

## CLINICAL INNOVATION: Fair & Effective Incentives for New Uses of Established Drugs

### What does the “ideal system” look like?

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### Fostering Clinical Innovation Through Fair and Effective Incentives For New Uses Of Established Drugs:

*The Current Patent System Doesn't Do It! – A Case Study  
What Would an Ideal System of Incentives Look Like?*

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## Inherent limitations of any patent system make non-patent incentives essential

What makes any patent-centric system of incentives to develop and commercialize new medicines—and new uses of established drugs—problematic and ultimately inadequate to assure development of the best medicines, and their best uses, rather than medicines with the best patents?

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### Incentives for developing the best medicines/uses, rather than medicines with the best patents?

- A most promising NME<sup>1</sup> drug or its most promising use may be **unpatentable**; have patent protection that is of **uncertain validity**; or be protected through a strong patent position that, even with patent extension opportunities, may have a **too-short, post-approval patent term**.
- A most promising new use of an approved drug may similarly be unpatentable; have patent protection that is similarly equivocal; or be protected through a strong patent position may have a too-short, post-approval term of protection against generic drug entry.
- **Even the strongest patent position carries with it a significant potential for an anomalous, unexpected litigation outcome.**

<sup>1</sup>NME is a reference to a “new molecular entity,” producing a drug based on a novel molecule.

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## An optimal IP regime protecting NME drugs/new uses from generic drug entry should not be patent-centric

- Relying on patent-centric protection from generic drug entry entails too much risk/uncertainty—*sitting atop research and market risks—exacerbating the need for rewards to match such aggregate risks.*
- The more innovative and unprecedented the drug, the more likely it is that unforeseeable development challenges may produce an unexpectedly long time to reach the market—rendering the post-marketing patent life shorter for the most innovative drugs.
- ***Patent protection for new medicines tends to be perverse—the least innovative drugs can be projected to have longer post-marketing patent life than the most innovative drugs.***

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## Atomoxetine (Strattera): A case study in why isn't the current patent system adequate?

1. Delays in the initial approval of a NME drug may preclude the development of additional indications given the timing of compound patent expiration.
2. Method of treatment patents are more vulnerable to attack once the compound and its mechanism of action are prior art.
3. Method of treatment patents are more vulnerable to attack if they encompass discoveries that are made during clinical trials.
4. Method of treatment patents can be difficult to enforce such that approval of additional indications even if they are patented can actually open the door to generic competition sooner rather than later.

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## The development of atomoxetine (Strattera) for the treatment of ADHD

- Early 1970s atomoxetine discovered.
- Jan. 10, 1974 - atomoxetine compound patent filed.
- Feb. 2, 1982 - US atomoxetine compound patent issued.
- 1980s - 1992 - atomoxetine studied for urinary incontinence through phase II and studied for depression through phase III.
  - Atomoxetine failed to show adequate efficacy for either indication.
- 1994 - Dr. John Heiligenstein convinced Lilly management to conduct a proof of concept (POC) study for ADHD before material expired following the depression studies.

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## The development of atomoxetine (Strattera) for the treatment of ADHD

- Jan. 1, 1995 - POC study begins.
- Jan. 11, 1995 - ADHD use patent filed without data.
- May 1995 - positive POC results obtained.
- 1995-1996 - atomoxetine development on hold given patent uncertainty.
- 1995 - thiotomoxetine pursued for ADHD.
- Aug. 1997 - US atomoxetine ADHD use patent issued.
- Sept. 1997 - decision to restart atomoxetine development for ADHD.

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## The development of atomoxetine (Strattera) for the treatment of ADHD

- 1997- 2001 - ADHD CTs continued.
  - *additional "uses" discovered during ADHD trials.*
- Feb. 2, 1999 - US compound patent expired.
- Nov. 26, 2002 FDA approval initial doses for ADHD – brand name Strattera.
- Feb. 14, 2005 additional doses for ADHD approved.
- *Decision made not to pursue additional indications for atomoxetine despite positive clinical data related to those indications.*
  - The “best” uses of this medicine may now never be studied or approved.

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## Why did the patent system fail patients that might have benefitted from atomoxetine's other uses?

- With no long-lived compound patent protection, it became more risky to develop an NME drug that was dependent on “use” protection.
  - Delays in the initial approval of atomoxetine could have precluded the development of additional indications given the timing of compound patent expiration.
  - 28 years between priority date for compound patent and first approval.
- Despite excellent PD, PK and safety profile, atomoxetine failed in the clinic for first two indications pursued.
- As a result the “compound” (active ingredient) patent expired 3 years prior to approval for first indication for atomoxetine.

