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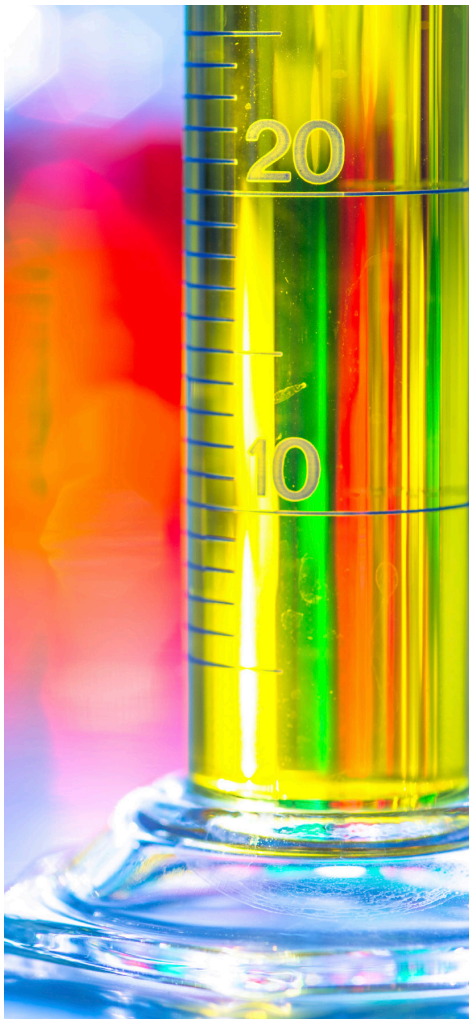
Brief

Causal Leverage Analysis: Obtaining Product Approval and Winning Approval Litigation



Today, strong evidence is needed to get and keep drugs, medical devices and other FDA-approved products on the market. Yet, from obtaining approval to maintaining marketing exclusivity and market share, studies generating evidence are becoming more sophisticated: examples are adaptive clinical trials, Bayesian designs, and use of patient preference and patient-reported outcomes methods. Especially in light of the 21st Century Cures Act, we can expect FDA to foster this trend through both internal, and public-private efforts such as the Clinical Trial Transformation Initiative and the Medical Device Innovation Consortium.

In this paper, we introduce Causal Leverage Analysis, a tool for developing credible information to support product approval applications and strong evidence for use in approval litigation and postmarketing litigation that may arise, such as products liability litigation. Using approval of biosimilar products as an example, we begin by reviewing information that will be needed to obtain approval, to protect market share, and for evidence in related litigation.

Information Needed for Approval of Biosimilar Products

The Biologics Price Competition and Innovation Act of 2009 (BPCIA)[1] created an accelerated pathway to approval for biological products that are "similar" to previously approved pioneer biological products (reference product or RP). "The objectives of the BPCI Act are conceptually similar to those of the ... 'Hatch-Waxman Act' ... which established abbreviated pathways for the approval of drug products. ..."[2] Thus, there exist two major pathways for marketing a biological product: an original biologics license application (351(a) BLA) under Section 351(a) of the Public Health Services Act (351(a) Pathway) and an application (351(k) BLA) under Section 351(k) of the same Act (351(k) Pathway).

A biological product is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein [and others] ... applicable to the prevention, treatment, or cure of a disease or condition of human beings."[3] Such a product may not be marketed unless a biologics license has been issued for it.[4]

The 351(k) Pathway allows a "biosimilar product" (BP or biosimilar) to be approved where FDA "determines that ... the biological product ... is **biosimilar** to the reference product; or ... is **interchangeable** with the reference product. ..."[5]

FDA has broad discretion in applying the approval provisions applicable to proposed biosimilar products, even discretion over whether and to what extent a biosimilar must undergo expanded safety or efficacy testing.

