



2016 Publications and White Papers



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Introduction

Each year, Friends of Cancer Research (*Friends*) convenes working groups, hosts scientific conferences, and conducts research on a range of topics in regulatory policy. Through collaborative and meaningful initiatives, *Friends* seeks to drive innovations in cancer research and patient care. *Friends'* programs foster solutions to issues that researchers and regulators encounter as they strive to translate discoveries into safe and effective new treatments.

Throughout the year, *Friends* publishes white papers and studies stemming from expert discussions at conferences, as well as policy research conducted by the organization. These publications are then used to provide ideas and inform federal officials, researchers, and policy makers as they create innovative strategies for the development of new treatments. In 2016, *Friends* initiated a period of rapid organizational growth and expansion into new areas of science and policy. Below are the areas of focus for *Friends'* work during the past year.

In early 2016, *Friends* published a piece on drug manufacturing, building off a 2015 conference on the same topic. In "Manufacturing and Breakthrough Drug Development," authors identify a consensus set of innovative best practices to introduce efficiencies into the manufacturing development for urgently needed products, including breakthrough therapies.

In March, *Friends* published two reports on FDA expedited approval programs. The first, entitled "A Century of Medical Product Regulation: The Historic Framework for Personalized Medicine in Oncology," covered more than a hundred years of FDA history, viewed in the context of recent advances in personalized medicine. Then, in "Regulatory Watch: Impact of Breakthrough Therapy Designation on Cancer Drug Development," *Friends* examined the effect of the FDA's breakthrough therapy designation on pre-market clinical development times.

At the fifth annual summit co-hosted by *Friends* and Alexandria Real Estate Equities in June, and again at the *Friends* Annual Meeting in November, a working group was convened to explore the use of real-world evidence to support regulatory decision making. In two white papers, "Case Studies – Data Collection and Application of Real World Evidence" and "Examining the Feasibility of Real World Evidence Through Pilot Studies," authors explore potential uses for real-world evidence to support and expand on safety and efficacy data collected in traditional pre-market clinical trials.

In September, *Friends* published a report on the regulation of molecular diagnostics in collaboration with the Deerfield Institute, a market research firm specializing in biotechnology. In "Use of FDA-Approved and Laboratory-Developed Tests in Advanced Non-Small Cell Lung Cancer: Results of a Retrospective Market Analysis," *Friends* evaluates utilization patterns of laboratory-developed tests in the treatment of non-small cell lung cancer, finding that most tests used to identify common mutations are laboratory developed and thus not approved by the FDA.

In October, *Friends*, in partnership with the Duke-Margolis Center for Health Policy, convened two working groups to assess the current landscape and future of the US biosimilars market. The resulting white papers outline current challenges in the development and regulatory review of biosimilars and propose methods of ensuring appropriate utilization through education and guidance. The first white paper, "The Current Landscape of Biosimilars Development, Regulatory

Review, and Stakeholder Education,” provides a series of case studies illustrating the biosimilar development process and summarizes methods of demonstrating biosimilarity between biosimilars and their reference products. The second white paper, “Biosimilar Uptake: Considerations for Clinical Decision-making, Coverage and Reimbursement Decisions, and Post-Market Evidence Development,” proposes payer strategies to drive biosimilar utilization and demonstrate value.

At the *Friends* Annual Meeting in November, expert panel discussions were organized on randomizing early-phase clinical studies and modernizing eligibility criteria, two critical aspects of clinical trial design. In “Optimization of Exploratory Randomized Trials,” the authors propose statistical approaches that can be used to help interpret the results of early-phase trials that show unexpected gains in overall survival, but were not prospectively designed to measure that outcome as a primary endpoint. As part of an ongoing collaboration with the American Society of Clinical Oncology, the authors of “Modernization of Eligibility Criteria,” provide recommendations for how sponsors, investigators, and regulators can work together to implement expanded clinical trial eligibility where appropriate, given that overly restrictive eligibility criteria can inhibit trial generalizability and slow trial accrual.

This booklet contains the full text of the *Friends* 2016 publications and white papers. It is the hope that this collection will be a resource for those in the drug development and regulatory space.

The Current Landscape of Biosimilars Development, Regulatory Review, and Stakeholder Education

Conference White Paper

The Future of the U.S. Biosimilars Market: Development, Education, and Utilization

Duke Margolis Center for Health Policy
Friends of Cancer Research

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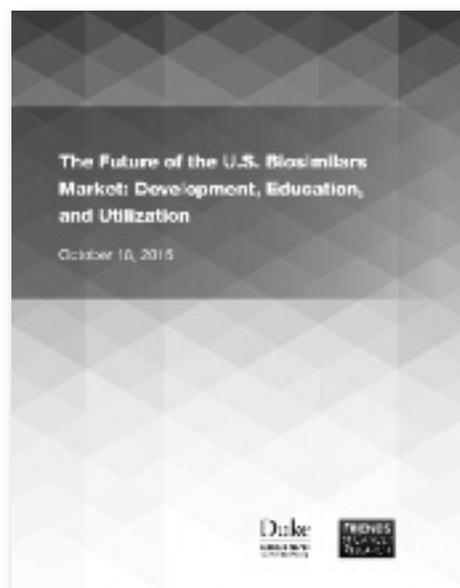
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INTRODUCTION

Therapeutic biologic products are large, complex molecules made in living systems and are used in a variety of diseases, such as cancer, rheumatology, and inflammatory bowel disease. In 2010, the Biologics Price Competition and Innovation Act (BPCIA) provided FDA the authority to establish an abbreviated approval pathway for biosimilar products, which are defined in this Act as those products which are highly similar to and have no clinically meaningful differences from a reference therapeutic biologic. Under the BPCIA, reference, or originator, biologics are provided 12 years of exclusivity from first licensure before a biosimilar can be approved and enter the market. Several reference biologics on the market are nearing or have already reached the end of this exclusivity period prompting companies to develop biosimilars. Although an abbreviated pathway (ANDA) for the approval of generic small-molecule drugs has existed since the passage of the 1984 Hatch-Waxman Act, the regulatory requirements for these do not reflect the greater complexity and testing needed for biologics.

In contrast to small molecule drugs, which are chemically-derived and can be readily characterized and purified, biologics are larger and more complex. Because of this, chemical synthesis is not sufficient, and biologics need to be produced and manufactured in living organisms. This manufacturing process results in differences between batches, and thus it is not possible to produce a 100% identical biologic. This is not specific to biosimilars, as it occurs with all biologics, and this variability is natural. In addition, manufacturing process changes during the life cycle of a biologic that occur also create differences between the pre- and post-change biologics. Manufacturing changes are a normal process of biologic drug development and occur for several reasons, such as site changes, scaling up capacity, improving Good Manufacturing Practice, and increasing purity and yield.¹ As such, the regulatory process for biosimilars is primarily focused on comparative analytical testing for structural and functional biosimilarity and the “totality of evidence” concept (as described below) that builds off of the comparability exercise outlined in FDA’s guidance document “Comparability of biotechnological/biological products subject to changes in their manufacturing process”.²

The European Union first developed a regulatory pathway for biosimilars in 2004 and has since licensed over 20 biosimilars.³ The uptake of biosimilars in Europe has varied among the different countries for various reasons that extend beyond potential concerns related to safety and efficacy, and these experiences may offer insights to improve the U.S. practice. The biosimilar paradigm and approval pathway is new, and as the field continues to evolve, education will remain important for all stakeholders. As such, building an educational campaign and identifying policy approaches to disseminate educational information and engage stakeholders is necessary. Stakeholder understanding of the regulatory pathway may not be well understood, as documented in recent FDA advisory committee meetings. An assessment of the educational needs of stakeholders (see Appendix) is necessary to identify where to direct educational efforts and optimize utilization of biosimilars to ensure patient access to these medicines. The FDA has released several guidance documents for biosimilar development to address these issues, and although there are no deadlines for issuing guidance, FDA has said it will also release guidance on the requirements to demonstrate interchangeability and the proper statistical analyses needed for analytical data by the end of 2017. To date, four biosimilars have been approved in the United States, and several other biosimilars are currently under review. Stakeholder involvement in identifying key issues is necessary to ensure current regulatory practices and guidance address stakeholder questions. Downstream issues related to utilization, coverage, and reimbursement are covered in the companion document to this white paper.* The

* For an overview of these outstanding issues, see “Biosimilar Uptake: Considerations for Clinical Decision-Making, Coverage and Reimbursement Decisions, and Postmarket Evidence Development” which was developed as the companion document to this white paper.

Center for Health Policy at Duke University and Friends of Cancer Research have therefore convened a multi-stakeholder working group for this purpose.

FDA REGULATORY PATHWAY FOR BIOSIMILARS

The BPCIA stipulates that a product may be designated as biosimilar to a reference product based on analytical studies, animal studies, and clinical studies, as needed. This abbreviated licensure pathway allows reliance on certain existing scientific knowledge about the biologic characteristics, safety, and effectiveness of the reference product and enables a biosimilar to be approved based on results from analytical tests and appropriate non-clinical studies, and supplemented by clinical studies as necessary. Analytical tests are routinely performed to measure quality attributes to ensure safety and efficacy throughout the life cycle of biologics, but are often unknown to physicians and patients. Building on this routine practice, FDA Guidances, “Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product” and “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,” were developed to outline the agency’s expectations for these studies.^{4,5} Analytical studies should determine structural and functional characteristics, critical quality attributes, identify clinically active and inactive components, and biochemical characterization to demonstrate that the biosimilar is “highly similar” to the reference product. Biosimilarity requires that there be “no clinically meaningful differences” in terms of safety, purity, and potency. The FDA guidance suggests biosimilar sponsors follow a stepwise approach:

- Analytical studies of the proposed biosimilar and reference product to assess physical, chemical and functional similarity;
- Nonclinical (animal) studies to assess toxicities;
- Comparative clinical studies to evaluate pharmacokinetic (PK) and pharmacodynamic (PD) profile of the proposed biosimilar and reference product, and to compare clinical immunogenicity; and
- Potentially, additional clinical studies if residual uncertainty remains.

The FDA utilizes the totality of evidence to determine biosimilarity (Figure 1). Evidence generally includes structural and functional data characterization, animal study data, human PK and PD data, clinical immunogenicity data, and other clinical safety and effectiveness data. The FDA has the discretion to decide whether one or more of these elements is not necessary. This approach allows for a biosimilar to build off of the foundation of knowledge of the reference product. The comparative analytical, nonclinical and clinical demonstrations decrease residual uncertainty regarding demonstration of biosimilarity and reduce the need for extensive clinical studies. Due to the nature of biologics, differences between the biosimilar and reference biologic will almost always be found (just as differences can be expected between batches of the reference product, particularly after manufacturing changes), but the key is determining the clinical relevance of those variations. The amount of clinical data requested is dependent upon the level of uncertainty that remains following analytical and nonclinical studies. Notwithstanding, if high similarity between the reference product and the biosimilar is not demonstrated at the structural and functional level, the proposed biosimilar cannot be approved, irrespective of any results obtained in clinical studies.