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## Why did the patent system fail patients that might have benefitted from atomoxetine's other uses?

- The atomoxetine ADHD method of treatment patent—like many such “secondary” patents—was more vulnerable to attack than an NCE patent.
  - No data in the “method of use” patent application as filed.
  - Some uncertainty in the law relating to utility/plausibility considerations.
  - The compound and its mechanism of action are known in the art.
  - Compounds with unrelated structure but partial sharing of the mechanism of action and associated efficacy for the treatment of ADHD known in the art.
- ***Would the filing of a method of treatment patent justify the resources and uncertainty involved in continuing to study the drug for more than one indication?***

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## Why did the patent system fail patients that might have benefitted from atomoxetine's other uses?

- Atomoxetine method of treatment patents were more vulnerable to attack since they encompassed discoveries made during clinical trials.
  - Prior art concerns associated with phase III clinical trials for depression – ADHD comorbid with depression in adults and children.
  - Prior art concerns associated with ADHD trials—ODD, OCD, Anxiety commonly comorbid with ADHD in children and adults.
- The individual atomoxetine method of treatment patents for each potential indication posed an impossible commercial challenge.
  - ***Once the ADHD use patent expired, generic competition available for all indications, even subsequent patented indications.***
  - ***If compound approved for multiple patented uses, the loss of any single method of use patent opened the compound to generic competition.***

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## There can be formidable challenges to making patents an effective incentive for NCE drugs or their new uses

- Patents may fail to protect effectively an **NCE medicine** if they are—
  - **Unavailable, found invalid, or provide too-short, post-approval protection.**
- Patents for **new uses of established medicines** may fail as an effective incentive without **heroic application of the relevant national law**:
  - Generics may escape infringement with “**skinny labels**” excising the new use.
  - The “skinny label” gambit can succeed if the generic manufacturer **neither knows nor should know** that the otherwise unpatented generic drug will be used for the patented new use.
  - Even if infringement arises under the knows/should know standard, the available remedies may be ineffective as an incentive—**by neither enjoining generic drug entry nor affording substantial royalties.**

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## Can the patent system be used together with “data package protection” to produce a win for patients, originators, and generics?

Can we define what patients want, what innovators need, and what can produce optimal benefits from generic drug entry to identify an “ideal system” of incentives—  
to develop the best new medicines and their best uses?

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## Taking a broader look at the underlying issue: *What is the “ideal system” for the “patient”?*

The ideal system for patients for both NME drugs and their new uses—

1. The NME drug is initially approved **as soon as possible** after NME discovery.
2. At approval, clinical data provides **the clearest possible picture of safety**.
3. The drug **is initially approved for as many indications as possible**.
4. Clinical data clearly defines patients **who can benefit from the medicine**.
5. Further approved uses come **as quickly as possible** after initial approval.
6. The drug is **affordably accessible** to patients who can benefit from the drug.
7. Generic drug entry is assured after an **appropriate period** of IP protection.
8. For generic drugs, the drug's cost is just above its **manufacturing cost**.
9. Even after generic drug entry, **mechanisms remain** for developing new uses.
10. The post-generic “new use” **mechanisms need not include IP incentives**.

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## Taking a broader look at the underlying issue: *Can patient “wants” and industry “needs” align?*

- There are potential conflicts between the 10 patient “wants” and the industry “needs” that must be taken into account and resolved in defining any “ideal” system and establishing its political viability, *e.g.*,
  - The higher the safety/efficacy hurdles before the initial NME drug approval or approval of new uses, the greater the cost and time to regulatory approval.
  - Substantial clinical experience with a drug is sometimes needed before undertaking new clinical work directed to additional indications for use can be justified.
  - No consensus exists on the “appropriate” IP protection for an NME drug.
  - Assuring that drugs are “affordably accessible” to all patients might impair the ability of innovators to charge fair and reasonable prices for a drug.
  - No consensus exists on what might be a fair and reasonable price for a drug.

