Health Economics & Outcomes Research, Real World Evidence and Comparative Effectiveness Research

An overview

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Today’s Discussion

Health economics & outcomes research, real world evidence and comparative effectiveness research

— Introduction
— Brief Overview of:
  - Health Economics Outcomes Research
  - Real World Evidence
  - Comparative Effectiveness Research
  - EvGen – Vision of the Future
— Summary
Overview – 21st Century Cures Act

The Cures Act includes proposals for the Precision Medicine and the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiatives, and provisions intended to enhance and accelerate the Food and Drug Administration’s processes for reviewing and approving new drugs, biologics, and medical devices.

Those provisions seek to expand the types of evidence manufacturers of such products may bring to the FDA to support approval, encourage patient-centered drug development, create greater transparency with regard to manufacturer expanded access programs, clarify the regulatory approach to combination products and medical software, and permit the agency to grant limited population approvals to certain antibiotics.

The Cures Act also includes US$1 billion in new funding to address the opioid crisis over two years; streamline administrative processes for the National Institutes of Health’s (NIH) funding of medical research; fund new NIH research on human genetics and neuroscience; and facilitate secure, interoperable exchange of electronic health record (EHRs) data while protecting patients’ privacy.

The new law also included provisions to accelerate the development of regenerative medicine treatments. Also the Cures Act institutes important changes in FDAMA 114, significantly changing the communication of healthcare economic information to payors.

Today we will address two specific provisions:

- Section 3037: Health Care Economic Information, and
- Section 3022: Real World Evidence
Evidentiary Standards used to Support Regulated Products

Substantial Evidence (21 CFR 314.126)
- The FDA considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act.
- Reports of adequate well-controlled investigations provide the primary basis for determining whether there is substantive evidence to support the claims of effectiveness for new drugs.

Competent and Reliable Scientific Evidence (FTC Standard)
- Tests, analyses, research, studies or evidence based upon the expertise of professionals in the relevant area…
- That have been conducted and evaluated in an objective manner by persons qualified to do so…
- Using procedures generally accepted in the profession to yield accurate and reliable results.
Background

- Under the Food Drug and Cosmetic Act (FDCA), a drug may be deemed “misbranded” if its labeling or advertising contain claims that are not supported by “substantial evidence.”

- **Substantial evidence** generally means support from two adequate and well controlled clinical studies.

- However, Section 114 of the Food and Drug Administration Modernization Act (1997) (FDAMA 114) amended the FDCA to establish a different evidentiary standard—“**competent and reliable scientific evidence**”—for certain pharmacoeconomic claims, or “healthcare economic information”, that are provided to a formulary committee or similar entity.

FDAMA Section 114

- Do the materials present health care economic information?

- Is the information being provided to a formulary committee or other similar entity in the course of carrying out its responsibilities for the selection of drugs for managed care or similar organizations?

- Is the information “directly related” to an approved indication?

- Are the claims supported by “competent and reliable scientific evidence”? 
The Cures Act: Health Care Economic Information

- The 21st Century Cures Act (2016) contains a provision, “Section 3037: Health Care Economic Information”, designed to facilitate communication between pharmaceutical companies and formulary committees and payors about the “real-word” impacts of prescription drugs, such as their potential to improve persistence, prevent hospitalization and reduce costs.

- Section 3037 amends FDAMA 114

Section 3037 of the Cures Act

- Retains “based on competent and reliable scientific evidence”
- Includes in the definition of HCEI terms such as “clinical data, inputs, clinical or other assumptions and such analysis may be comparative”
  - Clarifies that HCEI includes clinical input “underlying or comprising the analyses”
- Changes “directly related to an approved indication” to “relates to an approved indication”
  - Seems to allow some flexibility in communicating HCEI beyond the narrow labeled indication – FDA provides examples in the draft guidance
- Clarifies the audience of HCEI communication in addition to formulary committees and include similar entities and payors – i.e. acknowledges changing healthcare landscape
- Requires a disclaimer if there are material differences between the HCEI and the “labeling approved for the drug”

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2. Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Draft Guidance, FDA, January 2017
FDA Draft Guidance on Communication of HCEI with Payors, Formulary Committees and Similar Entities

• In context of Cures Act, FDA has recently issued a guidance which addresses key questions about communication of HCEI by drug companies to formulary committees