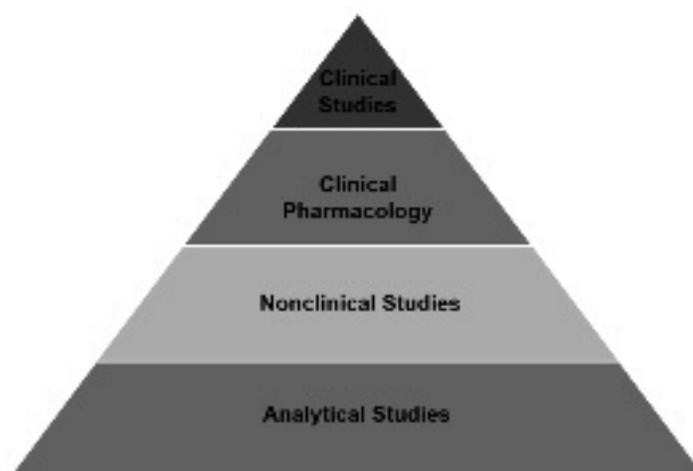


Figure 1. The Totality of Evidence Used to Demonstrate Biosimilarity to a Reference Product.

The FDA guidance discussed above also allows for and describes requirements for extrapolation. That is, if the totality of evidence, including data derived from a clinical study performed in one or more conditions of use of the reference product demonstrates biosimilarity, then the sponsor of the proposed biosimilar may seek approval for one or more additional conditions of use for which the reference product is approved. In these situations, clinical data would not be required for the additional indications if there is sufficient scientific justification for extrapolation, which should address the following issues for the tested and extrapolated conditions of use:

- Degree of structural and functional similarity;
- Mechanism of action;
- PK (and PD if there is a relevant PD measure) of the product;
- Immunogenicity of the product;
- Differences in expected toxicities in each condition of use; and
- Any other factor that may affect the safety and efficacy of the product.

Differences between indications in these factors do not necessarily preclude extrapolation. A scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity. The FDA recommends that clinical studies, if needed, be conducted in a patient population that is expected to be adequately sensitive to detect any clinically meaningful differences between the two products, if any were to exist.

BIOSIMILAR CASE STUDIES

In the United States, four biosimilars are currently approved for marketing in the US: Zarxio (filgrastim-sndz), Inflectra (infliximab-dyyb), Erelzi (etanercept-szsz) and Amjevita (adalimumab-atto). Though all are biosimilars, they vary in size and complexity.

BIOSIMILAR FILGRASTIM-SNDZ (ZARXIO)

Filgrastim is a hematopoietic agent that works by stimulating the production of neutrophils to reduce time and degree of neutropenia in patients receiving chemotherapy. Zarxio, a biosimilar to Neupogen (filgrastim), has a well characterized structure and established mechanism of action, and is a relatively simple biologic both because of its smaller relative size and lack of glycosylation (sugar side chains). Because Sandoz performed an adequate scientific bridge between EU-approved Neupogen, US-licensed Neupogen, and Zarxio, Sandoz was able to use data generated with the EU-approved product as part of the FDA biosimilar application. Sandoz submitted a variety of data to support biosimilarity between Zarxio and Neupogen:

- Analytical studies;
- PK and PD studies;
- Immunogenicity results from five clinical studies;
- Two efficacy and safety studies (one of which was pivotal and the other supportive); and
- Rationale for extrapolation to other indications.

Quality attributes were measured using multiple methods to evaluate analytical similarity of the biosimilar to the reference product. Quality attributes measured included primary structure, bioactivity, receptor binding, protein content, higher order structure, clarity, sequence variants, and posttranslational modifications. Zarxio demonstrated a high level of similarity in these attributes.

PK and PD were evaluated in four studies. The studies supported the demonstration of PK and PD similarity between Zarxio and the reference product Neupogen. Comparative safety and efficacy were evaluated in 214 patients with breast cancer. The study in breast cancer patients incorporated three switches between the two products and compared the results to that obtained with patients who were not switched. The switching had no impact on clinical response or safety. The primary endpoint was duration of severe neutropenia, and key secondary endpoints included febrile neutropenia, days of fever, absolute neutrophil count (ANC) nadir, and time to ANC recovery in Cycle 1. The safety and efficacy profile of Zarxio was similar to that of Neupogen in all measured parameters. Although, the pivotal study was performed in a patient population that addressed only one of the five indications approved for US-licensed Neupogen, Sandoz provided scientific justification for extrapolation in the following indications as US-licensed Neupogen:

- Patients with cancer receiving myelosuppressive chemotherapy;
- Patients with acute myeloid leukemia receiving induction or consolidation chemotherapy;
- Patients with cancer undergoing bone marrow transplantation;
- Patients undergoing autologous peripheral blood progenitor cell collection and therapy; and
- Patients with severe chronic neutropenia.

Ultimately, the totality of evidence led to a favorable Oncologic Drugs Advisory Committee vote and FDA approval in all US-licensed Neupogen indications. Finally, although not part of the decision making process of the FDA, the extensive post-licensure safety database generated since the product's approval in Europe in 2009 was reassuring to the Advisory Committee panel.⁶

BIOSIMILAR INFLIXIMAB-DYYB (INFLECTRA)

Inflectra, a biosimilar to Remicade®, was the first biosimilar monoclonal antibody approved in the US. The primary mechanism by which TNF-antagonists, including infliximab, act is by directly neutralizing the activity of soluble TNF α by preventing its binding to the two TNF α receptors. Celltrion submitted a variety of data to the FDA to support biosimilarity on the basis of the following:

- analytical data;
- PK studies;
- a comparative clinical study to demonstrate similarity in efficacy and safety;
- an assessment of safety and immunogenicity in patients undergoing a single transition from EU-approved Remicade to Inflectra; and
- rationale for extrapolation to other indications.

Similar to Sandoz's Zarxio, Celltrion performed a scientific bridge between EU-approved Remicade, US-licensed Remicade, and Inflectra to utilize data from the EU-approved product in the FDA application. Two comparative safety and efficacy studies were performed in patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA). The studies demonstrated similar safety and efficacy profiles between Inflectra and Remicade. Taking into account the totality of evidence, Celltrion sought approval in the six indications US-licensed Remicade is currently licensed for in the US:

- RA;
- AS;
- Psoriatic arthritis (PsA);
- Plaque psoriasis (PsO);
- Crohn's disease (CD; adult and pediatric); and
- Ulcerative colitis (UC; adult and pediatric).

During the advisory committee meeting, concerns were raised regarding whether comparative clinical studies in RA and AS were sufficient to warrant extrapolation to all Remicade approved indications, specifically IBD. However, because the primary mechanism of action is deemed the same as that for RA and AS, there is an expectation for similar responses across all indications. FDA included an independent FDA review of the pertinent scientific literature and deemed that reverse signaling together with TNF sequestration were likely the predominate mechanism of action for all indications, although other mechanisms may also be relevant for IBD. Ultimately, the totality of evidence led to a favorable Arthritis Advisory Committee vote and FDA approval in all US-licensed Remicade indications except for pediatric ulcerative colitis and Crohn's disease due to exclusivity limitations and not data-related issues.

BIOSIMILAR ETANERCEPT-SZZS (ERELZI)

In July 2016, the FDA approved Erelzi, a biosimilar to Enbrel®. The therapy works by reducing the effects of TNF by acting a decoy receptor for soluble TNF α . The application submitted by Sandoz for Erelzi consisted of the following components:

- Analytical data;

- Three single-dose PK studies in healthy volunteers;
- A comparative clinical trial between EU-approved Enbrel and Erelzi in patients with plaque psoriasis, including assessment of safety and immunogenicity in patients undergoing predefined switching between EU-approved Enbrel and Erelzi; and
- Scientific justification for extrapolation of data to unstudied indications.

Because Sandoz used a non-US-licensed comparator (EU-approved Enbrel) in some studies, a scientific bridge was established between EU-approved Enbrel, US-licensed Enbrel, and Erelzi. This allowed Sandoz to utilize data previously submitted for EU approval. Sandoz's application sought licensure in the following indications US-licensed Enbrel is licensed:

- RA;
- Polyarticular Juvenile Idiopathic Arthritis (JIA);
- PsA;
- AS; and
- PsO.

The review of submitted data resulted in the determination that there are no clinically meaningful differences between Erelzi and US-licensed Enbrel. In considering the totality of evidence, Erelzi was determined to be highly similar to US-licensed Enbrel with no clinically meaningful differences observed with safety and efficacy, and purity in clinical study of patients with PsO. The data package adequately addressed the scientific considerations for extrapolation, and the Arthritis Advisory Committee voted in favor and FDA approved Erelzi for US licensure.

BIOSIMILAR ADALIMUMAB-ATTO (AMJEVITA)

Adalimumab is a TNF inhibiting anti-inflammatory biologic medication. Amjevita, a biosimilar to Humira®, is the latest biosimilar approved by the FDA. The FDA's approval of Amjevita is based on review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates biosimilarity. The following data elements were included in the application:

- Analytical data to demonstrate similarity and justify relevance of comparative data using the EU-approved Humira;
- Single-dose PK study;
- Comparative clinical study in patients with RA to demonstrate no clinical meaningful differences;
- A second comparative clinical study in PsO to assess efficacy, safety, and immunogenicity in patients undergoing a single transition; and
- Scientific justification for extrapolation of data to support biosimilarity in additional indications.

The totality of evidence in combination with the data submitted by Amgen supported the demonstration that Amjevita was biosimilar to US-licensed Humira. The scientific considerations for extrapolation of data to support biosimilarity to other conditions of use for US-licensed Humira led to Amjevita approval for the following conditions:

- RA;

- PsA;
- AS;
- CD;
- UC;
- PsO; and
- JIA.

Amgen provided justification for the proposed extrapolation of clinical data from studies in RA and PsO to each of the other indications approved for US-licensed Humira. After analysis of known and potential mechanisms of action of US-licensed Humira in the conditions of use sought for licensure, it was determined reasonable to extrapolate to indications not directly tested in clinical studies. After reviewing and discussing the data, the FDA Arthritis Advisory Committee voted in favor of the biosimilar, and FDA approved Amjevita in September 2016.