The Biosimilarity Criterion

Unlike the Hatch-Waxman process for approving generic drugs, under the BPCIA, biosimilars are not required to be the same as the RP. Instead, biosimilarity to the reference product must be substantiated by evidence[6] derived from:

- Analytical studies that demonstrate the proposed biosimilar product to be *highly similar* to the reference product,
- Animal studies that assess toxicity, and
- A clinical study or studies that are sufficient to demonstrate safety, purity and potency in one or more appropriate conditions of use for which the reference product is approved and proposed biosimilar product is to be approved.[7]

In addition, the following must be substantiated:

- **Same mechanism:** The biological product and reference product utilize the same mechanism or mechanisms of action.
- **Conditions previously approved:** The condition or conditions of use prescribed, recommended or suggested in the labeling proposed for the BP have been previously approved for the RP.
- **Same route, dose and strength:** The route of administration, the dosage form and the strength of the BP are the same as those of the RP.
- **Compliant facility:** The facility in which the BP is manufactured, processed, packed or held meets standards designed to ensure that the biological product continues to be safe, pure and potent.[8]

The Interchangeability Criterion

As to interchangeability, FDA shall determine the BP to be interchangeable with the RP if the BP:

- Is biosimilar to the reference product,
- Can be expected to produce the same clinical result as the RP in any given patient; and
- Is administered more than once to an individual, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the BP and the RP is not greater than the risk of using the RP without such alternation or switch.[9]

FDA has broad discretion in applying the approval provisions applicable to proposed biosimilar products, even discretion over whether and to what extent a biosimilar must undergo expanded safety or efficacy testing.[10] The following table summarizes the criteria that must be satisfied to obtain findings that a proposed product is biosimilar to, and interchangeable with, the reference product.

1 The BPCIA was enacted as sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111–148), which amended section 351(k) of the Public Health Service Act.

2 FDA, Guidance for Industry - Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 2 (2012) (FDA Q&A 2012).

3 42 U.S.C. § 262(i).

4 42 U.S.C. § 262(a) ("No person shall introduce or deliver for introduction into interstate commerce any biological product unless a biologics license under this subsection or subsection (k) is in effect for the biological product. ..." (numbering and formatting omitted)).

5 42 U.S.C. § 262(k)(3) ("Upon review of an application ... the Secretary shall license the biological product under this subsection if ... the Secretary determines that ... the biological product ... is biosimilar to the reference product; or ... is interchangeable with the reference product; and ... the applicant. ... Consents to the inspection of the facility. ..." (emphasis added, numbering and formatting omitted)).

6 We concur with FDA that the terms "data," "information," and "evidence" often are misused:

> Although "data," "information," and "evidence" are often used as if they were interchangeable terms, they are not. Data are best understood as raw measurements of some thing or process. By themselves they are meaningless; only when we add critical context about what is being measured and how do they become information. That information can then be analyzed and combined to yield evidence, which in turn, can be used to guide decision making.

Robert M. Califf and Rachael Sherman, What We Mean When We Talk About Data, FDA Voice (Dec. 10, 2015), available at http://blogs.fda.gov/fdavoice/index.php/2015/12/what-we-mean-when-we-talk-about-data/ (last accessed Jan. 9, 2017).

7 42 U.S.C. § 262(k)(2)(a)(i) (paraphrased).

8 42 U.S.C. § 262(k)(2)(a)(ii)-(v) (paraphrased).

9 42 U.S.C. § 262(4) (paraphrased).

10 See, e.g., 42 U.S.C. § 262 ("The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(l) is unnecessary in an application submitted under this subsection" [in pertinent part, numbering omitted]).

Criteria for Approval

Biosimilarity:

- Highly similar;
- PK/PD data to show safe, pure and potent for condition of use;
- Same mechanism, route, dose, strength;
- Previously approved condition; and,
- Compliant facility.

Interchangeability:

- Biosimilarity;
- Same clinical result; and
- No increased risk from switching or alternating.

