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Stefan Felder and Anja Olbrich

Dealing with Excessive Off-label Drug Use: Liability vs. Patent Prolongation

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Stefan Felder and Anja Olbrich*

Dealing with Excessive Off-label Drug Use: Liability vs. Patent Prolongation

Abstract
The US and the EU recently introduced regulation to curb the extent of risky off-label drug use. It offers manufacturers a prolongation of patent protection or exclusivity if they invest in pediatric clinical tests. This paper shows that a reinforcement of physician liability for off-label use may be the preferred instrument for achieving dynamic efficiency. The liability threat reduces the demand for off-label use, giving manufacturers an appropriate incentive to invest in extended approval. By contrast, patent prolongation does not affect physicians' prescription decisions and increases the likelihood of investments in cases where the induced additional benefit falls short of testing costs.

JEL Classification: I11, K13

Keywords: Off-label use, patent protection, exclusivity, liability

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1 Introduction

Drugs must be authorized by a relevant regulatory body in order for physicians to be able to prescribe them. The marketing authorization is granted if the drug is judged to be safe and effective for a given population or indication. This is the drug 'label'. When the drug is used for other indications, it is used 'off label'.

The off-label use of drugs has been estimated to reach 20% of all prescriptions in Germany (Bücheler et al., 2003, Ehlers and Bitter, 2003) and even 40-60% in the US (Reilly and Dalal, 2003). In pediatrics, the off-label issue is particularly widespread, all the more in pediatric oncology where it reaches 80% in the US and 90% in Germany. Often, however, the effects of off-label drug use on patients' health status are uncertain. Radley et al. (2006) find in a representative US dataset that 73% of all out-patient prescriptions are only weakly or not at all evidence based. Off-label drug use for children is considered particularly risky, a claim supported by Turner et al. (1999).

The extensive and risky off-label use of drugs led governments to adjust patent and exclusivity regulations.[1] With the FDA Modernization Act of 1997, the US - followed by the European Union in 2006 - introduced a reward for pharmaceutical manufacturers if they strive for extended approval of off-label drugs in pediatrics. A six-month prolongation of the patent or exclusivity is granted for an investment in pediatric clinical tests.[2] For orphan drugs, the EU even offers the manufacturers a two year prolongation if they invest in additional tests. As manufacturers trade off the costs of pediatric testing and the expected additional sales, the extension of an exclusive marketing right can be decisive for their investment choice.

Aside from approval conditions, prevalent liability rules affect manufacturers' profits as well. For label drug use, a manufacturer providing full product information, including proper warnings about side effects in the physician's desk reference and package insert cannot be held liable for ordinary patient damages (see for Germany §84 AMG and for the US Calfee, 2006). If prescribing physicians comply with professional standards by following the manufacturer's

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[1] Regulation differentiates between exclusivity and patents. In the US, exclusivity is granted upon approval of a drug if the statutory requirements are met. It can run concurrently with a patent or not. In the EU, exclusivity can only follow a patent, compensating for the delay between patent application and the time of approval. Exclusivity rights extend up to seven years, while a patent life lasts 20 years.

[2] One further difference between the two laws is that the US grants the extension of patent protection only if the off-label drug passes the clinical tests while the EU does it irrespective of the test outcome.

instructions, they cannot be held liable either (see for Germany Laufs and Uhlenbruck, 2002 and for the US Evans and Flockhart, 2006).

For off-label use, instead of providing full product information, manufacturers are required to inform on a lack of information in order to avoid any liability (Reilly and Dalal, 2003). Consequently, if a manufacturer has complied with these obligations, physicians can always be held liable for damages; i.e. strict liability applies to physicians prescribing off-label. For label use, by contrast, the common negligence rule for physicians holds.