ANTI-CANCER THERAPEUTIC BIOSIMILAR PRODUCTS

Currently, there are no approved anti-cancer therapeutic biosimilars in the US. However, data were recently presented at the annual meeting of American Society of Clinical Oncology in Chicago, IL, June 3-7 for a biosimilar to trastuzumab (Herceptin), a monoclonal antibody which recognizes the HER2 receptor. According to the Phase 3 clinical trial data, the biosimilar showed similar safety, efficacy, and immunogenicity results as the reference biologic and could represent the first FDA approved biosimilar for cancer.⁷ In the Heritage trial, 500 patients with metastatic HER2-positive breast cancer were randomized into two arms to receive taxane chemotherapy plus the biosimilar or reference biologic every 3 weeks for 24 weeks, followed by trastuzumab alone until disease progression. Women treated with the trastuzumab biosimilar had a 69.9% objective response rate compared with 64% among women receiving the reference biologic. Serious adverse events were comparable, with neutropenia being the most common in both arms. Other anti-cancer biosimilar products currently being developed include rituximab, bevacizumab, and cetuximab.

The ongoing development of anti-cancer therapeutic biosimilars, many of which are monoclonal antibodies, has raised a number of questions among stakeholders:

- Is it important to have a distinction between a therapeutic biosimilar agent versus a supportive care biosimilar agent?
- What is the appropriate endpoint? Is response rate sufficient as a measure of biologic activity given the extent of analytical and functional data available?
- A single monoclonal antibody may act through different mechanisms to treat different diseases. Should clinical trials be required for every indication?
- Many therapeutic monoclonal antibodies are given as infusions in hospital settings. How does this impact concerns about pharmacy-based substitutions?
- How likely is it that a patient would be switched multiple times between the originator product and the biosimilar version during the course of cancer care?

DETERMINING THE LEVEL OF EVIDENCE REQUIRED TO DEMONSTRATE INTERCHANGEABILITY

Although four biosimilars have been approved by the FDA, there are currently no biosimilars approved as interchangeable biologics. The BPCIA allows a product to be designated as interchangeable with the reference if it is biosimilar and it is expected to produce the same clinical result in any given patient. In addition, for those products that are given for more than one dose, the risk, in terms of safety or diminished efficacy, of alternating or switching between the proposed interchangeable and the reference product is no greater than solely using the reference product. A product deemed interchangeable may be substituted by a pharmacist without prior consent of the prescribing physician. Post-dispensing communication and record keeping requirements are regulated by states, and about half of the U.S. states have passed legislation and more are considering such legislation. FDA is currently developing guidance on demonstrating interchangeability. Several topics may be addressed by this guidance:

- The nature and extent of similarity required;
- The clinical evidence that is required, including what clinical trial designs (e.g., crossover, parallel) may be needed to support interchangeability (see Figure 2 for an example of a potential trial design to support the designation of interchangeable biologic);
- Naming and labeling of interchangeable biologics; and
- The role, if any, postmarket data could play in supporting a determination of interchangeability.

FDA guidance states that applicants may need to submit data from a single transition (i.e., data from a small group of patients who change from the originator to the biosimilar) in order to rule out a major risk in terms of hypersensitivity, immunogenicity, or other reactions. FDA recently clarified that these type of data are used to support the safety of a biosimilar product because the biosimilars will not be limited to use in treatment-naïve populations. It is noted that these data may also show that patients that undergo a single transition from the reference product to the biosimilar do not suffer major immune-mediated adverse events. These data for a single transition may not sufficiently support a demonstration of interchangeability.

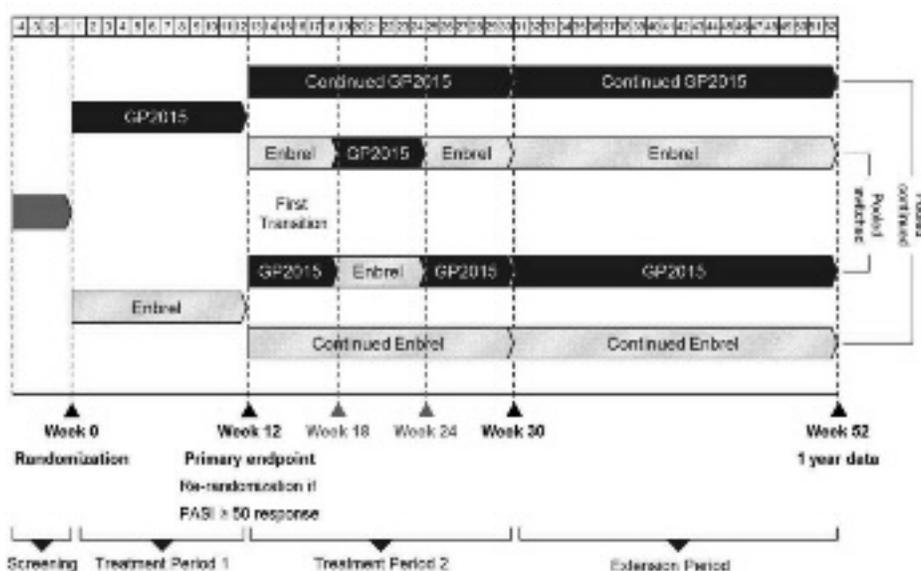


Figure 2. Schemata of a Clinical Trial Evaluating Multiple Switches Between Enbrel and Erelzi (GP2015).

Source: Figure is an excerpt from Sandoz 351(k) BLA submission FDA review documents.

Figure 2 provides an example of a completed biosimilar trial that incorporated multiple switches. The multi-switch clinical data may provide support for an interchangeability application in the future; however, an interchangeability designation was not sought at the time of the original approval. Until FDA releases guidance on demonstrating interchangeability, the clinical trial requirements to support regulatory approval will remain unclear.

There are theoretical concerns on whether substitution from a reference product to the corresponding biosimilar will lead to immunogenicity or diminished efficacy. To date, there is little evidence to suggest this will be the case, based on post-approval pharmacovigilance and other data derived from Europe, where biosimilars have been in the market since 2006, and where some patients on reference biologics have been switched to biosimilars due to various reasons, including tender decisions and payer coverage. There is also a growing body of evidence, including published data that suggest that switching between a reference product and a biosimilar does not result in safety issues or concerns.⁸ More recently, additional studies submitted to the FDA, including two single switch studies from infliximab and adalimumab reference product to the corresponding biosimilar, and two studies evaluating multiple switches between filgrastim and etanercept reference product and the corresponding biosimilar, did not reveal significant safety or efficacy concerns.⁹ Although it has been noted that some patients discontinue treatment after switching to a biosimilar, but presently, most existing data suggest that the process of switching or interchangeability is not inherently a reason for concern. However, it is important to continue to study the issue and to be open to the results that will be reported.^{10,11} The role of postmarket data collection for additional evidence development and demonstrating value is discussed in the companion document.*

Other considerations for a determination of interchangeability include how FDA will communicate data differences between a biosimilar and an interchangeable biosimilar, how will payers interpret biosimilarity versus interchangeability, and what impact will that interpretation have on patients that switch therapy to a biosimilar due to higher cost of the existing product (via mechanisms other than automatic substitution).

ADVANCING BIOSIMILARS THROUGH EDUCATION AND GUIDANCE

The novelty of the biosimilar pathway and its reduced emphasis on clinical testing has resulted in the need for education amongst stakeholders. An overarching concern for all stakeholders is whether a biosimilar product is as safe and effective as its reference biologic. Healthcare professionals have been trained to rely on clinical data in each indication as the primary determinant of the suitability of a given therapeutic agent for a given patient. Biosimilar development and review employs a different paradigm based on the totality of data, with an emphasis on structural and functional analytical data, and a tailored, more limited role of clinical studies as compared to the development and approval of originator drugs. Extensive education will be required to explain and gain acceptance of this concept by all stakeholders, including patients, physicians, nurses, pharmacists, and payers. This education will assist stakeholders in understanding how FDA ensures the safety of biosimilars, how biosimilar products work, and when they can be substituted for a reference product. Historically, physicians were initially concerned about the use of generic drugs and even the first monoclonal antibody therapies. A positive shift in views is credited to education efforts led by various stakeholders, which included industry, patients, advocacy groups, trade associations, and FDA.

* See “Biosimilar Uptake: Considerations for Clinical Decision-Making, Coverage and Reimbursement Decisions, and Postmarket Evidence Development” which was developed as the companion document to this white paper

In order to educate stakeholders, the FDA may need to play a more active role in providing education support than is typically expected of the agency. Currently, the FDA has developed a free Continuing Medical Education (CME) directed towards healthcare providers. Additional education efforts targeted to other stakeholder groups is also needed. To ensure appropriate utilization and adoption of biosimilars, a plan will need to be developed by the stakeholder community to effectively educate the community and address information gaps. Some questions to address to promote effective education include:

- What methods of dissemination and education are needed to reach all stakeholders? Is there a role for FDA in education dissemination?
- Who should be educating stakeholders? How to promote consistent messaging?
- What policy approaches are needed to help biosimilar adoption?
- What evidence will patient and providers require to alleviate concerns? Are there explicit topics which are not well understood and for which directed education is needed?
- Are there specific groups of stakeholders that need education on certain topics, perhaps, more than other groups?

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⁴ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

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⁷ Rugo HS, Barve A, Waller CF, et al. Heritage: A phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-14010 versus Herceptin. *J Clin Onco.* 2016;34 (suppl; abstr LBA503).

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APPENDIX - SURVEYS OF PATIENT AND PROVIDER GROUPS

Naming

Survey data

United States

- 68% of pharmacists believe the FDA should require non-proprietary names¹
- 81% of pharmacists believe the label should identify the product as a biosimilar; 88% believe the label should indicate if the product is interchangeable¹
- 90% believed that the name of the biosimilar should be uniquely different than the name of the original biologic medicine to allow for adequate tracking of any adverse reactions²
- Over 75% of rheumatologists surveyed say the FDA should mandate that biosimilars have a different non-proprietary name than the innovator biologic medicine³
- 74.6% of pharmacists indicated that they would be confident or very confident in substituting an interchangeable biosimilar with the reference product if both shared the same active ingredient or non-proprietary name of the reference biologic; 25.3% of pharmacists were confident in substituting when the non-proprietary name is not shared with the biologic; and 37.3% of pharmacists expressed confidence in substituting when the biologic and biosimilar product did not share the same non-proprietary name because of a prefix or suffix⁴
- The vast majority (99%) of physicians refer to biological medicines by name for both recording in charts and for reporting adverse events⁵
- Less than 1% of prescribers use national drug code numbers for records or reporting⁵
- 48.1% of participants reported a preference for the naming convention that used the nonproprietary (active ingredient) name plus suffix⁶
- Those participants reporting preferences for the nonproprietary name plus suffix preferred the use of a suffix tied to the manufacturer name (83.4%), compared with the random assignment of a 4-letter suffix (16.6%)⁶

Europe

- 53% of physicians surveyed felt that an identical non-proprietary name implies identical structure⁷
- 61% of surveyed physicians said that identical non-proprietary names imply that the medicines are approved for the same indications⁷
- 24% of reporting physicians record only the non-proprietary name of the biological product in the patient record⁷

Educational Needs

- Information on adverse event tracking
- Should FDA require non-proprietary information?