• Key points clarified by draft guidance:
  • Guidance provides specific examples of HCEI analyses that FDA believes could be considered related to an approved indication of a drug, including:
    ▪ Duration of treatment: When approved indication for drug does not limit duration of use, HCEI may incorporate information about long-term use of drug that is different from that addressed in studies described in FDA-approved labeling
    ▪ Burden of illness: HCEI analyses may be derived from burden of illness studies
    ▪ Dosing: HCEI may be based on data of approved dosage forms of a drug, where dosing regimen varies from FDA-approved labeling; e.g. drug utilization data from health plan database
    ▪ Patient subgroups: HCEI analyses may be derived from treatment effects in patient subgroups
    ▪ Length of hospital stay: HCEI analyses may be derived from studies of treatment impacts on length of hospital stay.
    ▪ Validated surrogate endpoints: HCEI analyses may be derived from clinical data demonstrating an effect on a surrogate endpoint that is known to predict clinical benefit (e.g. blood pressure reduction is a validated surrogate endpoint for reduction in certain CV events)
    ▪ Clinical outcome assessments: HCEI may be derived from studies involving approved indication of drug that assess COAs such as adherence, productivity and QALYs
    ▪ Persistence: HCEI may be based on data estimating patient persistence on a drug for its approved indication
    ▪ Comparisons: HCEI may be derived from studies comparing safety or effectiveness of a drug for its approved indication to another drug or intervention, or to no treatment

2Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Draft Guidance, FDA, January 2017
Section 3037 of the Cures Act

Draft FDA Guidance – Communication with Payors, Formulary Committees and Similar Entities

• Additional issues clarified by the draft guidance:
  • Evidentiary support: FDA considers HCEI to be based on competent and reliable scientific evidence if the HCEI has been developed using generally-accepted scientific standards for such information; e.g. International Society for Pharmacoeconomic and Outcomes Research (ISPOR), Patient-Centered Outcomes Research Institute (PCORI)

• Implications:
  • Section 3037 seems to suggest that claims about a drug’s impact on improved adherence or lowered hospitalization length of stay or based on model that extrapolated from valid surrogate to long-term endpoints are permissible, as long information is based on competent and reliable scientific evidence and communicated to appropriate audiences
  • However, details of the particular HCEI and analyses will be critical.
The Cures Act Real-World Evidence Provision

Real-World Evidence (RWE)

- For the purposes of the Cures Act, “real world evidence” is defined as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”
- The new provisions require FDA to establish a program to evaluate RWE for the following purposes:
  - To help to support the approval of a new indication for a drug approved under section 505(c); and
  - To help to support or satisfy post-approval study requirements.
- FDA must establish a framework for the RWE program, which must be developed in collaboration with relevant stakeholders in the drug industry, and implement that framework within two years after the enactment date of the Cures Act.
- In addition, within five years of the enactment date, FDA must issue draft guidance describing (1) “the circumstances under which sponsors of drugs may rely” on RWE, and (2) acceptable standards and methodologies for collecting and analyzing RWE.
Real World Evidence

FDA Draft Guidance on the Use of RWE to support regulatory decision-making for medical devices

FDA has issued a draft guidance\(^3\) to clarify how they evaluate real-world data to determine whether it may be sufficiently relevant and reliable to generate the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices. As of this date, there is no equivalent guidance for pharmaceuticals.

— Real-World Data (RWD) is data collected from sources outside of traditional clinical trials.
  - These sources may include large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries (e.g., device, procedural, or disease registries).
  - The data is typically derived from electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.

— Real-World Evidence (RWE) is the evidence derived from aggregation and analysis of RWD elements. RWD and associated RWE could constitute valid scientific evidence, depending on the characteristics of the data.

The FDA is not changing the evidentiary standards used in regulatory decision-making; rather, this guidance describes the circumstances under which RWD may be used in different FDA contexts based on the existing evidentiary standards.

\(^3\) Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – Draft Guidance, FDA, September, 2016
Real-World Evidence

Regulatory context in which RWE may be used

— FDA will consider the use of RWE to support regulatory decision-making for medical devices when it concludes that the clinical data contained within RWD source(s) used to generate the RWE are of sufficient quality to provide confidence in the analyses necessary to inform or support the regulatory decision throughout the total product life cycle.

— The threshold for sufficient quality will depend on the specific regulatory use of the evidence.