Given these liability circumstances, a manufacturer's sales in the off-label market will depend on physicians' expectations of possible damages to patients as well as on court decisions in malpractice lawsuits. The observed widespread off-label use of drugs, thus, might reflect biased physicians' estimation of the side effects, underreporting of patient damages or biased court decisions. In fact, current liability rules are likely to provide too positive information on off-label drugs, since type 2 errors, occurring when a lawsuit is not filed or liability not found in true instances of negligence, are more prevalent than type 1 errors (Danzon, 2000). As for the pharmaceutical manufacturers, one can observe that they tend to underreport negative information on off-label use of their drugs (see Kmietowitz, 2009 for a lawsuit on this issue). For the physicians, both effects and the lack of evidence-based information will shed a very positive light on the off-label use of drugs.

If their off-label sales are upwardly biased, manufacturers will be reluctant to invest in extended approval. Although a prolongation of patent duration would increase profits, manufacturer will not necessarily undertake the corresponding investment. If the physicians' damage perception is particularly weak, off-label drug sales will be large and manufacturers will not want to change to label use. By contrast, if physicians rarely prescribe off-label, sales might substantially increase following extended approval, even though in some cases the corresponding costs will still exceed the additional net benefits to the patients. A well functioning liability system may prevent dynamically inefficient outcomes, as it affects patients' and physicians' demand for drugs.

This paper compares two instruments for the regulation of off-label drug use: prolongation of patent protection and reinforcement of physician liability. To this end, we first introduce the social optimum for off-label drug use. It is assumed that a pediatric population benefits from off-label drug use but, as the optimal intake is unknown, expected damages are larger than for label use. Additional testing comes with costs to the pharmaceutical manufacturer but will reduce

expected damages. As a result, the drug is approved and thus becomes a label drug. We show that the effect of clinical tests on expected damages determines whether off-label or label drug use is optimal from a social perspective.

We then set up an equilibrium model where a manufacturer can always avoid liability by providing full product information about label drug use and by informing on a lack of information on off-label use. Altruistic physicians maximize their patients' expected utility, which incorporates the benefits and perceived expected damages of treatment. We assume that physicians underestimate damages, implying that they tend to prescribe off-label too often. A manufacturer will seek extended approval when expected additional profits are positive. Given that the price of the drug is fixed at its level in the original label market, the manufacturer's main focus is on the expected change of prescriptions and the testing costs.

Finally, the paper analyzes the extent to which prolongation of patent protection or enforced liability can lead to a statically and dynamically efficient allocation. Patent prolongation cannot restore static efficiency, as it does not affect physicians' decisions. It can induce manufacturers to seek extended approval in cases where this is socially indicated. However, a prolongation of patent protection may also result in biased investment decisions. If the liability system enforces the internalization of patient damages in the physicians' decisions, dynamic and static efficiency is restored.

The paper is organized as follows: Section 2 derives the first-best solution. The market equilibrium under current liability rules is presented in section 3. In section 4 the regulatory schemes to ensure the first best are characterized. It is shown that the reinforcement of physicians is the dominant instrument. Conclusions are provided in section 5.

2 Static and dynamic efficiency

A drug which has been successfully tested and approved for an adult population is potentially also beneficial for children, even if it has not yet been tested for this population. The question then arises whether the drug is best used off-label in pediatrics or clinically tested to receive extended approval. The answer depends on the relative sizes of testing costs and additional patient net benefit from label drug use.

The pediatric patients' benefits b from consumption of the drug is assumed to be distributed in the interval $[0,\bar{b}]$ according to the distribution function $F(x)$ and the density function $f(x)$. The lifetime of the drug is *L* years and the marginal cost of producing the drug is assumed to be zero.

Consider first the off-label use of the drug. Without additional testing, the optimal mode of drug intake (e.g. timing or dosage) is unknown, leading to expected damages $E[D]>0$ per patient. The expected social welfare of an off-label drug is the sum of expected health effects minus expected damages over the drug's lifetime:

$$W^{ol} = L\int_{\tilde{b}}^{\bar{b}} xf(x)\,dx - L\left[1-F(\tilde{b})\right]E[D]\,, \tag{1}$$

where the superscript *ol* denotes the off-label regime. Off-label use welfare is maximized if the drug is prescribed to all patients with $b \geq \tilde{b}^{ol} = E[D]$.[3]