Complexities in Approval Information

Those criteria require the applicant to address scientific and technical complexities. "Biologicals" are large molecules that are used for a variety of serious diseases, such as cancer, rheumatoid arthritis, Crohn's disease, multiple sclerosis and hemophilia. Given the size of the molecules, it is difficult to fully characterize their structures. FDA explains that "[t]he ... abbreviated approval pathway for biological products can present challenges given the scientific and technical complexities ... associated with the larger and typically more complex structure of biological products, as well as the processes by which such products are manufactured."[11]

The agency has issued a large number of guidance documents to address those complexities. Given the importance of FDA's expression of the concepts set forth in those highly technical guidance documents, the following discussion of them relies heavily on the agency's own words.

To give guidance on approval challenges, FDA has focused on protein products as examples of potential BPs.[12] The agency explains that challenges are expected to arise due to structural differences:

> "Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise ... even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety and/or effectiveness. ..."[13]

Also, challenges are expected due to manufacturing differences:

> "Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product ... differences in biological systems used to manufacture a protein product may cause different post-translational modifications, which in turn may affect the safety and/or effectiveness of the product."[14]

To meet such approval challenges, FDA is examining the totality of the information submitted by the sponsor. The agency explains:

> "In evaluating a sponsor's demonstration of biosimilarity, FDA will consider the totality of the data and information submitted in the application, including structural and functional characterization, nonclinical evaluation, human PK [pharmacokinetics] and PD [pharmacodynamics] data, clinical immunogenicity data and comparative clinical study(ies) data."[15]

The agency suggests that the sponsor develop approval information in a stepwise approach:

> "The stepwise approach should start with extensive structural and functional characterization of both the proposed product and the reference product, which serves as the foundation of a biosimilar development program."[16] "The sponsor should then consider the role of animal data in assessing toxicity and, in some cases, providing additional support for demonstrating biosimilarity and in contributing to the immunogenicity assessment."[17]

Since passage of Hatch-Waxman, many lawsuits have arisen in connection with generic drug approval. Administrative proceedings leading to litigation over approval of biosimilar products under the BPCIA have commenced.

Following those steps:

> "The sponsor should then conduct comparative human PK studies, and PD studies if there is a clinically relevant PD measure, in an appropriate study population. Sponsors should then compare the clinical immunogenicity of the two products. … If there is residual uncertainty about biosimilarity after conducting structural analyses, functional assays, animal testing, human PK and PD studies, and the clinical immunogenicity assessment, the sponsor should then consider what additional clinical data may be needed to adequately address that uncertainty."[18]

11 FDA Q&A 2012 at 2.

12 FDA, Guidance for Industry – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 1 (2015) (FDA Scientific Considerations). ("Although the 351(k) Pathway applies generally to biological products, this guidance focuses on therapeutic protein products and gives an overview of important scientific considerations for demonstrating biosimilarity. The scientific principles described in this guidance may also apply to other types of proposed biosimilar biological products.").

