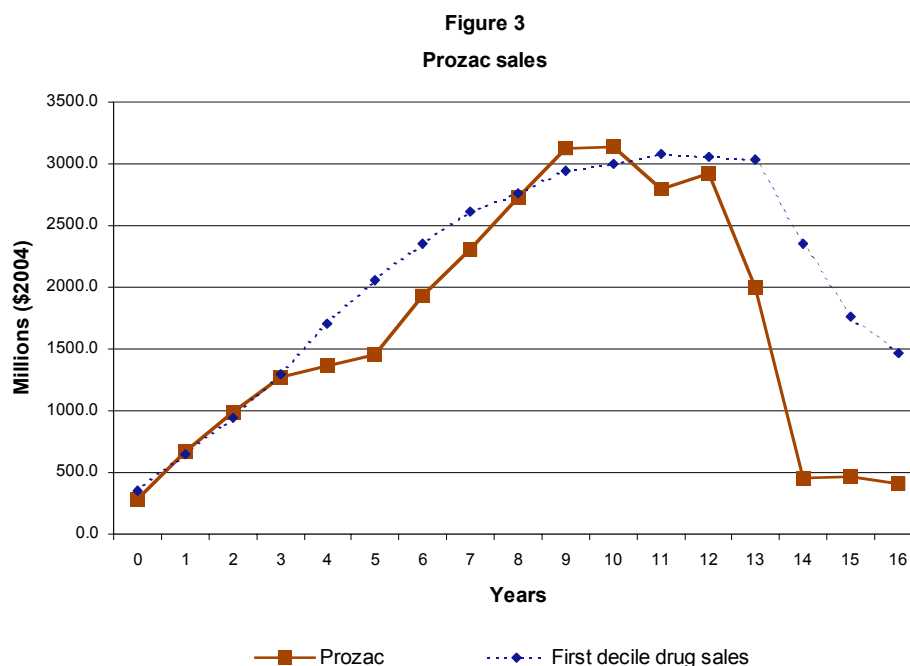
### Maximum FTO gain

Maximum FTO gain not only moves the revenue stream earlier but also changes the overall shape of the curve since it extends market life, which in most cases increases the peak sales period.

In calculating maximum FTO gain, we have assumed for the purposes of simplicity that the revenues in the additional year(s) of patent protected market life obtained from the FTO are equal to the revenues during the last year of patent protection without the FTO (see figure 5). The effects of depreciation on free cash flows vary from year to year with this modified revenue pattern (this does not happen with basic gain, where all yearly revenues/ CAPEX move simultaneously one or two years earlier). Therefore, the NPV gain from Maximum FTO benefit cannot be expressed in a simple formula as above. A straight NPV calculation at time of decision to purchase an FTO was run and the NPV differences found between the no-FTO and FTO scenarios are indicated in Table 3 below.

### The Prozac example

Using these calculations, we now demonstrate the potential financial gains if a company chose to apply an FTO to a drug with the same expected development time and earnings profile as Prozac. Prozac is a particularly helpful example, since the shape and length of its market life are typical of a 1<sup>st</sup> decile drug (see Fig.3) and because 17 years of sales data are available.<sup>20</sup>



Prozac was launched by Eli Lilly and Company in 1986 in Europe (1988 in the US), and is a typical blockbuster. The drug experienced steadily growing sales for the first 12 years of its market life, generating a third of the company's earnings by 1996 and reaching global peak sales of nearly \$2.9 billion in 1998. From 1999 onwards, the entrance of newer anti-depressants such as Zoloft and Paxil started eroding Prozac's market share. Between 2000 and 2002, the patents protecting the drug expired across the globe. This led to a record drop in sales of more than 80% within a year.