Alternatively, the drug might be clinically tested at costs *C*. For simplicity, we assume that testing can be done immediately and that it would provide information about the optimal mode of drug intake. This would decrease expected damages to $\theta E[D]$, with $\theta \in (0,1)$, and lead to an extended approval of the drug.[4]

The expected net social welfare of an approved drug (indicated by the superscript *l*) equals

$$W^{l} = L\int_{\tilde{b}}^{\bar{b}} xf(x)\,dx - L\left[1-F(\tilde{b})\right]\theta E[D] - C\,. \tag{2}$$

Label use welfare is maximized if all patients with $b \geq \tilde{b}^{l} = \theta E[D]$ receive a prescription. Since $\tilde{b}^{l} < \tilde{b}^{ol}$, more prescriptions $\left[1-F(\tilde{b}^{l})\right] > \left[1-F(\tilde{b}^{ol})\right]$ and higher average health effects $\int_{\tilde{b}^{a}}^{\bar{b}} xf(x)\,dx > \int_{\tilde{b}^{o}}^{\bar{b}} xf(x)\,dx$ result from approval of the drug.

Static efficiency in the label and off-label regimes is achieved if benefits equal expected damages for the marginal patient ($\tilde{b}^{ol} = E[D]$ and $\tilde{b}^{l} = \theta E[D]$ resp.). Dynamic efficiency however

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[3] This implies that with particularly large expected damages $E[D] \geq \bar{b}$ no prescriptions at all are first-best.

[4] Considering a possible negative test outcome would complicate matters without yielding further insights.

requires more: a comparison of (1) and (2) shows that social welfare is maximized over the long run if expected additional benefits of an extended approval exceed testing costs:

$$\int_{\theta E[D]}^{E[D]} x f(x)\,dx + \left[(1-\theta) \int_{E[D]}^{\bar{b}} f(x)\,dx - \theta \int_{\theta E[D]}^{E[D]} f(x)\,dx \right] E[D] > \frac{C}{L}. \tag{3}$$

The gain in social welfare, including health benefits of additionally treated patients in the label regime (first term) and reduced expected damages to patients in the former off-label regime (second term), has to be sufficiently larger than the expected damages to additionally treated patients (third term).

Since the left-hand side of (3) is zero if additional testing is ineffective $\theta = 1$ and its derivation with respect to test effectiveness is negative (see Appendix A),

$$\frac{\partial}{\partial \theta} = -E[D] \int_{\theta E[D]}^{\bar{b}} f(x)\,dx < 0, \tag{4}$$

a threshold $0 < \bar{\theta} < 1$ exists where society is indifferent between off-label and label use. Therefore, testing is always socially indicated if it decreases expected damages sufficiently, or $\theta < \bar{\theta}$ to fulfill (3). In this case, drug demand equals $\left[1 - F(\tilde{b}^{l})\right]$. If $\theta \geq \bar{\theta}$, additional testing is not socially beneficial and a lower demand for drug $\left[1 - F(\tilde{b}^{ol})\right]$ should be met.

3 The markets for off-label and label drugs

3.1 The prescription decision by physicians

Physicians are assumed to show altruistic preferences. More specifically, we assume that physicians maximize their patients' expected utility. Beyond the Hippocratic oath, existing liability rules will lead physicians to adequately consider expected damages of drug therapy, in particular. For label use, where the negligence rule applies, the physician has to inform the patient about benefits and risks of the treatment. And for off-label use, strict liability applies, so that the physician can always be held liable for damages. Hence under both regimes, physicians will have to consider expected damages to the patients when deciding on drug prescription.

To the extent that a patient's health insurance covers drug expenses[5], the drug price will not enter the physician's decision. For the physicians, neither the cost of approval nor the lifetime of the drug is decisive; thus we cannot expect that their decisions will be consistent with the dynamic efficiency concept characterized in the last section. Furthermore, their behavior will not even comply with static efficiency if they have biased expectations about the possible damage of off-label drug use. We assume that physicians could underestimate or overestimate expected damages according to $\lambda \in (0,1)$ or $\lambda > 1,$ respectively, giving rise to expected damages equal to $\lambda E[D]$. By contrast, for label drug use, we assume accurate damage expectations, i.e. $\theta E[D]$.