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## Taking a broader look at the underlying issue: *Is there a consensus hierarchy for IP incentives?*

- The primary focus for incentives: *encourage the development of the best medicines, not the medicines that may qualify for the best patent or other IP protection.*
- The secondary focus for incentives: *the best medicinal uses for a new medicine are developed and approved at the earliest possible point in time after initial regulatory approval.*
- The tertiary focus for incentives: *identify additional means for developing new uses only if the primary and secondary incentives are no longer effective to elicit investments in the continuing development and commercialization of such new uses.*

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## Taking a broader look at the underlying issue: *The hierarchy reveals a critical interdependency*

- To the extent primary/secondary incentives result in early approval of all important uses, *the lesser the need for incentives motivated by the tertiary focus on new uses for well-established drugs.*
- The converse is also true—the need for “tertiary focus” incentives rises substantially if the primary/secondary incentives prove to be ineffective in getting all significant uses approved sooner.
- *As a result, it is impossible to address the issue of optimal IP incentives based on this tertiary focus—protection for new uses of established drugs—without first addressing the question of optimal IP incentives for the development of NME drugs.*

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*The solution: an appropriate and fixed IP protection period for the NME “data package” and for patents.*

*The option to elect an adequate, but fixed, IP protection period be created—one that would categorically bar generic drug entry prior to the expiration of the IP protection period.*

- To assure the best medicines are developed, rather than just the medicines with the best patents.
- To assure that IP protection is not perverse—with the most innovative medicines having shorter periods of protection from generic competition.
- *To assure that innovators have incentives to continue to develop new uses for approved drugs during at least the decade following initial regulatory approval.*
- *To thereby address both the primary and secondary focus for IP incentives.*

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*The fixed period of IP protection: the 14-year Hatch-Waxman “floor” on post-approval patent life*

- In 1984, Congress set what should have been a **floor** on patent protection for new medicines with the **14-year cap on patent term extensions**, applied to a single patent listed in the FDA Orange Book.
- In 1984, the pre-URAA patent law’s 17-year patent term from the patent issue date afforded the opportunity for > 14 years of post-approval patent life for patents issued < 3 years from FDA approval.
- If a relevant patent issued > 3 years from initial FDA approval, Hatch-Waxman then permitted adding back up to 5 years of post-marketing patent life—thereby generally creating the 14-year, patent-life floor so long as the patent issued < 8 years from NDA approval.

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## Key aspects of an option *to elect* a 14-year fixed period of IP protection for newly approved drugs

1. If the innovator elects the 14-year fixed period, the NME drug will receive **a 14-year data package protection period**.
2. If the 14-year election is made, **all Orange Book-listed patents** will be set **to expire at 14 years** from the date of NME drug approval.
3. All OB-listed patents with < 14 years of post-approval patent life would be extended to expire at the 14-year mark; **all OB-listed patents with > 14 years of post-approval patent life would required to be terminally disclaimed to 14 years** by the patent owner in order for the innovator to qualify for the 14-year election.
4. **Patent term extension would no longer be available for any NME drug absent such election for the 14-year fixed IP protection.**

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## The 14-year period of combined patent and data package protection is economically justified

- The 14-year period is adequate, but not excessive, in terms of affording innovators the opportunity to recoup the investment needed to discover, develop, and commercialize an NME medicine.
- The most recent analysis describing the payback period applicable to NME biologic products was published in 2008. **"The break-even lifetimes for the mean product were found to be between 12.9 and 16.2 years** at alternative discount rates of 11.5% and 12.5%, respectively." Henry Grabowski, "Follow-on biologics: data exclusivity and the balance between innovation and competition," *Nature Reviews Drug Discovery*, published online 12 May 2008; available at <http://fds.duke.edu/db?attachment-25--1301-view-503>, at p. 486-487.

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## The *14-year election option* is a win-win-win regime for patients, innovators, and generic companies

- Assures innovators can develop the best medicines, rather than medicines with the best patents.
- Affords generic companies complete risk-free, cost-free certainty as to the date of generic drug entry.
- Affords strong incentives to develop new indications for use during the decade after initial regulatory approval for marketing.
- Minimizes the need for incentives with a tertiary focus to achieve the objective of assuring that the highest, best, and most complete indications for use are developed and approved for marketing.

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## Where would the foregoing leave the issue of incentives specifically focused on new uses?

- The 14-year election option, together with the ancillary labeling reform (see appendix), should produce a bright line between the 14-year period of IP protection and the time at which generic drug entry would produce immediate access to low-cost versions of the drug.
- At the same time, the 14-year election option effectively precludes any traditional notion of data package protection or patent-like protection from serving as an incentive to develop further uses.
- ***The 14-year election option dictates finding non-IP-based incentives to develop new uses for drugs that have reached the point where low-cost generic versions of the drug dominate the market.***

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## Considerations relating to the development of new uses once generic drug entry commences

- At the date of generic drug entry, an innovator will already have spent between 20 and 30 years—or more—investigating its “new” drug.
- An innovator rarely develops new uses for another innovator’s drug, particularly once the generic versions of the drug enter the market.
- The development of new uses after generic drug entry by any of the generic manufacturers is unknown.
- If new uses of the medicine are developed in the post-IP era—and made immediately available to patients through low-cost generic versions—the potential exists to create enormous benefits for patients, their insurers, and governments as payors.