FDA Guidance

- FDA’s non-proprietary naming proposal would permit a biosimilar to use the same core name as the reference biological product, but then add a unique four-letter suffix to identify each product

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf>

Labeling**Survey data****United States**

- 96% of rheumatologists surveyed said the FDA should require labeling to identify a medication as a biosimilar and distinguish any important differences between it and the innovator biologic³
- 90% of respondents believe the label should indicate the biologic is a biosimilar⁸
- 79% of respondents believe the product label for a biosimilar should define what biosimilarity means⁸
- 82% of respondents find it important to include analytical data developed by the biosimilar sponsor to demonstrate its analytical similarity to the reference product on the label⁸
- 83% of respondents find it important to include clinical data from the biosimilar sponsor to demonstrate that it is highly similar to the reference product on the label⁸
- 79% of respondents find it important that a label clearly distinguishes those data generated by the biosimilar sponsor from those generated by the originator sponsor⁸

Educational Needs

- Should labels include clinical trial data collected for the biosimilar?
- Should the label indicate which tests were done to determine biosimilarity?

FDA Guidance

- Biosimilar labeling should be consistent with the label of the reference product
- Biosimilar labels should heavily rely upon their reference products
- Biosimilar product labeling should not need to describe the specific studies and data collected by the biosimilar developer to demonstrate that it is “highly similar” to the reference product
- Biosimilar labels should only include biosimilar-specific information when that information is “necessary to inform safe and effective use of the product”
- The Agency is requiring “biosimilarity statement” at the top of the professional package insert

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>

Biosimilarity

Survey data

United States

- Over 90% of seniors did not know that ACA allowed for approval of biosimilar²
- 86% wanted a requirement that drug companies that are developing biosimilars conduct human clinical trials to ensure a given biosimilar is safe²
- 93% do not believe all biologics are equally effective⁹
- 72% of AGA members report that they would be likely to prescribe biosimilars if they became available in the U.S.¹⁰
- 80% of respondents say they are very concerned with the level of clinical similarity in terms of effectiveness and safety to the reference biologic and the biosimilar efficacy¹⁰
- 78% of respondents are very concerned about biosimilar safety/immunogenicity¹⁰
- Among respondents who are unlikely to prescribe biosimilars, 69% report that they would be unlikely to prescribe biosimilars because they do not have experience with biosimilars¹⁰
- 66% of respondents who are unlikely to prescribe biosimilars believe there will not be enough clinical data on biosimilars¹⁰
- 80% of prescribing specialists say they would want to learn about biosimilars through expert-led digital content¹¹
- Only 17% of prescribing specialists report they would be “very likely” to prescribe biosimilars to eligible patients¹¹
- Specialty societies were prescribing specialists’ most trusted source of information about biosimilars (25%), followed by peers (19%), and key opinion leaders (18%)¹¹

Canada

- 59% of survey participants (rheumatologists) think it is appropriate to offer a biologic-naïve patient a biosimilar¹²
- 31% of survey participants would feel comfortable prescribing biosimilars to patients if approved today¹²

Educational Needs

- Should biosimilars be tested in every indication?
- Concerns include safety/efficacy, drug substitution regulations, and accurate evaluation of when to prescribe a biosimilar vs. branded therapy

FDA Guidance

- In order to establish biosimilarity, the Biologics Price Competition and Innovation Act (“BPCIA”) requires that the proposed biosimilar product:
 1. be “highly similar” to the reference product (i.e., the FDA-approved biological product that the biosimilar sponsor is seeking to copy) based on data derived from analytical studies, animal studies, and one or more clinical studies;

2. utilize the same mechanism of action as the reference product, to the extent known;
 3. be for one or more conditions of use previously approved for the reference product;
 4. have the same route of administration, dosage form, and strength as the reference product; and
 5. be manufactured in a facility that meets standards designed to assure the biosimilar is and will continue to be safe, pure, and potent
- FDA evaluates biosimilarity on a product-by-product basis considering the “totality of the evidence.” In addition to the five statutory biosimilarity requirements above, FDA has provided informative guidance regarding data necessary to support a biosimilarity showing. For example, biosimilars may have a different formulation from the reference product, so long as the biosimilar remains “highly similar” and any formulation differences are not clinically meaningful
 - FDA’s “stepwise approach” to assessing biosimilarity means that more robust initial analytical and comparative evidence of biosimilarity – e.g., structural comparisons, functional in vitro and in vivo assays – may reduce any remaining “residual uncertainty” regarding biosimilarity. Minimized “residual uncertainty,” in turn, may reduce the nature and scope of clinical studies that FDA will require in order for the sponsor to demonstrate biosimilarity

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>

Indication Extrapolation

Survey data

United States

- 92% of seniors wanted a requirement that drug companies test the safety of biosimilars for all conditions the drug will be used to treat²
- 67% of AGA members favored a policy whereby FDA would not allow indication extrapolation in the approval of biosimilars for IBD¹⁰

Europe

- 63.7% of respondents said that they would not switch a patient onto a biosimilar monoclonal antibody as there is no disease-specific evidence about their interchangeability¹³

Educational Needs

- Is it reasonable to assume that efficacy and safety in one indication will be similar in other indications?
- How do you identify the most sensitive patient population to test?

FDA Guidance

- Scientific justification for extrapolation should address:
 1. the mechanism of action (MOA) in each condition
 2. the PK and bio-distribution of the product in different patient populations
 3. PD may provide important info on MOA
 4. Differences in expected toxicities in each condition and patient population
 5. Any other factor that may affect safety and effectiveness in each condition and patient population

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

Interchangeability**Survey data****United States**

- 91% want physicians to be notified when a biosimilar is substituted for the original biologic drug they prescribed for their patient²
- 94% believe patients should be notified when a biosimilar is substituted for the original drug prescribed by their doctor²
- 95% of respondents were concerned their disease would worsen if their biologic medicine were switched⁹
- 98% support legislation that would prohibit non-medical switching without patient/provider notification⁹
- 86% agreed that only patients should have a say in which biologic medicine they are prescribed⁹
- More than 82% of respondents believe that the U.S. Food and Drug Administration (FDA) approval standards for designating a biosimilar as "interchangeable" must be very rigorous to ensure patient safety³
- 35% of respondents believe that pharmacy-level substitution should never be allowed¹⁰
- 85% of responding physicians want the authority to designate a biological medicine as 'Dispensed as Written', just as they have it for chemical products⁵
- 86% of physicians want to be notified before a patient is switched to a biological other than the one prescribed even if there are no known concerns associated with the product⁵

Canada

- Only 7.5% of survey participants (rheumatologists) think it is appropriate to switch a biologic treatment-stable patient to a biosimilar.¹²

Educational Needs

- Concern about switching when currently stable on a biologic
- Should the label indicate whether a biologic is biosimilar or interchangeable?
- If clinical trials are required, how many switches should be required to demonstrate interchangeability?

FDA Guidance

- Draft guidance not provided yet
- FDA may deem a biological product “interchangeable” with a reference product if the sponsor can show that the product is biosimilar to the reference product, that the biosimilar product is expected to produce the same clinical result as the reference product, and that the risk of switching between the biosimilar and reference product is not greater than the risk of using the reference product alone

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2. RetireSafe (<http://www.prnewswire.com/news-releases/statement-from-retiresafe-to-congress-274605751.html>)
3. The Coalition of State Rheumatology Organizations (<http://csro.info/app/document/8382846;jsessionid=P5zJOo6TwPYoXVXzwSYawvyM.undefined>)
4. The Academy of Managed Care Pharmacy, the American Pharmacists Association, and the American Society of Health-System Pharmacists (J Manag Care Spec Pharm. 2015. 3:188-195)
5. Alliance for Safe Biologic Medicines (<http://gabionline.net/Biosimilars/General/Naming-and-interchangeability-of-biosimilars-raised-in-new-survey>)
6. The Journal of Managed Care and Specialty Pharmacy, ([http://www.jmcp.org/doi/pdf/10.18553/jmcp.2016.22.8.919/Biosimilar Naming Conventions: Pharmacist Perceptions and Impact on Confidence in Dispensing Biologics](http://www.jmcp.org/doi/pdf/10.18553/jmcp.2016.22.8.919/Biosimilar%20Naming%20Conventions%20Pharmacist%20Perceptions%20and%20Impact%20on%20Confidence%20in%20Dispensing%20Biologics))
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8. Alliance for Safe Biologic Medicines (<http://docs.house.gov/meetings/IF/IF14/20160204/104408/HHRG-114-IF14-20160204-SD010.pdf>)
9. Global Healthy Living Foundation (<http://www.50statenetwork.org/wp-content/uploads/2015/04/GHLF-survey-4-222.png>)
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13. European Crohn’s and Colitis Organisation (<http://gabi-journal.net/ecco-2013-survey-highlights-lack-of-confidence-in-biosimilars.html>)

Biosimilar Uptake: Considerations for Clinical Decision-Making, Coverage And Reimbursement Decisions, And Post-market Evidence Development

Conference White Paper

The Future of the U.S. Biosimilars Market: Development, Education, and Utilization

Duke Margolis Center for Health Policy
Friends of Cancer Research

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INTRODUCTION

The enactment of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) marked the culmination of a years-long effort to create an abbreviated licensure pathway for biological products that are demonstrated to be either “biosimilar” to or “interchangeable” with an existing FDA-licensed biological product [For full definitions of key terms, please see the glossary on page 37].¹ The legislation was also an important step in the broader effort to foster competition in the US biologic drug market after a period of patent exclusivity, with the goal of generating substantial long-term cost savings in the health care system while still providing financial returns to innovation in biologics. In 2013, the top 10 highest-expenditure drugs covered under Medicare Part B were all biologics, and spending on those drugs alone represented 48 percent of all Part B drug expenditures. (By contrast, total spending on the ten most frequently used Part B drugs accounted for less spending than any one of the top ten highest-expenditure Part B drugs.)²

The review and approval process established under the BPCIA (also known as the 351(k) pathway) was designed to provide an expedited pathway for the approval of biosimilars, similar to the Abbreviated New Drug Application pathway established under the Hatch-Waxman Act of 1984 (a key factor in the development of the modern generic drug market). One study estimates that overall savings in Europe and the US will be between \$56-\$110 billion through 2020 as a result of biosimilar market entry and use.³ However, market competition between biosimilars and their reference products will not be a perfect analogue of the generic small-molecule market, owing to fundamental differences between biologic and small-molecule drugs. Biologic drugs are more complex, more expensive to develop and produce, more sensitive to manufacturing changes, and pose immunogenicity risks that may make substitution or therapeutic switching challenging.