When prescribing an off-label drug, physicians maximize expected patient utility $\int_b^{\bar{b}} xf(x)\,dx - [1-F(b)]\lambda E[D]$. The threshold for prescribing the drug off label thus is $\lambda E[D]$ and demand equals $1-F(\lambda E[D])$. However, the condition for static efficiency will only be met if $\lambda = 1$.

With approved label drug use, physicians act according to the perceived expected patient utility $\int_b^{\bar{b}} xf(x)\,dx - [1-F(b)]\theta E[D]$ if they treat all patients with positive health effects equal to or higher than expected damages $b \geq \theta E[D]$. Demand for label drug use thus amounts to $1-F(\theta E[D])$ and is in line with static efficiency. The number of label prescriptions will increase from off-label to label use only if $\lambda > \theta$. Thus, a pharmaceutical manufacturer will only seek extended approval if physicians do not underestimate the potential damages of off-label use too much.

3.2 The investment decision by the manufacturer

Manufacturers decide whether to invest in extended approval of a drug or remain with off-label sales depending on the expected profits. One of the manufacturers' decisive parameters is the price *p* which we assume to be given (naturally it is the manufacturer's price in the label market).

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[5] Danzon (1997) estimates that 60% of drug sales in the US and an even higher share in the EU are paid for by health insurance. Hellerstein (1998) and Lundin (2000) argue that even if patients pay for drugs themselves, physicians won't take this into account because they simply don't know the price.

Demand is assumed to be price inelastic; it is the physicians' prescription decision which determines the manufacturers' sales. Patent duration is given by P years.

In the off-label regime, the manufacturer's profits amount to

$$\pi^{ol} = P\left[1 - F\left(\lambda E[D]\right)\right] p \ . \tag{5}$$

This shows that expected profits decrease with damage perception $\partial \pi^{ol} / \partial \lambda < 0$ and can even converge to zero if damages are sufficiently overestimated with $\lambda \geq \bar{b} / \mathrm{E}[\mathrm{D}]$. Therefore, it is safe to assume that manufacturers will try to extenuate the physicians' damage perception as far as possible by issuing appropriate information. Physicians might possibly perceive the true damage level, but it is more likely that their perceived damages fall below $\mathrm{E}[\mathrm{D}]$; in the following we will in fact assume that $\lambda \leq 1$.[6]

If the manufacturer decides to test the drug for extended use, profits in the label regime equal

$$\pi^{l} = P\left[1 - F\left(\theta E[D]\right)\right] p - C \ . \tag{6}$$

Therefore it follows that a manufacturer will invest in extended approval if expected additional period profits are sufficiently high. From (5) and (6) we obtain the corresponding condition:

$$\left[F\left(\lambda E[D]\right) - F\left(\theta E[D]\right)\right] p > \frac{C}{P}. \tag{7}$$

This equation clarifies that an increase in sales is a necessary condition for an investment in extended approval; sales will only increase if $\lambda > \theta$. From (7) one can determine a function of combinations (λ, θ) which render a manufacturer indifferent between label and off-label drug use:

$$\tilde{\lambda}(\theta) = \frac{1}{E[D]} F^{-1}\left(F\left(\theta E[D]\right) + \frac{C}{pP} \right). \tag{8}$$

As $F(x)$ is an increasing function, its inverse and, thus, $\tilde{\lambda}(\theta)$ exists. This function crosses the ordinate at $\tilde{\lambda}(0) = \frac{1}{E[D]} F^{-1}\left(\frac{C}{pP} \right) > 0$, indicating that correct damage perception $\lambda = 1$ can lead