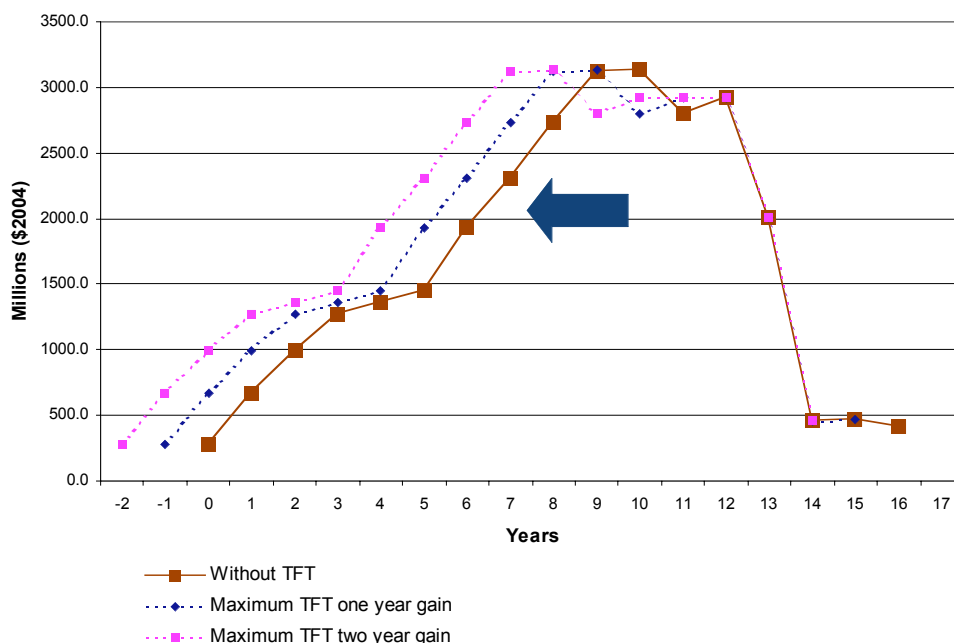
<sup>20</sup> Global sales are based on 17 years of US sales data divided by 90% (the US market share of the global Prozac market)

The success of Prozac ranks the drug within the top-decile revenue earners group (defined by Grabowski et al. as earning at their peak an average of 2.6 billion a year in 2000 dollars<sup>21</sup> - equivalent to 2.5 billion in 1998 dollars). Prozac sales between 1998 and 2004 yielded an NPV at launch of about \$3.2 billion<sup>22</sup> in 2004 dollars.

In the UK, Prozac was introduced in 1988, with its main patent due to expire in January 1995. Because time between patent lodging and marketing approval was 13+ years, the drug was granted an SPC capped at 5 years (to compensate for regulatory delays of 8+ years as per the SPC calculation – see Appendix 1).

If Prozac had benefited from an FTO in Europe and been launched one or two years earlier, the SPC would have remained at 5 years (to compensate for regulatory delays of 6+ or 7+ years, instead of 8+, as per the SPC calculation). Prozac therefore belongs to the group of drugs eligible for Maximum FTO gain. An FTO for Prozac would therefore have resulted in the drug coming to market one or two years earlier, hence achieving peak sales earlier and extending its patent-protected market life by one or two additional years (see Fig. 4).

**Figure 4**  
Impact of Maximum TFT gain on Prozac sales

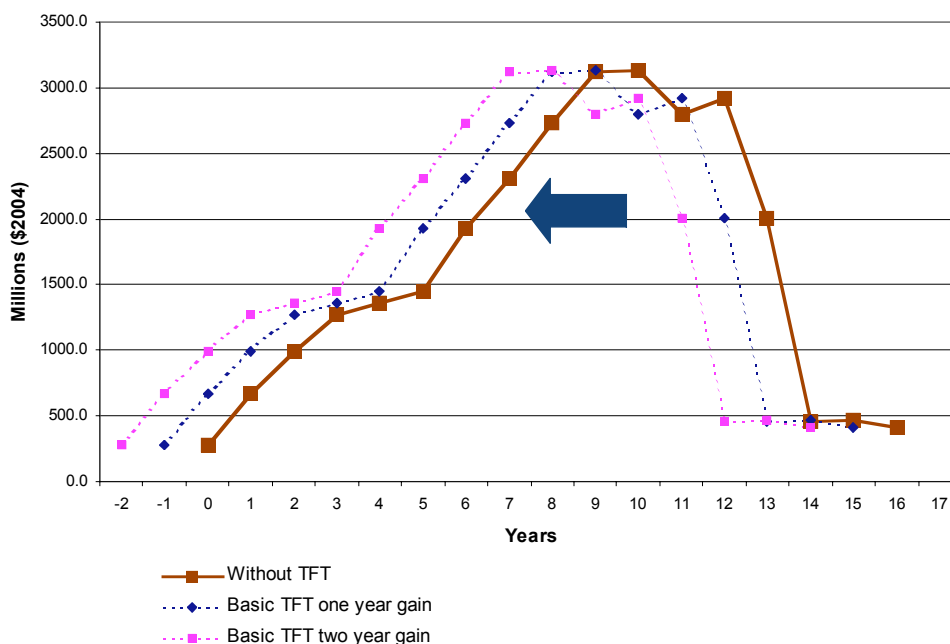


A drug X with an earnings curve similar to that of Prozac but which is ineligible for market extension (i.e. because its shorter development time reduces the SPC gain) would still benefit from Basic FTO gain - in other words, from early access to market and to peak sales (see Fig.5).