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## Resources that could be focused on developing new uses for old drugs after generic drug entry

- **National governments**—Agencies such as the National Institutes of Health in the United States have multi-billion dollar research budgets, some of which is focused on new uses for drugs.
- **Disease-focused charitable foundations**—An array of foundations, largely dependent on private contributions, exist throughout the world. In the UK, for example, such charities include (1) Leukaemia and Lymphoma Research, (2) Breakthrough Breast Cancer, (3) The Brain Tumour Charity, (4) Myeloma UK, and (5) the Roy Castle Lung Cancer Foundation.
- **Not-for-profit-research hospitals**—Organizations such as St. Jude’s Medical Center raise funds for research into new uses of existing medicines. In 2016, St. Jude’s alone reported \$1.2 billion in contributions and grants.

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## Resources that could be focused on developing new uses for old drugs after generic drug entry.

- Could the United States create an agency like the National Cancer Institute (NCI) focused on developing new uses for generic drugs, *i.e.*, **the National Generic Drug Institute (NGDI)**? Such an institute could be entirely focused on the study of safety and effectiveness for drugs once generic drug entry has taken place or is approaching.
- **Could an NGDI be partially or entirely industry funded?** An industry funding mechanism including contributions from makers of any version of the drug, whether the original version or a generic version.
- Could such resources for developing new uses **obviate the need for new IP incentives for already-generic medicines?**

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## Given the fixed 14-year period assures *generic drug entry*, what could assure *generic drug competition*?

- The 14-year IP protection period, with the patent waiver provisions, **assures generic drug entry at a date fixed upon NCE drug approval.**
- It obviates the possibility for Hatch-Waxman litigation, **eliminating the 180-day generic drug marketing monopoly for “first-filers.”**
- The 180-day period, while a potential incentive (bonanza) for first filers, actually **discourages all second and subsequent filers**—chilling and potentially **delaying generic drug competition.**
- **This perverse incentive could be replaced with an alternative incentive—one providing assured “pricing protection” for all generic marketers during the same 180-period!**

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## Conclusions

- The objective of identifying incentives for developing “new uses for established drugs” can be best understood as the quest for incentives to assure the highest, best, and most complete set of uses for new medicines are developed and marketed at the earliest possible time.
- The starting point for such a quest could lie in the 14-year election option for NME medicines, affording innovators assured protection from generic drug entry for a period sufficient to discover and develop multiple additional uses of an NME medicine.
- Following generic drug entry, primary reliance for funding the development of further uses could be through public and private sources—obviating the need for new and complicated IP protections.

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## Appendix: Complementary Labeling Reforms

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## The 14-year election option should be further enhanced through accompanying “label” reforms

- Drug labeling reforms benefitting both NME and generic drugs—
  - Overall objective: remove any label-based “failure to warn” product liability risk under state laws, through federal preemption, barring states from setting different safety-efficacy standards than those determined by the FDA.
  - FDA would have more complete control of the drug’s label—the NDA holder could not alter safety or efficacy content; the FDA would be solely responsible for the adequacy of a medicine’s labelled safety information.
  - Just as the 14-year election option reduces IP risk, the drug labeling reform would remove label-based, failure-to-warn product liability risks.
  - Taken together, the effective elimination of IP and product liability risks would contribute to the important policy objective of creating an innovator business model *in which lower risks have the potential to translate into lower rewards*.

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## The 14-year election option should be further enhanced through accompanying “label” reforms

- Drug labeling reforms specifically benefitting generic manufacturers—
  - Additional labeling reforms for the generic drug manufacturer would be incremental to the product liability-focused reforms discussed above.
  - Approved generic drugs, in particular each approved dosage form eligible for generic drug entry, would have no label whatsoever—generic drug approval would be a limited approval *to offer for sale the approved dosage form*.
  - Since generic drug manufacturers under ANDAs are barred from submitting safety and effectiveness data to the FDA for review, the ANDA approval of a generic drug would not include authority to promote or market the approved generic dosage form for any indication for use.
  - As a result, selling an ANDA-approved generic drug could never constitute inducement to infringe a patent relating to the use of the medicine.

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