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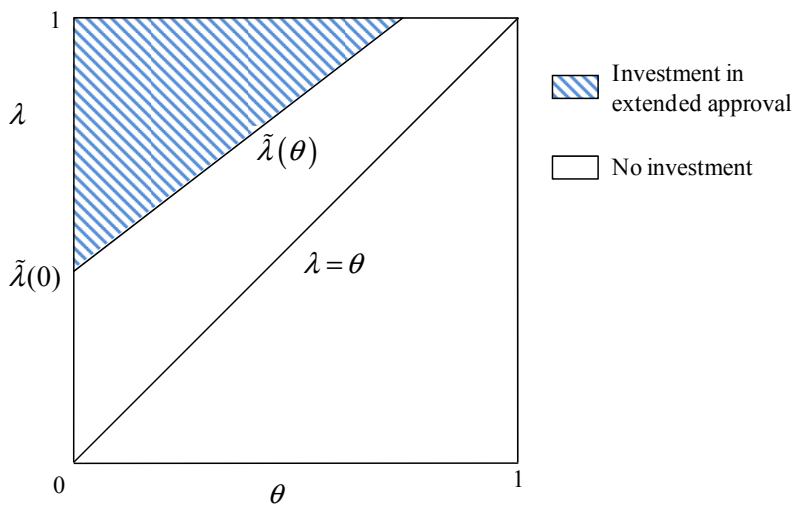
[6] If $E[D] \geq \bar{b}$, the incentive for lowering damage perceptions, is particularly strong because otherwise demand is zero.

to an additional approval only if $\tilde{\lambda}(0) < 1$ or $E[D] > F^{-1}\left(\frac{C}{pP}\right)$. Furthermore, the function lies above the diagonal $\lambda = \theta$[7] – otherwise sales would not increase under label use – and has a positive slope:[8]

$$\frac{\partial \tilde{\lambda}(\theta)}{\partial \theta} = \frac{f\left(\theta E[D]\right)}{f\left(F(\theta E[D]) + C/pP\right)} > 0 . \tag{9}$$

A manufacturer will invest in extended approval where $\lambda > \tilde{\lambda}(\theta)$ (see the hatched area in Figure 1). When $\lambda \leq \tilde{\lambda}(\theta)$ off-label use will prevail.

Figure 1: A manufacturer's investment decision



If demand for the drug under label use exceeds demand for off-label use because $\lambda > \theta$, the manufacturer is more likely to invest the more sales increase with label use. A high drug price also increases the probability of an investment. The comparative static analysis also shows that

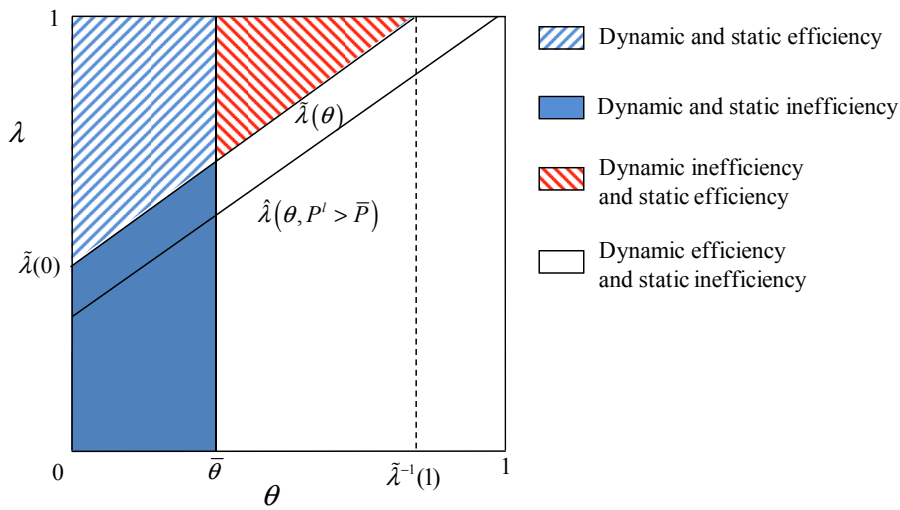
[7] See Appendix B for proof.

[8] For the uniform distribution with $f = \frac{1}{b}$, $F(x) = \frac{x}{b}$, and $F^{-1} = x$, we obtain $\tilde{\lambda}(\theta) = \theta + \frac{\bar{b}}{pE[D]}$ and slope $\frac{\partial \tilde{\lambda}(\theta)}{\partial \theta} = 1$.

the incentive for gaining extended approval becomes stronger if testing costs are low, the drug price is high, patent duration is long and expected damages are large.