<sup>21</sup> Returns on R&D for 1990s new drug introductions, Grabowski et al., 2002

<sup>22</sup> Assumptions used: 11% real discount rate; EBITDA margin increases from year 0 to Year 8 with the following progression: -35%, -10%, 10%, 30%,40%, 45%, 50%, 55%, 60%, and remains constant from year 9 onwards (margin accounts for heavy sales and marketing expenses in the first years of market life, which lead to negative earnings in first 2 years); average effective tax rate: 30%; Post-launch CAPEX assumed to be 20% of 10th year of sales, split over first ten years of market life; straight line depreciation over 10 years.

**Figure 5**  
**Impact of basic TFT gain on a drug with a sales curve similar to that of Prozac**



The financial benefits that an FTO would deliver today in both these scenarios are set out in Table 3 below – (we note again that these figures exclude the significant benefits to be obtained from first-mover advantage and from savings in the R&D process).

The table includes estimates of NPV gains using both time of launch and time of purchase of the FTO as base years. Although, as discussed above, we believe the latter calculation more accurately reflects the way companies will value an FTO, we have included the former to allow a comparison to the anticipated gains as estimated for other incentives (PRVs/TIPR).

**Table 3: FTO impact on NPV of free cash flows using Prozac as an example (2004 US dollars)**

	Launch 1 Year early			Launch 2 Years early		
	NPV gain estimated at time of launch*	NPV gain estimated at time of purchase (2 years before launch)		NPV gain estimated at time of launch*	NPV gain estimated at time of purchase (5 years before launch)	
		On a successful drug	Discounting for risk		On a successful drug	Discounting for risk
<b>Basic gain</b>	+\$357m	+\$290m	<b>+\$275m</b>	+\$753m	+\$447m	+\$306m
<b>Maximum gain</b>	+\$610m	+\$495m	+\$470m	+\$1,282m	<b>+\$761m</b>	<b>+\$521m</b>

\* For comparison purposes only

## Appendix 3

### PRV gain: the example of Prozac

Under the PRV concept developed by Grabowski (2003) and Ridley et al. (2004), companies who create and license a drug for neglected diseases would be rewarded with a voucher offering FDA priority review status for another (commercial) drug. The voucher would be tradable.

Table 4 below gives estimates of the financial benefits of a PRV if applied to a drug with a profile similar to Prozac, accounting for:

- Length of ND R&D, which determines the time at which a PRV will be granted in the future;
- Industry cost of capital, at which future earnings must be discounted;
- Benefits of earlier returns;
- Risk of failure of the ND drug, to reflect the risk that the company may not receive a PRV if the drug fails;
- Longer patent-protected market life associated with the PRV, when applicable.

The table includes estimates of NPV gains using as base year both time of launch and time of making the decision to develop a ND drug, this to allow comparison with the Ridley et al. model.

**Table 4: PRV impact on NPV of free cash flows using Prozac as an example (2004 US dollars)**

NPV gain, estimated at time of:	Launch 6 months early (EU)			Launch 8 months early (US)		
	Launch*	Starting 5 year ND R&D program**	Starting 10 year ND R&D program***	Launch*	Starting 5 year ND R&D program**	Starting 10 year ND R&D program***
<b>Basic gain</b>	+\$174m	+\$71m	+\$13m	+\$234m	+\$95m	+\$18m
<b>Maximum gain</b>	+\$308m	+\$125m	+\$23m	+\$416m	+\$169m	+\$31m

\* For comparison purposes only

\*\* Assuming only phase III trials and regulatory dossier need to be completed to license a ND drug; expected launch (and hence award of PRV) in 5 years; chance the ND drug will reach the market assumed to be 68.5% (DiMasi et al. 2002)

\*\*\* Assuming ND drug is at IND stage; expected launch (and hence award of PRV) in 10 years; chance the ND drug will reach the market assumed to be 21.5% (DiMasi et al. 2002)