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

A critical review of the current landscape - Discussion

Moderator: Dr Ute Kilger Boehmert & Boehmert

Presenters:
- Prof. Arti Rai Professor of Law, Duke University
- Prof. Rebecca Eisenberg Professor of Law, Michigan University
- Prof. Ben Roin MIT Sloan School of Management
- Todd Volyn Patent Attorney, Johnson & Johnson

Panellists:
- James Horgan Head of European Patents, Merck Sharp & Dohme

Private and Public Approaches to New Uses

Arti K. Rai
Elvin R. Latty Professor
Founding Director, Center for Innovation Policy
Duke Law School
Rescuing failures

- Life on composition of matter patent
- Use patent that cannot carved out
- No concern about discovering negative information on marketed drug
- Some de-risking
- Use patent may be vulnerable

*Private rescue does happen (though public role can be useful)*

Repurposing generics

- No life on composition of matter patent
- Skinny labeling
- Hard to win indirect infringement theories
- Significant de-risking

*Generic repurposing rare, usually involves public funds – can private incentives work?*

Historical Data on Rescue

- 12/170 new molecules approved between 1996-2004 relied solely on use patents (Rai and Rice (2014))

“Contracting for Rescue”

[NIH National Center for Advancing Translational Sciences]

Discovering New Therapeutic Uses for Existing Diseases
**Goal:**
To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

- Match candidate Agents from pharmaceutical partners with innovative ideas for new indications from the biomedical research community.
  - **NIH provides:** template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, and oversight
  - **Pharmaceutical partners provide:** compounds, biologics, in kind support, and pertinent data
  - **Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to appropriate patient populations

[Adapted from Presentation by Christine Colvis PhD]

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**Repurposing generics**

- Historically, public/non-profit funds
- Stevens et al. (2011): in period from **1990-2007**, only **10/1541** new drug approvals for new uses
  - 9 of 10 involved public funding
Potential private incentives

- Mechanisms for preventing generic substitution
  - Regulatory
  - Formulation patents
- \textit{Ex ante} commitments by buyers’ side?
- How much off-label is okay?

Clinical Trial Data Infrastructure
References


New Uses Under the 21st Century Cures Act

Rebecca S. Eisenberg
Robert & Barbara Luciano Professor of Law
University of Michigan Law School
Thursday, February 8, 2018
21st Century Cures Act § 3022
(codified at 21 U.S.C. § 355g)

(a) The Secretary shall establish a program to evaluate the potential use of real world evidence —
(1) to help to support the approval of a new indication for a drug approved under section 355(c); and
(2) to help to support or satisfy postapproval study requirements.
(b) In this section, the term “real world evidence” means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials.

(f) Rule of construction
(1) Subject to paragraph (2), nothing in this section prohibits the Secretary from using real world evidence for purposes not specified in this section, provided the Secretary determines that sufficient basis exists for any such nonspecified use.
(2) This section shall not be construed to alter—
(A) the standards of evidence under—
(i) subsection (c) or (d) of section 355, including the substantial evidence standard in such subsection (d);
(ii) ... or
(B) the Secretary's authority to require postapproval studies or clinical trials, or the standards of evidence under which studies or trials are evaluated.

21 U.S.C. § 355(d)

If the Secretary finds ... that
(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;
(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; ... he shall issue an order refusing to approve the application. ...

As used in this subsection and subsection (e), the term “substantial evidence” means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.
Real-World Evidence — What Is It and What Can It Tell Us?

- Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

FDA Guidance Document

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff


The draft of this document was issued on July 27, 2016
Nudges towards postmarket evidence for medical device regulation

Preference for postapproval standards where adequate to meet statutory standards for medical device approval, e.g., 21 U.S.C. § 360c(a)(3)(C):

“In making a determination of a reasonable assurance of the effectiveness of a device for which an application... has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.”


“Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”

*Nothing in this subparagraph shall alter the criteria for evaluating an application for premarket approval of a device.

Usefulness of real-world evidence

• Key to understanding the usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect actual use in practice.

• Real-world evidence can inform therapeutic development, outcomes research, patient care, research on health care systems, quality improvement, safety surveillance, and well-controlled effectiveness studies. Real-world evidence can also provide information on how factors such as clinical setting and provider and health-system characteristics influence treatment effects and outcomes. Importantly, the use of such evidence has the potential to allow researchers to answer these questions efficiently, saving time and money while yielding answers relevant to broader populations of patients than would be possible in a specialized research environment.
Nudges towards postmarket evidence for drugs

Food & Drug Administration Amendments Act of 2007
Directed FDA to assemble a network of sources of health-related electronic data for postapproval monitoring now up and running (Sentinel System)
Expanded FDA’s postapproval regulatory authorities
Without changing approval standards, directed FDA to avoid requiring postapproval RCTs when other data sources might suffice, 21 U.S.C. § 355(o)(3)(D):
(i) Postapproval studies
The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).
(ii) Postapproval clinical trials
The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).
Other legislation and FDA initiatives have encouraged earlier approval of many new drugs, making postapproval studies and monitoring more important to ensure safety and efficacy.
“Accelerated approval,” “Breakthrough therapy” designation, “Fast track designation,” “Priority review designation,” often allow drugs to get to market earlier, but with further postapproval requirements.