Figure 2 characterizes the private decisions from the perspectives of dynamic and static efficiency. $\bar{\theta}$ indicates the minimal damage decrease due to testing that renders the investment in extended approval socially beneficial. For $\theta < \bar{\theta}$, the manufacturer will comply with the social optimum if condition (7) is fulfilled, e.g. $\lambda > \tilde{\lambda}(\theta)$ (hatched rectangle). In this case, the expected additional period profits from label drug use are sufficiently large, as physicians prescribe much more than under off-label use. Static efficiency is also achieved, since physicians use the correct information in their treatment decisions.

Figure 2: Static and dynamic efficiency of private decisions



By contrast, a lower risk perception of physicians increases demand for off-label use. This in turn decreases expected additional period profits from label drug use and thus deters the manufacturer from undertaking socially worthwhile investment in additional testing ($\lambda \leq \tilde{\lambda}(\theta)$). Due to the underestimated damages, the resulting demand for off-label use will be inefficiently high (shaded area).

When off-label use is the first-best regime, $\theta \geq \bar{\theta}$, a manufacturer's choice will be consistent if

$\lambda \le \tilde{\lambda}(\theta)$. However, demand will again be above first best as physicians underestimate possible damages to patients (white area). If $\lambda > \tilde{\lambda}$, the manufacturer's decision to seek approval is inefficient (hatched triangle). Still, given that the approval signals the true expected damages and thus corrects a possibly distorted damage perception, static efficiency will be reached.

4 Liability vs. patent prolongation

Let us first consider the current regulation that rewards manufacturers that invest in additional pediatric tests with a prolongation of patent protection. As an increase of the patent life only applies when investment is undertaken, we differentiate between off-label patent duration $\overline{P}$ and label use patent duration P^l, with $P^l \ge \overline{P}$. Equation (8) then changes slightly to:

$$\hat{\lambda}(\theta) = \frac{1}{E[D]} F^{-1}\left(\left\{ F\left(\theta E[D]\right) - 1 \right\} \frac{P^l}{\overline{P}} + 1 + \frac{C}{p\overline{P}} \right), \tag{10}$$

If $P^l = \overline{P}$, we have $\hat{\lambda}(\theta) = \tilde{\lambda}(\theta)$. Define $y = \left\{ F\left(\theta E[D]\right) - 1 \right\} \frac{P^l}{\overline{P}} + 1 + \frac{C}{p\overline{P}}$. For the comparative statics, we then obtain

$$\frac{\partial \hat{\lambda}(\theta))}{\partial P^l} = -\frac{1 - F\left(\theta E[D]\right)}{f(y)} \frac{1}{E[D]\overline{P}} < 0 \,. \tag{11}$$

When the patent duration for label use is increased, testing cost per period decreases, which in turn is likely to induce manufacturers to invest in extended drug approval (in Figure 2 depicted by a shift of $\hat{\lambda}\left(\theta, P^l > \overline{P}\right)$ to the south-east). From a social perspective, this is warranted if dynamic and static efficiency is achieved with label use, i.e. in Figure 2, where the hatched area in the interval $0 < \theta < \overline{\theta}$ is enlarged.

However, as an increase of patent duration has no effect on physician behavior, $\tilde{\lambda}(\theta)$ keeps its shape and inefficiency persists if damage perception is low $\lambda \le \tilde{\lambda}(\theta)$ and $\theta < \overline{\theta}$. Moreover, the range of inefficient approvals increases: For $\theta \ge \overline{\theta}$, it is more likely that manufacturers seek extended approval.

The analysis has so far neglected the fact that the prolongation of a patent does not only refer to

the new label-use market but also to the original label-use market. Additional sales in the original market have a leverage effect on the investment decision. Investment is then more likely both in situations where this is socially indicated and situations where it is not.

Alternatively, let us consider the possibilities of enforced physician liability to induce the correct investment decision and the first-best amount of drug consumption. Here, the patent duration remains unchanged at *P* years.