— For example, a specific patient registry might be informative for postmarket surveillance, but not adequate for a premarket determination of safety and effectiveness, while another patient registry may be suitable to address both pre- and postmarket evidence requirements.
Real-World Data

Characteristic of RWD

FDA does not endorse one type of RWD over another

— RWD sources should be selected based on the ability to address specific regulatory questions.

— Collection of RWD should not dictate, interfere with or alter the normal clinical care of the patient, including choice of treatment.

— In cases where RWE is derived from multiple data sources, each data source will be evaluated individually and together in the aggregate to determine the relevance and reliability of the RWD to address the specific regulatory question.

— The FDA will evaluate the:
  - Regulatory relevance of RWD
  - Reliability of the data and the data sources, and
  - Data assurance and quality control
Additional Insight into FDA’s View of Real World Evidence

NEJM Publication from the FDA's Commissioner's office entitled, “Real World Evidence – What is it and What Can It Tell Us?”

- 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.

- It is important to distinguish two key dimensions of real-world evidence. The first is the setting in which evidence is generated, which includes the population defined by the data source as well as the specific methods used to collect and curate the data on that population. The second is the methodologic approach used to conduct the surveillance or research.

- These (clinical) trials are often needed because they are designed to provide an essential element of the premarket evaluation of a medical product — namely, robust evidence that a treatment may “work.”

- However, internal validity attained in these trials is often achieved at the expense of uncertainty and generalizability, since the population enrolled may differ in significant ways than those seen in practice.

- In traditional trials, randomization has long been an essential tool for minimizing bias by balancing underlying risk between treatment and groups, but it can be just as useful and important in real-world studies.

- In addition to its application in interventional studies, real-world-evidence is also valuable in observational settings, where it is used to generate hypotheses for prospective trials, assess the generalizability of findings for interventional trials (including RCTs), conduct safety surveillance of medical products, examine changes in patterns of therapeutic use, and measure and implement quality in health care delivery.

- The FDA is committed to robust policy development...

- The agency will initiate activities to address key concerns and publish draft guidance on how such evidence can be used to assess safety and effectiveness in both premarketing and postmarketing regulatory requirements.

- 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 evidence is gathered… in clinical care and home or community settings as opposed to research intensive or academic requirements.

- Most important, the distinction should not be based on the presence or absence of a planned intervention or the use of randomization.
Comparative Effectiveness Research

Definition

Comparative Effectiveness Research (CER)

— CER is the direct comparison of existing healthcare interventions to determine which works best for which patients and which pose the greatest benefits and harms.

— RWD is used for CER studies

— CER is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.

— The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver health care.

— There are two ways that this evidence is found:
  - Researchers look at all of the available evidence about the benefits and harms of each choice for different groups of people from existing clinical trials, clinical studies, and other research. These are called research reviews, because they are systematic reviews of existing evidence.
  - Researchers conduct studies that generate new evidence of effectiveness or comparative effectiveness of a test, treatment, procedure, or health-care service.

— No designated evidentiary standard for the regulatory use of CER studies.

— It has been suggested that the FTC definition of “competent and reliable scientific evidence” should be used.
Decisions made today in our health care system are not necessarily supported by high quality data derived from randomized, controlled trials or well-designed observational studies.

As diverse sources of digital data become widely available for research and as analytical tools continue to grow in power and sophistication, the research and health care communities now have the opportunity to quickly and efficiently generate the scientific evidence needed to support improved decision making about health and health care.

“EvGen – Vision of the Future”, FDA, January 2017
Proposed EvGen collaborative

— The use of high-quality, data-driven evidence, expert opinion and qualitative information will be used as a complementary source of knowledge to inform policy decisions or population and individual choices.

— In this model there is an opportunity to use qualitative methods to supplement high-quality quantitative data with a more focused approach

“EvGen – Vision of the Future”, FDA, January 2017
Summary

- Section 3037 of the Cures Act made significant changes on the use of health care information to support claims.
- The use of Real World Evidence is evolving for medical devices and will play a greater central role in assessing effectiveness and safety of products.
- The regulatory role of the use of RWE for drugs continues to be under discussion.
- Comparative Effectiveness Research continues to be a mainstay of comparing interventions.
- Given the growth of diverse digital sources of data and improved analytical tools, the FDA looks to the future on how best to develop evidence that supports product approval.
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