13 Id. at 5.

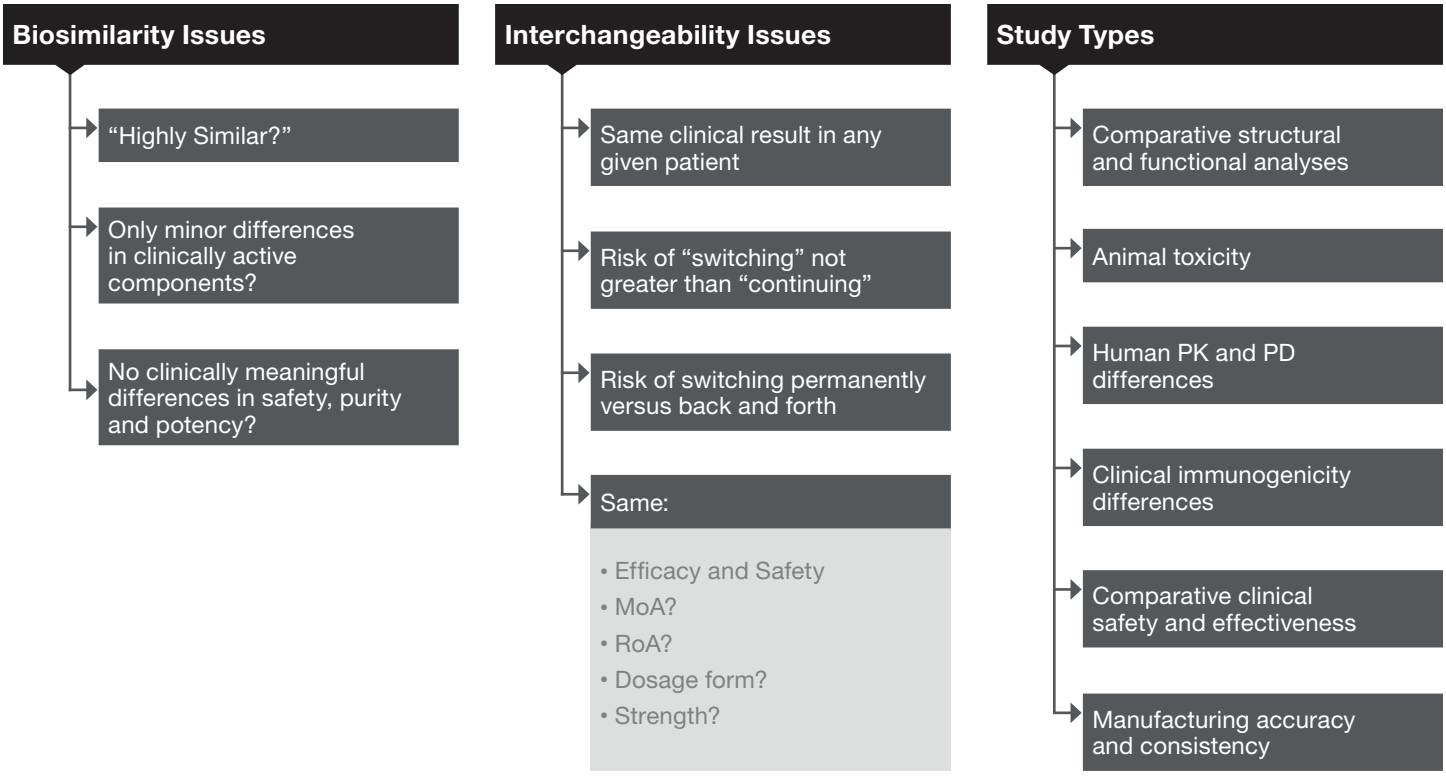
14 Id.

15 Id. at 8.

16 Id. at 7.

17 Id. at 8.

18 Id. at 8 (internal citation omitted).



Regarding evidence needed to substantiate that the proposed BP is *highly similar* to the RP, FDA expects "that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product."[19] Yet, "[m]inor modifications ... that will not have an effect on safety, purity, or potency, may be justified by the applicant."[20]

As to manufacturing processes, FDA expects that "characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed biosimilar product and manufacturing process."[21]

As to physicochemical properties, FDA expects that "[p]hysicochemical assessment of the proposed biosimilar product and the reference product should consider all relevant characteristics of the protein product. ..."[22] Additional quality considerations should include, where applicable, information on the following: functional activities, receptor binding and immunochemical properties, impurities, reference product and reference standards, finished drug product and stability.

An overview of issues and study types involved in approval are given in the chart above. We can expect those and other issues to be contested in approval litigation.

19 FDA Quality Considerations at 9.
20 Id.
21 Id. at 10.
22 Id.

Meeting the Need for Approval and Litigation Evidence: Causal Leverage Analysis

Scientifically reliable and relevant evidence is needed to obtain or oppose approval of any FDA-regulated product, be it a pioneer drug, generic drug, RP or BP. Such evidence also must be persuasive in licensure litigation.