Biosimilar	Approval date	Sponsor	Reference product	Approved for same indications?
Zarxio	March 2015	Sandoz	Neupogen (Amgen)	Yes
Inflectra	April 2016	Pfizer/ Celltrion	Remicade (Janssen)	No—Remicade holds pediatric exclusivity for one indication
Erelzi	August 2016	Sandoz	Enbrel (Amgen)	Yes
Amjevita	September 2016	Amgen	Humira (AbbVie)	No—Humira holds orphan exclusivity for four indications

Table 1: Biosimilars approved by FDA as of October 2016

As a result, overall progress in the development of a robust biosimilars market has been limited. Since the passage of the BPCIA, FDA has approved four biosimilar products (see Table 1).⁴ Though the approval of these drugs has

helped to clarify some of the uncertainties surrounding FDA’s requirements for approval, there are a number of outstanding regulatory, legal, and scientific questions that must be addressed in order to facilitate development and approval of more biosimilars.* These include clarification on the standards for interchangeability, extrapolation of biosimilar approval for one disease or condition to additional indications, and the finalization of guidance on naming and labeling.

Further, there are a number of downstream issues related to utilization, coverage, and reimbursement that also raise distinct concerns. The majority of biologic drugs are reimbursed under the medical benefit rather than under the pharmacy benefit (though at least two of the four approved biosimilars are largely reimbursed under the pharmacy benefit). Consequently it may be necessary to adapt traditional payer strategies aimed at encouraging generic substitution in order to more effectively drive biosimilar use. Additionally, continued postmarket evidence development will be important to build trust in biosimilar safety and efficacy, demonstrate value to stakeholders, and inform approaches to clinical practice and payer decision-making.

Ultimately, the uptake of biosimilars—and the resulting cost savings, access to biologics, and health outcomes—depends on a range of factors that are not yet resolved. This paper reviews several of the major issues that will influence biosimilar availability and use beyond regulatory marketing approval, including: 1) existing and emerging coverage and reimbursement strategies that payers and pharmacy benefit managers (PBMs) could employ to guide utilization; and 2) the potential role that postmarket evidence generation could play, both in terms of informing the design and implementation of these payment strategies, as well as in addressing outstanding questions related to the relative cost, quality, and effectiveness of biosimilars.

GUIDING BIOSIMILAR UTILIZATION - POTENTIAL PAYER STRATEGIES

As with generic drugs, payers and PBMs will play a critical role in influencing biosimilar utilization and price discounts from manufacturers. Many of the tools that have been used by these stakeholders to encourage generic drug use could be adapted and leveraged to promote the adoption of biosimilars and facilitate lower negotiated prices for the original biologics. However, the design and application of these tools and strategies will depend on whether a given biosimilar is administered by clinicians in an office setting (generally covered under a medical benefit plan) or obtained from outpatient pharmacies and self-administered by patients or their caregivers (usually covered under a pharmacy benefit plan).

BIOSIMILAR COVERAGE UNDER THE PHARMACY BENEFIT: FORMULARY DEVELOPMENT AND IMPLEMENTATION

For drugs covered under the pharmacy benefit (typically dispensed by a retail or specialty pharmacy and self-administered by the patient), a key approach to utilization management is through the formulary. Pharmacy and Therapeutics (P&T) Committees—which develop and maintain formularies for organizations—traditionally base formulary inclusion and tiering decisions on a range of considerations, including the potential cost savings, current

* For an overview of these outstanding issues, see “The Current Landscape of Biosimilars Development, Regulatory Review, and Stakeholder Education” which was developed as the companion document to this white paper.

clinical guidelines and practices, logistical implications, and physician and patient preferences.⁵ Importantly, the actual price paid for a given drug—as well as its placement on a payer or PBM formulary—depends in part on that payer’s ability to negotiate volume-based discounts or rebates, which pharmaceutical companies may offer in exchange for more favorable placement on a formulary.

Formulary tiering

Most US payers—including Medicare Part D—rely on a tiered formulary structure designed to encourage the use of preferred therapies. Based on the P&T evaluations, drugs are generally assigned to a particular tier according to their cost and their incremental value (uniqueness). Generic drugs are typically assigned to the tier with the lowest patient copay, while more costly drugs are grouped into tiers with progressively higher copays or coinsurance rates. The most expensive therapies—many of which are biologics—are often grouped into a specialty tier that includes both higher levels of cost-sharing as well as additional layers of utilization control, such as prior authorization from the payer or limits on the number of units administered or dispensed at a single time.⁶

It is unclear how tiering and cost-sharing approaches will impact the uptake and utilization of biosimilars. While an online survey of 102 health plans found that 49 percent intend to place biosimilars at a lower tier than branded specialty biologics, a number of characteristics unique to the biosimilars market may limit how effective these approaches are when compared to their success in accelerating uptake for small-molecule generics.^{7,8} For example, most biologics are intended for patients with chronic, complex conditions that require ongoing treatment, which means that if these drugs are on a higher tier, affected patients will incur substantial costs before reaching the out-of-pocket maximums. For example, the exchange plans established by the ACA set the out-of-pocket maximum at \$7,150 for individual coverage and \$14,300 for family coverage in 2017. The continued proliferation of patient assistance programs (many of which are funded by pharmaceutical manufacturers) will further limit how cost-sharing arrangements affect patient behavior, patient costs, and total spending on biologics.

Formulary exclusion and step therapy requirements

Related key strategies for enabling formulary design to influence utilization and costs are formulary exclusion and step therapy requirements. These approaches are typically applied in cases where there are multiple therapies that are highly similar in terms of both safety and efficacy.⁹ In such cases, payers and PBMs may choose to exclude certain products from their formulary or engage in exclusive contracts with a single manufacturer in exchange for price discounts or rebates, thus incentivizing (or requiring) the selection of preferred options. Plans may also require a step therapy process that requires patients to try a preferred option first, with the option to switch to an alternative therapy at a later date. These strategies have been successful in driving down costs in certain therapeutic classes, and can be applied to biosimilars. Payers may also apply prior authorization (also called pre-certification), requiring patients and their providers to document that diagnostic criteria and, in some cases, prior treatment criteria are met before receiving payment for the more expensive options.

The extent to which these strategies are applied will depend on several considerations. One is the therapeutic context. For certain cancers, for example, a step therapy process that requires a preferred option prior to switching to an alternative in the same drug class would likely not be appropriate owing to concerns over emergence of drug resistance following exposure to the initial drug. In addition, state and federal regulations restrict the design and application of these approaches. For most categories of drugs covered under Medicare Part D, for example, plans are required to include at least two drugs from each drug category or class unless only

one is available, or only two are available but one drug is clinically superior to the other. In the six protected classes – including oncology drugs, drugs for autoimmune conditions, and other conditions where biologics are common treatment – CMS initially mandated and then Congress legislated that all drugs must be covered (though potentially on higher tiers or with prior authorization).¹⁰ CMS indicated in 2015 that it would review off-cycle plan decisions to remove biologic products from their formulary and replace them with a biosimilar on a case-by-case basis.¹¹

State laws regarding pharmacy substitution may also have an impact. While small-molecule generic drugs can typically be automatically substituted without authorization by the prescriber, (provided that the prescriber does not explicitly request the branded drug), non-interchangeable biosimilars are not considered therapeutically equivalent, and no biosimilar appears on track for approval as interchangeable at this time.¹² In addition, over the last four years, 36 states have either considered or enacted laws that would introduce additional administrative controls on the automatic substitution of interchangeable biosimilars. These provisions vary but share common features, including requirements that pharmacists notify physicians or patients when a substitution has been made, or that pharmacists obtain patient consent before substituting the interchangeable biosimilar. Many states would also require that pharmacies retain a record of this substitution for a certain number of years.¹³

In addition to such policy decisions, the extent to which price competition and shifting occurs will depend importantly on the level of evidence available to demonstrate that the differences between the biosimilar and its reference product are inconsequential, particularly for scenarios where a payer may seek to induce a patient already on an originator to switch to the biosimilar, or vice versa. Extensive price competition and shifting from brand to generics has occurred because patients and physicians generally view the drugs as therapeutically equivalent. The evidence, and thus the willingness to switch, will differ for biosimilars. While postmarket surveillance in Europe has not detected immunogenicity concerns related to switching between biosimilar and reference products, payers and PBMs will need to evaluate the potential impact of any therapeutic interchange or step therapy requirements on a case-by-case basis, as switching patients from one biologic therapy to another may have clinical implications and the evidence is still evolving on how individual patients may respond differently to such substitutions.

Payers and PBMs may instead consider limiting step therapy requirements to treatment-naïve patients until further postmarket safety and substitution evidence becomes available. A given patient's treatment status or history may be challenging to determine if they are newly enrolled, and will likely require a prior authorization process to ensure that patients have not previously been treated with another biologic.

These various factors are likely to promote more intense competition between reference and biosimilar manufacturers to capture initial administration of a therapy.¹⁴ Payers will need to implement strategies to ensure patients receive a prescription in line with their insurer's formulary. Such strategies could include making patient-specific formulary information more widely available at the point of prescribing and implementing prior authorization requirements. It will also be necessary to develop coverage policies to address cases where the biosimilar might be approved for fewer indications than the reference product, as well as cases where the branded biologic is routinely prescribed off-label as part of standard of care practices.

BIOSIMILAR COVERAGE UNDER THE MEDICAL BENEFIT: PROVIDER FEE SCHEDULES

The majority of biologics are covered under a patient's medical benefit and are purchased by providers and administered in an inpatient setting, physician's office, or other outpatient setting. Drugs administered in these

contexts are processed as a medical claim rather than as a pharmacy claim. Hospitals and health systems purchase these drugs from distributors, often through group purchasing organizations, and like PBMs or other payers, may be able to negotiate lower drug prices in return for emphasizing use of certain drugs where alternatives exist (historically, this process has been developed much more extensively for devices). The reimbursement mechanisms for medical benefit therapies—which include high priced cancer and rheumatoid arthritis drugs as well as comparatively inexpensive products such as corticosteroids and vitamin B12—are structured very differently from pharmacy benefit drugs and the prices paid are influenced in different ways.

Inpatient hospitalizations and procedures are typically reimbursed on either a prospective, bundled basis (e.g., Medicare’s Diagnosis Related Group payment structure under Part A) or a per diem basis (e.g., many commercial insurance plans). These payments are intended to cover all costs related to care, generally including drugs, though specific providers may bill separately for the administration of the drug. Hospital or health system formularies may diverge from those of third-party payers and PBMs, which can complicate care transition. For example, patients in an inpatient setting may receive a therapy based on the hospital’s formulary, but upon discharge to the outpatient setting may find that their insurer’s formulary specifies a different therapy for their condition. As noted above, formulary decision support at the point of prescribing can help address this issue.