Due to the biased estimation of possible damage to the patients $\lambda < 1$, off-label demand is generally different from the socially optimal choice. Assume that a multiplier *m* applies to expected damages, $mE[D]$, in the off-label use regime where physicians are held liable for damages from treatment. The physician's expected utility then changes to $\int_b^{\bar{b}} xf(x)dx - [1-F(b)]m\lambda E[D]$ and the treatment threshold becomes $m\lambda E[D]$. Demand for off-label use finally is $1-F(m\lambda E[D])$ and decreases with the multiplier:

$$\frac{\partial(1-F(m\lambda E[D]))}{\partial m} = -\lambda E[D] < 0 . \tag{12}$$

It follows that the multiplier

$$m^o = \frac{1}{\lambda} \tag{13}$$

will correct for physicians' biased expectations and thus restore static efficiency. The question remains, however, whether the multiplier will also suffice to achieve dynamic efficiency.

Consider first $\theta < \overline{\theta}$, where dynamic inefficiency arises if $\lambda \le \tilde{\lambda}(\theta)$. Since $\tilde{\lambda}(\theta) < 1$ an even smaller multiplier than m^o would do to restore dynamic efficiency. Dynamic efficiency is reached when a multiplier equal to

$$m^{\min} = \frac{\tilde{\lambda}(\theta)}{\lambda} < 1 \tag{14}$$

is applied. The manufacturer will invest in extended approval, since the resulting additional sales are sufficiently high to recoup the fixed costs. If investments take place, static efficiency will also be restored, assuming that information from the drug approval process realigns physicians' expectations of damage to the patients.

However, for $\bar{\theta} \le \theta < \tilde{\lambda}^{-1}(1)$ where off-label use is the socially preferred regime, the multiplier m^o is too large and $m^{\min}$ is too small. While with the former off-label use will be too low so that manufacturers would still invest in order to increase drug sales, the latter avoids an investment but leads to excessive off-label demand.[9] In order to foster overall efficiency, m^o and an ad valorem subsidy equal to

$$s = \frac{F\left(E[D]\right) - F\left(\theta E[D]\right) - C/(pP)}{1 - F\left(E[D]\right)} \tag{15}$$

are required. The subsidy rate s on off-label sales will ensure that profits from label and off-label use are the same.

Such a two-tiered instrument with a damage multiplier and a higher price for off-label sales ($p(1+s)$) cannot, however, be advised in general, since it could lead to wrong incentives in the range $\theta < \bar{\theta}$. In other words, investments in extended approvals could be prevented in situations where they are socially indicated. This leads to the conjecture that dynamic and static efficiency cannot be achieved simultaneously.

5. Conclusions

This paper deals with off-label use of drugs, a field of medicine that, until recently, has hardly been subject to regulation. If a pharmaceutical manufacturer proved safety and effectiveness of its drug, it received a marketing authorization for the tested population. Moreover, the drug could be legally sold to any other untested population. The liability system was the only incentive mechanism that affected manufacturers' and physicians' behavior.

The effect of off-label drug use on social welfare bears a trade-off: on one side, social benefits arise from an untested population that derives positive health effects and from manufacturers that save testing costs. On the other side, due to the lack of systematic evidence, off-label drug use is more risky than label drug use. Social costs always arise if potential damages are underestimated. A priori, this trade-off renders the total welfare effect unclear.

Over the last two decades, the extensive use of off-label drugs in pediatrics has led legislators in

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[9] For $\theta \ge \tilde{\lambda}^{-1}(1)$ multiplier m^o achieves static as well as dynamic efficiency.

the US and EU to adjust approval rules. If a pharmaceutical company strives for more evidence on off-label drug use in children by investing in additional tests, it will receive a prolongation of patent protection or exclusivity. This change in politics was long awaited and welcomed by national ministries and pharmaceutical manufacturers (for Germany, see the press releases of the Federal Ministry of Health, 01/23/2007 and of the Association of Research-Based Pharmaceutical Companies, 01/25/2007).