Causal Leverage Analysis (CLA) is a tool designed for development or assessment of such evidence. By *causal leverage,* we mean *credible evidence about product performance developed through use of causation analysis of relevant health science information*. Here, *product performance* refers to safety, efficacy, bioequivalence, biosimilarity and similar issues. Thus, CLA can be applied to various types of health science information (PK or PD studies, clinical trials of efficacy, postmarketing observational studies of safety or effectiveness, etc.).

CLA involves the following steps:

1. Frame or understand the research question;
2. Synthesize prior knowledge to collect important information;
3. Categorize important information;

4. Assess reliability of important information; and
5. Assess aggregate evidence of association or causal association.

These steps may appear familiar to many science-savvy readers; however, CLA is not merely a collection of familiar scientific methods. Instead, it is a synergy of scientific methods used to design and interpret health science information and legal methods used to assess *legal cause-in-fact* (or *but-for causation*).[23] CLA is intended to sharpen analysis of information that is pertinent to product-outcome relationships that arise in efficacy, safety, bioequivalence, biosimilarity and other performance issues that are presented in regulatory and litigation matters. It is pursued with a mindset different from that routinely employed by human health science researchers.

Usually, existing information does not provide support sufficient to allow an inference that the product causes the outcome of interest (OI).[24] Where insufficient support exists, decision makers often assess the reliability of available information and reach opinions as to whether use of the product *raises the probability* that the OI will occur. CLA is used as a standard to gauge evidentiary support for those opinions. It provides a set of causal inference criteria that, if fulfilled, establishes a *causal association* between the product and the OI. Where the set is not fulfilled, CLA allows systematic assessment of whether a credible *association* exists and of the association's meaningfulness.

More specifically, CLA makes use of both controlled and "real-world" data to provide sharpened analysis by deep development of prior knowledge[25] and application of causal inference criteria. Those criteria are intended to probe whether evidence exists to demonstrate that the putative product is a cause in fact of the OI and, if such does not exist, to determine the strength of available data, the importance of unavailable data and, finally, the meaningfulness of the putative product-outcome relationship.

Myriad technical and legal considerations are involved in CLA. The figure in the Appendix provides a brief overview of the methodology. A complete dissertation of it is beyond the scope of this introductory paper.

Two foundations of CLA differentiate it from more traditional methods. Those foundations are employed throughout each of the CLA steps. The first foundation is incorporation of all prior knowledge – that is all controlled, traditional anecdotal and real-world data.[26] Through available collection methods, a rigorous systematic review of published and unpublished information is conducted. Such information may concern the product's attributes and performance (characteristics distinguishing it from other members of its class, PK/PD data, dissolution data, mode of action, etc.), the condition being treated (incidence, prevalence, risk factors, usual disease course, etc.), the OI (measure of success), or alternative therapies.

The second foundation is identification of all prior knowledge that is not open to question. This activity goes beyond a traditional systematic review, as it distinguishes information that likely will not be contested from that which will be viewed as arguable. Of course, the uncontested information will comprise a small minority of all prior knowledge – yet it is the most solid basis for formulating opinions about, or conducting further research to generate additional information to answer the question at issue.

Starting from that basis, the steps of CLA are applied to assess internal validity of individual studies or support for causal association from the body of pertinent prior knowledge. In effect, CLA sets up the causal inference factors as a standard against which evidence relevant to the association at issue can be measured. Although a causal association rarely is fully supported, the analysis gives a systematic view of how much support is available.