Reimbursement for biologics administered in the outpatient setting is typically structured as a flat rate per dose. Medicare Part B drug payments are based on the average sales price (ASP) of the drug plus a fixed percentage mark-up, so the total payment to the provider who “buys and bills” for the drug is ASP plus six percent.¹⁵ The ASP of a given drug is updated on a regular basis to reflect price changes over time, with a lag. Many commercial payers follow the Medicare structure, generally with a higher markup rate above ASP. This reimbursement structure means that higher-priced drugs generate larger margins for the administering provider.

Reimbursement levels for biosimilars covered under medical benefits—and the corresponding margins they generate for providers—will also be influenced by how they are treated in the ASP system. Drugs that are reimbursed under the medical benefit are billed using a Healthcare Common Procedure Coding System (HCPCS) code. Under recently finalized CMS rules, an originator biologic will continue to receive its own HCPCS billing code, while all biosimilar products that reference that biologic will be grouped together under a single separate HCPCS code.¹⁶ Reimbursement for all biosimilars will be set at the ASP of all of the biosimilars grouped under that code, plus six percent of the *reference* product’s ASP.

Though this policy is intended to spur price competition between biosimilar manufacturers, there are ongoing questions about how it may affect prescriber behavior and the potential downstream consequences for biosimilar market entry. While the payment rule provides a higher percentage mark-up for selecting biosimilars, in some cases the absolute dollar margins may still be higher for the reference product, giving providers a financial incentive to select the more expensive products.¹⁷ The separate (and potentially higher) payment for the reference product provides a stronger incentive for providers to prescribe it than if all products were grouped into the same payment code. On the other hand, grouping all biosimilars together under a single billing code may discourage manufacturers from competing based on the relative value of their products (such as the quality, safety, or effectiveness of the products for certain types of patients). Grouped coding may also discourage manufacturers from remaining in this nascent market long-term, thus limiting competition and potential savings of biosimilars. Grouping all biosimilars together does not create a structure that supports payers in selectively negotiating preferred pricing and access from one company. Private payers may have more flexibility to shift margins away from reference products to cheaper biosimilars, but additional incentives and tools (e.g., separate

coding modifiers and other steps to encourage formulary approaches within the medical benefit) may be necessary to encourage such approaches.

Alternatives to provider fee schedules

Given the challenges associated with buy-and-bill reimbursement under the medical benefit, commercial payers have begun piloting alternative approaches to managing utilization and costs for drugs covered under the medical benefit. Under one approach, providers are required to purchase specialty pharmaceuticals from a contracted specialty pharmacy which has negotiated a particular price for that drug.¹⁸ Because the cost of infusible or injectable drugs can vary depending on the setting where the drug is administered, some plans have also used patient cost-sharing incentives in benefit design to encourage the selection of less-expensive drugs and drug administration settings.

In addition, several payment methods have been proposed or are currently being implemented as alternatives to traditional buy-and-bill reimbursement methods, including:

- reference pricing, which sets a drug's payment rate no higher than that for currently available treatments, unless evidence shows that the drug improves patient outcomes;
- indication-based pricing, which allows the negotiated price for a drug to vary based on its demonstrated clinical effectiveness for different indications; and
- outcomes-based payment, which links a drug's payment level to beneficiaries' observed outcomes (or markers of outcomes) through a risk-sharing agreement with the manufacturer.¹⁹

Experience with these arrangements to date has identified a number of practical challenges and has proven controversial, including in a recent CMS pilot proposal to test many of these approaches for drugs reimbursed under Part B (in the second, currently conceptual phase of the pilot).

These value-based pricing models have also been proposed for drugs covered under the pharmacy benefit. Broader obstacles to implementation need to be addressed, including off-label communication restrictions, anti-kickback statutes, and best price regulation. It may also be necessary to address the uncertainties regarding FDA's promotional and scientific exchange rules on companies' abilities to discuss postmarket data. This additional clarity could help to further encourage data generation in the biosimilars context, ultimately leading to better health outcomes and lower overall costs.

EMERGING VALUE-BASED PAYMENT APPROACHES THAT MAY IMPACT BIOSIMILAR USE

Broader changes to the healthcare system, spurred in part by the ACA, have led payers and providers to begin experimenting with payment models that seek to align payment with better patient outcomes, higher-value care, and more flexible and innovative care delivery. Because these value-based payment models are expanding, they may have a greater short-term impact on biosimilar use than reforms in drug pricing. Some of these reforms may involve modifications of the fee-for-service payment rates for providers. Some private payers currently reward higher generic prescribing with a payment bonus incentive, which could be extended to biosimilars.²⁰ For example, biosimilar prescribing could potentially contribute to provider value metrics under the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA).

Beyond fee-for-service payment adjustments, many emerging alternative payment models (APMs)—such as accountable care organizations, patient-centered medical homes with accountability for costs and outcomes, and bundled payments for episodes of care tied to quality incentives—could have a significant impact on biosimilar use, depending on how utilization and spending for physician-administered drugs is incorporated into these models. The models shift some financial risk from payers to providers, in conjunction with more flexibility in how providers can deliver services (e.g., extended office hours, team-based care, telemedicine, and other services could get more financial support) and more accountability for improvements in performance metrics and other quality outcomes. These broader changes to the way care is reimbursed may help to drive clinical decision-making toward the use of lower-cost biosimilars, particularly if the benefit to given categories of patients is similar.

Some commercial health plans have implemented reimbursement linked to greater use of clinical pathways based on evidence and expert consensus, particularly in oncology. Standardized clinical pathways are designed to support provider decision-making and will often specify the selection, dosing, and ordering of drugs for a given condition, as well as the use of supportive therapies. Under these programs, providers are offered financial incentives to follow pathway recommendations, such as higher reimbursement rates or care management fees.²¹ The Anthem Cancer Care Quality Program, is one of the largest clinical pathway programs.²² Launched in 2014, the program is designed to reduce the variation in treatment and cost of 19 types of cancer by providing a \$350 monthly care management fee to providers whose treatment regimen adheres to a standardized clinical pathway that specifies the use of treatments selected on the basis of efficacy, toxicity, and cost.^{23,24}

Bundled or episode-based payments reimburse providers at a prospectively set rate for a group of services they furnish during an episode of care. These bundles often include associated pharmaceutical costs as part of the medical benefit. Even without changes in medical benefit payment for physician-administered drugs, this new financial accountability could help to shift providers towards using less-costly biosimilars.

Payers and PBMs have also begun implementing alternative cost-sharing strategies aimed at linking patient decision-making to higher-value care, referred to as “value-based insurance design”, or VBID. These strategies vary, but typically include cost-sharing reductions for patients that meet certain criteria (e.g., particularly high-risk patients, or patients that enroll in disease management or wellness programs).²⁵ Though VBID strategies have shown some success in increasing adherence, most strategies employed to-date have been applied to small-molecule drugs rather than biologics. Such approaches could be generally applicable to biosimilars covered under the pharmacy benefit by waving copays or setting lower fixed copays for the biosimilar.²⁶ Similarly, VBID could be matched to episode payments and other alternative payment models, enabling patients to save money or receive other nonfinancial benefits if they choose providers who are higher-performers in the models.

CMS recently announced that it would be expanding its own VBID pilot to include rheumatoid arthritis (RA) patients, which could potentially incorporate biosimilars.²⁷ Two of the recently approved biosimilars – Erelzi, which is biosimilar to Enbrel, and Amjevita, which is a biosimilar to Humira – are alternatives to leading treatments for RA and could be eligible for the pilot. However, the pilot ends in 2022 and it is currently unclear when these two products might formally launch in the US market, owing to pending patent disputes.

SUPPORTIVE STRATEGIES: PROVIDER EDUCATION

Payers and PBMs have employed a range of education and information-supplying strategies to help guide prescriber decision-making. In addition to the formulary decision support approaches described above, another

approach is to provide individually tailored information on optimal drug use. Trained educators visit providers to share neutral, up-to-date information on the safety, efficacy, and cost-effectiveness of medications and other therapeutic options, including any available information on comparative effectiveness.²⁸ This approach, known as academic detailing, is modeled after the interactive communication practices used by medical sales staff. Though academic detailing may involve many different kinds of approaches, evaluations have found that it can be effective in influencing prescribing behavior.^{29, 30} However, the quality and effectiveness of treatment guidelines or academic detailing efforts will largely depend on what is known about the relative safety, value, and effectiveness of a given treatment.

ADDITIONAL CONSIDERATIONS AFFECTING PRICING AND UPTAKE OF BIOSIMILARS

FDA has issued a number of guidance documents related to biosimilar development and approval to date, but there are still several outstanding questions that could impact payer decision-making and, ultimately, biosimilar uptake and access. For example, FDA has not yet finalized guidance on naming, label format, and interchangeability. It is also unclear whether FDA will view two biosimilars of the same reference product as biosimilar to each other, or whether two interchangeable biosimilars will also be considered interchangeable with each other. The final FDA positions on these issues might affect payers' decisions to shift patients from one biologic to another (singly or in multiple incidences). It is unclear what standard payers will use to assess whether it is safe to transition patients from an originator biologic to a biosimilar. The standards that payers set will also have broad implications for provider and patient trust and could affect confidence in switching to a biosimilar.

Until these issues are more clearly resolved, supply chain maintenance will be an important consideration. Retail and specialty pharmacies may need to take steps to ensure that patients maintain access to a single biosimilar product, and payers and providers may also need to assess a manufacturer's capacity to reliably supply the product as one of the criteria included in the formulary review process.

DEMONSTRATING BIOSIMILAR VALUE THROUGH POSTMARKET EVIDENCE DEVELOPMENT

A key factor in payer and PBM decision-making will be the level of evidence supporting the use of a biosimilar within a particular disease context or in specific patient populations, relative to the reference product. Continued postmarket evidence development and dissemination of that evidence will be an important component in building trust in the safety and efficacy of the therapies, demonstrating value to stakeholders, and informing the approaches to clinical practice and payer decision-making described above. This is particularly important given that, compared to originator drugs, the biosimilar development paradigm relies heavily on analytical characterization and to a lesser extent on clinical data.

Prospective, randomized controlled trials (RCTs) are and will remain an important source of information on long-term outcomes and comparative effectiveness, but due to their cost, complexity, and duration, they are challenging to implement in practice. RCTs also have well-known limitations in terms of understanding a treatment's effect outside of the population studied in the trial. For many outcomes or populations of interest, alternative approaches such as pragmatic clinical trials, adaptive clinical trials, observational studies, and meta-analyses will play an important role.