This paper shows that a prolongation of patent protection, given both the prevalent liability incentives and a lack of evidence based information, might not be the best strategy. A longer patent duration does not lead to socially beneficial investment in additional tests if the damages from off-label use are underestimated. Even worse, additional tests might be undertaken despite a societal preference for off-label use. Rather than prolonging patent protection, reinforcing liability for physicians should be the preferred instrument. Applying a multiplier to patient damages will reduce the number of off-label prescriptions and thus give manufacturers an incentive to invest in extended approval.

The reinforcement of liability is similar to punitive damages applied in claims trials. Punitive damages internalize the patients' utility loss not covered by common damage payments (Cooter 1982). The multiplier similarly augments expected damages. As it corrects for biased risk perception and can be applied to a strict liability rule as well, it represents a more general concept.

The argument for strengthening liability incentives instead of rather unspecific regulation measures is in line with other authors' recommendations. Shavell (1984), Kolstad, Ulen and Johnson (1990) or, more recently, Schmitz (2000) show that safety regulation alone is inefficient and argue for a balance between ex post liability and ex ante safety measures. Still, the approach of connecting liability incentives with R&D investments is new.

The model could be extended to include a preference for risk. If patients suffering from a severe illness are risk-loving and physicians act altruistically, off-label use will be upwardly biased. Following our paper's rationale, this again gives scope for reinforced liability. Moreover, given that clinical tests do not only reduce expected damages to patients but also the variance of damages, further reason for fostering R&D through enforced liability is provided.

The framework of this model could also be used to analyze the conditions under which pharmaceutical manufacturers will truthfully reveal a drug's characteristics, including its potential side effects. As providing full information will avoid liability but also decrease demand for the corresponding drug, the risk perception of physicians and patients and the drug price will be important factors in a manufacturer's decision to truthfully inform on the drug. The higher the drug price, the more likely a manufacturer will hide information, as the profit loss from a decrease in demand increases with the price.

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Appendix

Appendix A

To find the inequality (4) we differentiate the l.h.s. of (3) w.r.t. θ, using Leibniz' rule:

$$\frac{\partial \left[\int_{\theta E[D]}^{E[D]} xf(x)dx + \left[(1-\theta)\int_{E[D]}^{\bar{b}} f(x)dx - \theta\int_{\theta E[D]}^{E[D]} f(x)dx\right]E[D]\right]}{\partial\theta}$$

$$= -\theta E[D] f\left(\theta E[D]\right) E[D] - \left\{\int_{E[D]}^{\bar{b}} f(x)dx + \int_{\theta E[D]}^{E[D]} f(x)dx - \theta f\left(\theta E[D]\right) E[D]\right\} E[D]$$

$$-E[D]\left\{\theta E[D] f\left(\theta E[D]\right) - \theta E[D] f\left(\theta E[D]\right) + \int_{\theta E[D]}^{\bar{b}} f(x)dx\right\}$$

$$= -E[D]\int_{\theta E[D]}^{\bar{b}} f(x)dx < 0.$$

Appendix B

We have to prove that $\tilde{\lambda}(\theta) > \theta$. Assume by contradiction that $\tilde{\lambda}(\theta) < \theta$. Then an $\alpha > 0$ exists such that

$$\tilde{\lambda}(\theta) = \theta - \alpha.$$

Inserting (8) for $\tilde{\lambda}(\theta)$, we find

$$\frac{1}{E[D]} F^{-1}\left(F\left(\theta E[D]\right) + \frac{C}{pP}\right) = \theta - \alpha \text{ or}$$

$$F^{-1}\left(F\left(\theta E[D]\right) + \frac{C}{pP}\right) = E[D](\theta - \alpha). \text{ Then,}$$

$$F\left(\theta E[D]\right) + \frac{C}{pP} = F\left((\theta - \alpha) E[D]\right).$$

Since $\frac{C}{pP} > 0$ and $F\left(\theta E[D]\right) > F\left((\theta - \alpha) E[D]\right)$ it follows that $\tilde{\lambda}(\theta) < \theta$ cannot be true. □