The Need for CLA

Readers may ask, "Is this all necessary? After all, the need for prior knowledge development is hardly a new idea." Those readers would be correct. In fact, the first sentence written in *The New England Journal of Medicine* stated: "In our inquiries into any particular subject of Medicine our labours will generally be shortened and directed to their proper objects, by a knowledge of preceding discoveries."[27] Jumping forward 200 years, cancer researchers stated: "Models are ideally developed based on a combination of prior knowledge of the disease with judicious and informed use of statistical methods."[28]

23 See Restatement (Third) of Torts: Liability for Physical Harm § 26 cmt. b (2006) ("[A]n act is a factual cause of an outcome if, in the absence of the act, the outcome would not have occurred."). This is substantially similar to scientific principles of causal inference methodologies. See Douglas L. Weed, Truth, Epidemiology, and General Causation, 73 Brooklyn L. Rev. 943, 950 (2008):

> First, the fundamental problem of causal inference is that we cannot observe on the same individual both the effect of a cause (e.g., a disease outcome) and what would have occurred had the cause not acted to produce its effect. ... This constraint is sometimes called the "counterfactual" condition. If, for example, an individual begins taking a new medication and is later diagnosed with an illness or condition, we cannot know if that person would have contracted that illness or condition without taking the medication.

24 The Cochrane Glossary defines "outcome" as follows: "A component of a participant's clinical and functional status after an intervention has been applied, that is used to assess the effectiveness of an intervention." We use "outcome of interest" to mean the outcome selected as the endpoint of the study at issue. See http://community-archive.cochrane.org/glossary/5#lettero.

25 Prior knowledge is the existing health science information that is pertinent to the research question of an individual study, or relevant to the regulatory or litigation decision to be made.

26 Real-world data are those generated by networked care systems, electronic or paper medical records, insurance claims databases, social media, patient registries and personal devices.

27 Warren, Remarks on Angina Pectoris, 1 New Engl. J. Med. 1 (1812).

28 Mallett, et al., Reporting methods in studies developing prognostic models in cancer: a review, BMC Medicine 8:20, 1 (2010).

With published opinions that most research findings are wrong and most of the resources spent on clinical trial research are being wasted, it is clear that we need a sea change. ... Use of Causal Leverage Analysis ... can help that change take place ... leading to development of more reliable information for biological product approval and stronger evidence for approval, products liability or other litigation where product performance is at issue.

Yet, prior knowledge has not been – and is not being – sufficiently developed in the practice of research. In 2005, Dr. John Ioannidis stated: "It can be proven that most claimed research findings are false."[29] He pointed out that "[t]he probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance." He recommended: "[I]nstead of chasing statistical significance,[30] we should improve our understanding of ... the pre-study odds ... where research efforts operate."[31] In other words, prior knowledge is not developed sufficiently and it leads to major failings in research results.

These failings have led experts in research design and interpretation to estimate – in 2009 – "that more than 85 percent of the resources invested in medical research was being avoidably wasted."[32] In 2014, those authors recommended that research be stopped until prior knowledge was better developed:

> "[R]esearch funders and regulators should demand that proposals for additional primary research are justified by **systematic reviews of what is already known** and increase funding for the **necessary syntheses of existing evidence.** Two decades ago, Bausell invited the readers of *Evaluation and the Health Professions* to consider a moratorium on all proposals for new investigations **until the results of existing research had been incorporated in scientifically defensible reviews.** In the light of the evidence of waste that we have presented here, Bausell's proposal and its potential benefits should not seem far-fetched."[33]

29 Ioannidis, Why Most Published Research Findings Are False, PLoS Medicine 2:8, 0696 (2005).
30 Id.
31 Id. at 701.
32 Treweek, et al., Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform, Trials, 16:261 2 (2015) (hereinafter Treweek 2015) (citing Chalmers, et al., Avoidable waste in the production and reporting of research evidence, The Lancet, 374: 86-89 (2009)).
33 Chalmers, et al., How to increase value and reduce waste when research priorities are set, 383: 156-165 (2014) (emphasis added).