Data quality

- “EHR and claims data are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes, and the accuracy and reliability of data gathered by many personal devices and health-related apps are unknown. Furthermore, the use of any of these sources, including social media, raises important questions about the quality of the data they provide and about privacy.” [NEJM Sounding Board]
Bias

• “An existing RWD source, however, may have some inherent bias that could limit its value for drawing causal inferences between medical device exposures and outcomes. Therefore, to mitigate potential bias, careful study design is needed, and a study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD, regardless of whether the RWD are already collected (retrospective) or if they are to be collected in the future (prospective design). Protocols and analysis plans for RWD should address the same elements that a traditional clinical trial protocol and statistical analysis plan would cover. FDA recommends use of the pre-submission process when considering the development of a study using RWD in a regulatory submission.” [FDA Guidance]

“Plus ça change, plus ça reste la meme chose?”

• “We believe that when the term ‘real-world evidence’ is used, the primary attribute that distinguishes it from other kinds of evidence is related to the context in which the evidence is gathered – in other words, in clinical care and home or community settings as opposed to research-intensive or academic environments. Most important, the distinction should not be based on the presence or absence of a planned intervention or the use of randomization. Real-world research and the concepts of a planned intervention and randomization are entirely compatible.” [NEJM Sounding Board]
Second Medical Use Patents in the US

Todd Volyn
February, 2018

Standard Regime

• Use Claims: Use of Composition X to treat Disease A

• Method of Treating: Administering an effective amount of X to treat A

• Determining the concentration of Y [some diagnostic marker] and administering an effective amount of X to treat patients with more than A concentration of Y [the diagnostic marker]

• Combination products: Treating a patient with an effective amount of composition X and effective amount of composition Y to treat B
Regulatory Exclusivity

• Not a property right but...
  - Three years of market exclusivity may be available for a new indication.
  - The exclusivity is limited to the new indication
  - Skinny labeling

Enforcement

• Generally, induced infringement requires “Active encouragement of infringement”

• Takeda v. West-Ward, 785 F.3d 625 (Fed. Cir. 2015):
  - “The label must encourage, recommend, or promote infringement.” 631.
  - “But we need not decide whether evidence as to the invariable response could ever transform a vague label into active encouragement.” 632.

• Eli Lilly v. Teva, 845 F.3d 845 (Fed. Cir. 2017):
  - “The product labeling here is not so tenuously related to the use covered…and Eli Lilly does not need to rely on speculation about physician behavior.” 1369
  - “…evidence that the product labeling…would inevitably lead some physicians to infringe establishes the requisite intent…” 1369.

• Can a skinny label avoid induced infringement? Sometimes, always, or never?
Where do we stand on the law in Europe?

a) German Federal Court of Justice Carvedilol II requires wording on label that would infringe claim.

b) Two Supreme Court decisions in NL.
   - MSD v Teva ribavirin case. Went to a hearing (about 6 a year). Complex claim but Teva made a very imperfect carve-out of their label.
   - Having lost at first and second instance MSD won at Supreme Court.
   - SMU claims are no different to any other patent claim. They can be infringed directly and indirectly.
   - Direct infringement when manufacturer foresees or ought to foresee an infringement. Has to take all effective measures that can reasonably be required of him to avoid this.
   - Earlier Novartis v Sun zoledronate case (which did not have a hearing) reached similar conclusions.
Where do we stand on the law in Europe?

c) Warner-Lambert before the UK Supreme Court.
   - Court of Appeal decision upholds its earlier objective view of infringement from its decision on summary proceedings. Intention negative when manufacturer taken all reasonable steps in his power to prevent the consequences occurring.
   - Indirect infringement requires supply of means for putting the invention into effect. Does not need downstream manufacture. Can include packaging/labelling by pharmacist.

What do I think will happen?

- Assuming Warner-Lambert’s patent survives on insufficiency then hope Supreme Court will follow CA on infringement. Position similar to NL.
- The question that arises is what reasonable steps must a generic take? May be different answers in different countries due to differences in prescribing, dispensing and reimbursement laws.