Postmarket research can provide additional evidence on the risks and benefits of switching biologic therapies, on the use of the originator and biosimilar, and on the impact of formulary designs and other policies affecting this use. Studies could also assess the impact of patient support programs on outcomes with various biologic therapies. Just as with traditional small-molecule drugs and medical devices, stakeholder groups will need evidence and information that can be met through more systematic data capture and dedicated postmarket studies.

European Union health systems have already adapted their postmarket surveillance approaches to monitor biosimilar products specifically, as these products have been available since 2006. Some post-approval studies have been designed to confirm biosimilarity for extrapolated indications. Many are designed to assess the safety and efficacy of switching from an originator biologic to a biosimilar. There are several well-known examples, including NOR-SWITCH, an ongoing study sponsored by the Norwegian government where patients will undergo a single switch from Remicade to an infliximab biosimilar across several disease states. Data are expected to be available by early October 2016. One of the largest data points on switching is the recently published data from the DANBIO registry in Denmark. This study assessed 647 patients with rheumatoid arthritis, psoriatic arthritis, or axial spondylitis who had been treated with Remicade for a median of nearly 7 years before undergoing a switch to the biosimilar infliximab. The authors conclude that “[d]isease activity remained largely unchanged 3 months prior to vs. after the switch.” However, more long-term follow-up is needed, as roughly 6 percent stopped treatment due to loss of efficacy or adverse event.³¹

In the United States, there are a number of challenges associated with collecting robust, reliable postmarket data. The fragmented nature of the U.S. healthcare system makes it difficult to follow patients across multiple providers, systems, and payers.³² Healthcare settings differ in the level of detail that is captured for health records and claims, and electronic health records (EHRs) are often extensively customized within institutions, which can result in significant variation in how data are characterized and catalogued.³³ Reimbursement models for outpatient and inpatient settings can further complicate efforts to make comparisons between patients or synthesize outcomes data, as coding requirements for healthcare claims may be different in each of these settings.³⁴ Creating stronger incentives for the development of a postmarket evidence infrastructure could be an associated benefit of a shift to more value-based payment models, where such evidence has more direct bearing on payment. It has been challenging to ensure that postmarket studies, including those tracking safety issues, are completed in a timely manner.^{35, 36} These issues cut across all postmarket research activities and would pose similar issues for biosimilars.

FACILITATING AND INCENTIVIZING POSTMARKET EVIDENCE GENERATION

One of the key issues in developing postmarket evidence is the broader research infrastructure necessary to support studies. In the last decade, there has been substantial investment from the public sector in building more robust and comprehensive data networks that can develop real-world evidence more effectively and comprehensively, including FDA’s Sentinel System, PCORnet, and the Medical Device Epidemiology Network. Efforts are currently underway to expand and harness the Sentinel System to conduct studies that go beyond safety surveillance. The Innovation in Medical Evidence Development and Surveillance (IMEDS) program is in the process of developing the governance and processes for non-FDA entities such as manufacturers to sponsor safety queries utilizing the Sentinel infrastructure.³⁷ Importantly, Sentinel is also part of a collaboration formed by the Academy of Managed Care Pharmacy to monitor and assess the impact of biosimilars on patients. The Biologics and Biosimilars Intelligence Consortium, or BBIC, is currently using Sentinel’s data and infrastructure to conduct

descriptive analyses of four biologic drug classes. These analyses are intended to lay the groundwork for future studies of biosimilars and their reference products.³⁸

These efforts will help to reduce operational and technical barriers to research and bring down the costs of evidence generation. Engaging patients at the outset of a research project before the launch of clinical trials and studies by asking for signed consent to authorize data linkages for aggregate use (such as the approach set forth in the Precision Medicine Initiative) could facilitate these efforts.³⁹ Existing health IT platforms, such as the American Society of Clinical Oncology's CancerLinQ, can also be leveraged to track and evaluate patient outcomes after the introduction of biosimilars into the market, providing evidence on long-term safety and efficacy.

Additional incentives will likely be necessary to support systematic postmarket evidence generation. As noted above, new APMs being adopted and tested by payers and providers to drive higher value care could encourage more utilization of biosimilars. In turn, the expected pressure from value-based payment reform could increase incentives for developing a stronger postmarket evidence infrastructure, which will be critical to understanding the real impact of these payment models on the uptake and use of biosimilars on cost and quality outcomes. Value-based purchasing contracts between payers and manufacturers, such as those utilizing outcome- or indication-based pricing, may also create stronger incentives for the development of better evidence on biosimilars.

Successful implementation of these approaches will require better and standardized measures that can adequately capture the value of alternative treatments, and the underlying data to construct the measures.

DATA SOURCES FOR POSTMARKET EVIDENCE GENERATION

Post-approval safety and comparative effectiveness studies commonly rely on data collected through registries or databases derived from administrative or EHR data, which is used to measure exposure to the drug and the associated outcomes.⁴⁰ Prospective registries have several advantages for research purposes, as they contain very complete information on exposures and outcomes for as long as they are maintained (this adherence is often enforced by restricting distribution of the drug to providers who have joined the registry). However, registries are complex and expensive to establish and maintain, particularly for a large cohort of patients. They also do not typically contain data on control groups of similar patients who do not receive the medication, and thus are not able to address questions of comparative safety or effectiveness. As a result, registries are typically used for safety surveillance of specific products that are particularly expensive or carry significant risks.⁴¹

By contrast, large databases draw from routinely collected claims and clinical data, which reduces the burden on the health system and in some cases can be used to identify control groups of patients for comparative purposes. Using these databases to evaluate biosimilars and their outcomes depends on the ability to distinguish biosimilars from each other and from their reference product in the data. The most widely used identifiers for research purposes are billing codes; namely, National Drug Codes (NDCs), which are applied to claims for drugs reimbursed under the pharmacy benefit, and HCPCS codes, which are used for drugs reimbursed under the medical benefit.⁴² In some cases, EHR data may contain NDCs or a proprietary coding system that can be used to identify the product prescribed.⁴³

As the majority of biologics are administered by physicians and billed as medical claims, HCPCS codes will be an important component of postmarket research on biosimilars. However, this presents several challenges. First, while NDCs are drug-, manufacturer-, and dosage-specific, HCPCS codes are not, which can make it difficult to

identify which product was administered. CMS recently finalized its rules for biosimilar reimbursement under Part B, mandating that all biosimilars that reference a particular product will share the same HCPCS code. To facilitate pharmacovigilance, the agency will assign a manufacturer-specific, two-digit modifiers to each biosimilar product.⁴⁴ The assignment of permanent HCPCS codes is a months-long process, which can hinder surveillance in the first 6 to 18 months of utilization. Once CMS publishes the modifier its use will be mandatory.

There are several strategies that could be implemented or expanded to improve the completeness, timeliness, and accuracy of the data that supports postmarket evidence generation. For example, billing could be shifted for physician-administered drugs from HCPCS to NDCs, though in the hospital system setting this may present an informatics challenge. Barcode administration could allow these sorts of data to travel from the pharmacy with the product to the patient bedside and the EHR. Researchers could also make increased use of new analytic approaches to safety surveillance, such as data mining (i.e. the use of computational processes to discover patterns or relationships in large data sets). Such approaches can be used to identify early safety signals that can then be investigated further to determine if the link between the biosimilar and the identified adverse event was valid and clinically meaningful.⁴⁵

TARGETING KEY QUESTIONS AND OUTCOMES

The outcomes targeted through postmarket research will naturally depend on the purpose of the study and the stakeholders interested in the results. While many outcomes (such as immunogenicity and other serious adverse events) are important to all stakeholder groups, the value proposition for a given biosimilar may vary somewhat among patients, clinicians, and payers. For example, providers and patients may place relatively more emphasis on comparative clinical effectiveness or ease of use or administration, while payers and PBMs may place relatively more emphasis on cost or the dependability of supply (See Table 2 for a list of key questions that could be addressed through postmarket evidence development). It will be important for those involved in evidence development to consider the information needs of each group when planning a study.

Well-designed outcomes research on biosimilars could not only align across multiple stakeholder needs, but also contribute to broader efforts to establish a national evidence development system. This has been identified by FDA, policymakers, and others as a key national priority and efforts are already underway to address the outstanding questions and uncertainties related to the collection and use of the evidence that could be generated. Enhancing the use of real-world evidence in regulatory decision-making has also been identified as a key commitment for FDA under the next iteration of the Prescription Drug User Fee Act (expected in 2017), and several groups are working in parallel to support the agency's efforts in this area.

Tracking the utilization and effectiveness of biosimilar products could further motivate sponsors, payers, and others to contribute toward building this system. Making meaningful connections among the constellation of ongoing evidence development systems mentioned above and tackling challenges with data standardization and integrity will require the investment of substantial time and resources. Biosimilars could prove an important test case for addressing these issues and realizing a national infrastructure.

Question/Outcome of interest	Primary audience
Does the biosimilar product lead to lower total costs of care without any impact on quality, safety, effectiveness outcomes compared to the reference product?	Physicians, patients, payers, manufacturers
Do lower out-of-pocket costs associated with biosimilars lead to increased utilization and adherence? (i.e., is there a net benefit with using a biosimilar because of improved access?)	Payers, manufacturers, patients
Is switching or alternating between the biologic therapies safe and effective for all patients?	Physicians, patients, payers
What value – in terms of improved compliance, better outcomes, and/or reduced costs – do ancillary services such as patient and physician support services provide to the healthcare system?	Physicians, patients, payers

Table 2: Key Questions/Outcomes of Interest in Biologic Evidence Generation

CONCLUSION AND NEXT STEPS

The emerging biosimilars market offers enormous potential to reduce healthcare spending and expand access to life-saving drugs. However, a number of issues relating to utilization, coverage, reimbursement, and postmarket evidence generation remain that may inhibit biosimilar uptake. Building consensus on the optimal approaches for addressing the challenges outlined in this white paper will be essential for ensuring the success of this nascent market. In particular, determining which payment reforms are most promising for the effective use of biosimilars and what evidence capabilities would be most helpful for implementing those reforms will be important. Building physician and patient confidence in the use of biosimilars will require additional investment in both postmarket research as well as stakeholder education.

While building consensus in these areas is no small task, a concerted effort by stakeholders to tackle these issues is an important next step to fulfill the promise of biosimilars. The key next steps for addressing the gaps and challenges identified in this white paper are:

- Further FDA guidance or general principles regarding issues like interchangeability or patient switching that will impact price negotiation and use;
- Ongoing stakeholder education efforts to increase confidence in the use of biosimilars;
- Continuing to build the infrastructure for the capture of high-priority postmarket data and methods for using these data to develop more extensive evidence on biosimilar comparative effectiveness and impacts on costs of care;
- Development of evidence on PBM and payment reform strategies that will impact drug choice and switching.