In 2015, an expanded group of authors stated: "Tens of billions of dollars of public and private money are invested globally in trials every year. ... Many of these resources are wasted, often because insufficient account is taken of existing evidence. ..."[34]

With published opinions that most research findings are wrong and most of the resources spent on clinical trial research are being wasted, it is clear that we need a sea change in the development and analysis of prior knowledge. Use of Causal Leverage Analysis to assess each piece of important information and to interpret the body of that information can help that change take place. We expect that it will lead to development of more reliable information for product approval and stronger evidence for approval, products liability or other litigation where product performance is at issue.

34 Treweek 2015 at 2.

Appendix

Causal Leverage Analysis – Overview of Exemplar Elements

Frame or understand the research question

- Understand the exposure
- Understand the outcome
- Understand the circumstances

Synthesize prior knowledge

- Sources generally
  - Scientific publication
  - Unpublished reports
  - Conference proceedings
  - Non-periodical treatises
- Research sources
  - Basic research
    - *In vitro*
    - *In vivo animal*
    - *OMICS*
    - *Structure/Activity*
  - Epidemiology
    - *Controlled clinical trials*
    - *Cohort studies*
    - *Case-control studies*
    - *Anecdotal reports*
- Data sources
  - Scientific publications (data)
  - Publicly available databases
  - Limited access databases
  - Healthcare information
    - *Electronic medical records*
    - *Insurance claims data*
- Target sources/information
  - Research
    - *Structure/Activity studies of mechanism*
    - *Animal studies of mechanism or outcome*
    - *Phenomena in other studies*
    - *Patterns of outcomes*
  - Epidemiology
    - *Similar observational studies*
    - *Observational studies of similar mechanism*
    - *Phenomena in other studies*
    - *Patterns of outcome*
  - Healthcare information
    - *Observations about nature or progression*

Categorize important information

- Experimental
- Observational – hypothesis tested
  - Prospective designs
  - Retrospective designs
  - Cohort designs
  - Case-control designs
- Observational – hypothesis not tested
  - Prospective designs
  - Retrospective designs
  - Case reports
    - *Post hoc ergo propter hoc*
  - Adverse event reports
  - Patient data
- Structure/Activity
- Animal

Access reliability of important information

- Reliability
  - Experimental result is primary aim
    - *Research question viable/tested*
    - *Allocation method successful*
      - *Baseline balance of confounders*
      - *Randomization plan appropriate*
      - *Randomization plan followed*
      - *Concealment*
    - *Adequate power*
    - *Intervention-only treatment difference*
    - *Subject attrition/switching*
    - *Blinding*
    - *Adjustment*
    - *Unplanned looks*
    - *Dose timing*
    - *Subject selection*
  - Observational/experimental result is not primary aim
    - *Research question viable/tested*
    - *Subject selection/cohort, case, control definition*
    - *Adequate power*
    - *Database/population appropriate*
    - *Data collection appropriate/accurate*
    - *Control method effective*
      - *Cohort size/characteristics*
      - *Case/control matching*
      - *Blinding*
      - *Unplanned looks*
      - *Dose timing*
      - *Adjustment*
        - *Method/model appropriate*
        - *Specific design defensible/fit*
        - *Prognostic covariates complete/accurate/parsimonious*
      - *Results comparable to existing experimental results*
- Fit

Assess aggregate evidence of association or causal association

- Effect strength
- Dose-response
- Biological mechanism
- Consistency
- Specificity
- Analogy

Lance Shea, M.S., J.D., is a partner at BakerHostetler. He focuses his practice on legal science advocacy, and represents clients in medical products industries such as drugs, medical devices and biotechnology products. Matters span regulatory (e.g., FDA and EPA) and litigation forums (e.g., federal and state courts) and often involve complex scientific evidence and cutting-edge arguments based on interpretation of scientific studies.

Contact

Lance L. Shea, M.S., J.D.
Partner
202.861.1648
lshea@bakerlaw.com

bakerlaw.com

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