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GLOSSARY OF TERMS

Biologic	Medical products derived from a variety of natural sources (human, animal or microorganism) and used for the prevention or treatment of disease. Examples of biological products include: vaccines; blood and blood products for transfusion; human cells and tissues used for transplantation; gene therapies; and cellular therapies.
Biosimilar	A biological product that is approved based on a demonstration that it is highly similar to an FDA-approved biological product, such that there is no clinically meaningful difference in terms of safety, purity, and potency between the two products.
Comparability	Refers to the practice of assessing biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process.
Immunogenicity	The propensity of a biologic drug product to generate a host immune response to itself and to related proteins, or to induce immunologically related adverse clinical events.
Indication extrapolation	If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed.
Interchangeable	Refers to the medical/pharmaceutical practice of switching one medicine for another that is equivalent, in a given clinical setting. A product is considered to be interchangeable if it can be administered or dispensed instead of another clinically equivalence product without significant risk of an adverse health outcome.
Reference product	A biological product licensed under section 351(a) of the Public Health Service (PHS) Act against which a biological product is evaluated in a 351(k) application for biosimilarity or interchangeability.

Substitution	<p>The practice of dispensing one medicine instead of another equivalent and interchangeable medicine in any given patient at the pharmacy level without consulting the prescriber.</p> <p>The FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. There is no ‘substitutability determination’ at the EU level</p>
Small molecule drug	<p>Medical products typically derived from a process of chemical synthesis; comparatively much smaller in chemical size and less structurally complex than biologic (also known as large molecule) drugs.</p>
Switching	<p>Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent (e.g., from originator to generic/biosimilar or vice versa, or among different drugs within the same therapeutic class) in a patient during the course of treatment. In hospitals, the decision to switch a medicine is made by a multidisciplinary team including the clinical community (therapeutic/formulary committee). <i>Non-medical Switching</i> is also a term that has been increasingly used in the biosimilar field to describe a situation where a patient’s medicine is switched to a chemically distinct alternative for reasons other than the patient’s health and safety. Examples of non-medical switching include switching between structurally distinct blood pressure medications, statins, NSAIDs, or anti TNFs.</p>
Therapeutic equivalence	<p>The determination that a particular drug can be substituted for another (or vice versa) with the expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Drug products are considered to be therapeutically equivalent if they are pharmaceutical equivalents (contain the same active ingredients; dosage form and route of administration; and strength).</p>
Therapeutic interchange	<p>The dispensing of a drug that is therapeutically equivalent to but chemically different from the drug originally prescribed by a physician.</p>

Modernization of Eligibility Criteria

Conference White Paper

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Summary

Eligibility criteria are a critical component of clinical trials and serve to define the patient population under study. They can be inclusionary, perhaps by specifying a tumor type or molecular alteration needed for study entry, or exclusionary by specifying certain characteristics such as comorbidities that would render a patient ineligible for enrollment. While restricting trial eligibility to a homogenous patient group improves the ability of a trial to detect a treatment effect, should one exist, a primary purpose of eligibility criteria is to protect the safety of those patients who are thought to be at increased risk of experiencing a treatment-related adverse effect. However, excessive or overly restrictive eligibility criteria can impair clinical trial accrual and the applicability of trial results to heterogeneous “real-world” patients who ultimately may receive the drug in the post-market setting. It also delays access to investigational agents for patients who may in fact stand to benefit. In 2016, the American Society of Clinical Oncology (ASCO), Food and Drug Administration (FDA), and Friends of Cancer Research (Friends), launched an initiative to re-assess the current approach to determining clinical trial eligibility. We will build on these and other efforts and provide recommendations for how sponsors, investigators, and regulators can work together to implement expanded clinical trial eligibility where appropriate.

Background

Common exclusion/inclusion criteria have developed over time, primarily through experience with cytotoxic chemotherapeutics. Many of these are grandfathered from prior trial protocols, with little consideration as to whether they are truly appropriate for the specific clinical question being asked. Given the increase in complexity of cancer treatment, and the advent of novel therapeutic modalities, many have called for simplified, rational eligibility criteria.^{1,2} Newer, molecularly targeted agents generally do not have the same safety profiles as chemotherapies and often require additional biomarker-driven patient selection parameters that may severely limit the number of patients eligible for a trial; therefore, identifying opportunities to safely broaden eligibility has been recognized as a priority.³

Recent cooperative group studies of the impact of different eligibility criteria on trial and patient outcomes support the need for a re-evaluation of clinical trial eligibility. Gerber *et al* reviewed lung cancer trials sponsored by the Eastern Cooperative Oncology Group (ECOG) between 1986 and 2013 and determined that patients with prior malignancies were excluded from 94% of trials that used survival as a primary endpoint and 73% of trials that used other primary endpoints.⁴ This study also analyzed the SEER-Medicare database and determined that up to 18% of lung cancer patients have prior cancer diagnoses, and therefore a substantial portion of patients are potentially excluded from trials for this reason alone. Subsequent work by this group showed that prior malignancies did not impact survival outcomes in patients with stage IV lung cancer or locally advanced lung cancer, suggesting that clinical trial outcomes would not be adversely impacted by inclusion of patients with a history of prior cancer.^{5,6} A similar case-by-case, evidence-based approach to assessing other common eligibility criteria will be useful to determine when they can be safely relaxed.

¹ George SL. “Reducing patient eligibility criteria in cancer clinical trials.” *J Clin Oncol*. 1996 Apr;14(4):1364-70.”

² Fuks A, Weijer C, Freedman B, Shapiro S, Skrutkowska M, Riaz A. “A study in contrasts: eligibility criteria in a twenty-year sample of NSABP and POG clinical trials. National Surgical Adjuvant Breast and Bowel Program. Pediatric Oncology Group.” *J Clin Epidemiol*. 1998 Feb;51(2):69-79.

³ Kim ES, Bernstein D, Hilsenbeck SG, Chung CH, Dickler AP, Ersek JL, et al. “Modernizing Eligibility Criteria for Molecularly Driven Trials.” *J Clin Oncol*. 2015 Sep 1;33(25):2815-20.

⁴ Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. “Impact of prior cancer on eligibility for lung cancer clinical trials.” *J Natl Cancer Inst*. 2014 Sep 24;106(11).

⁵ Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. “Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual.” *J Natl Cancer Inst*. 2015 Feb 9;107(4).

⁶ Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. “Prior cancer does not adversely affect survival in locally advanced lung cancer: A national SEER-medicare analysis.” *Lung Cancer*. 2016 Aug;98:106-13.

ASCO-FDA-Friends Eligibility Criteria Initiative

In an effort to modernize clinical trial eligibility criteria to better reflect intended-to-treat populations and allow broader and more representative enrollment of patients in trials, four working groups composed of multiple stakeholders, including sponsors, investigators, biostatisticians, pharmacologists, regulators, and patient representatives, developed detailed consensus-driven recommendations regarding where it is scientifically and clinically appropriate to expand eligibility criteria. The four working groups considered: 1) patients who have brain metastases, 2) the minimum age of patients eligible for enrollment, 3) patients who are HIV positive, and 4) patients with organ dysfunction. In developing these recommendations, the working groups reviewed the state of the science, any existing case studies, and attempted to balance the needs of protecting patient safety, facilitating access to investigational therapies, and protecting trial integrity (including safety, efficacy, and statistical considerations). To maximize the generalizability of results, clinical trial enrollment criteria should strive for inclusiveness and provide justification for the selected inclusion and exclusion criteria if compelling safety or efficacy concerns mandate the exclusion of specific populations. Recommendations were presented at a public workshop on May 12th, 2016, and are summarized below.

Brain Metastases⁷

Broad exclusion of patients with brain metastases is common despite the very high incidence of brain metastases in some tumor types. Although life expectancy may be reduced for some patients with brain metastases, and there may be greater risk of neurological toxicity, existing literature does not indicate that these patients experience higher rates of serious adverse events. This working group developed recommendations specific to: 1) patients with treated or stable brain metastases, 2) patients with new/active/progressive brain metastases, and 3) patients with leptomeningeal disease. For patients with treated or stable brain metastases, the working group concluded that, without a compelling rationale for exclusion, these patients should be routinely included in prospective clinical trials of all phases. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to blanket exclusion of all brain metastasis patients. For patients with active brain metastases, the working group concluded that a one-size-fits-all approach is not appropriate, and factors such as natural history of the disease, trial phase and design, and the drug mechanism and potential for CNS penetration should determine whether such patients are included in a trial. If patients with active brain metastases are included, additional prospective planning may be required to better define safety and response. Early stopping rules may be appropriate should excessive toxicity be observed. Finally, the working group concluded that in most trials, it remains appropriate to exclude patients with leptomeningeal disease due to their poor prognosis, although there may be situations that warrant a cohort of such patients in early phase trials – for example, when CNS activity is anticipated.

Minimum Age⁸

Children and adolescents under the age of 18 years are often excluded from participating in clinical trials with novel agents until extensive adult data are available, sometimes many years after the introduction of an agent. Because pediatric patients have historically been considered a vulnerable population, there is concern that a high profile adverse event in a child could endanger the entire drug development program. However, there is no evidence to support this concern. The main scientific barriers that preclude enrollment of pediatric patients in most “adult” clinical trials are the lack of overlap between some types of cancers that adult and pediatric patients develop, the potential for developmental toxicity, as well as differences in metabolism between the age groups. The working group developed recommendations for inclusion of pediatric patients in early and late phase trials. In initial dose-finding trials, the group recommended the

⁷ Recommendations of the 2016 ASCO-Friends Brain Metastases Eligibility Criteria Working Group (N Lin, E Kim, A Tan, K Beal, J White, J Sul, T Prowell, LA Kordestani, I Perkins, O Rosen). In preparation for publication.

⁸ Recommendations of the 2016 ASCO-Friends Minimum Age Eligibility Criteria Working Group (L Gore, F Balis, M Donoghue, N Goodman, P Ivy, G Reaman, E Rubin, K Thornton). In preparation for publication.

inclusion of pediatric-specific cohorts when there is a strong scientific rationale, based on molecular pathways or histology as well as preclinical data, to believe that a specific pediatric population could benefit from a drug under study. These cohorts would assess dose and pharmacokinetics separately in the pediatric population. Staggered enrollment starting with older children followed by younger children could be considered to address potential concerns specific to younger pediatric patients, including not only metabolic differences but also challenges related to the availability of appropriate formulations for young children. The working group also recommended that later phase trials in diseases which span adult and pediatric populations include pediatric patients with the specific disease under study. Based on the similarity in metabolism between adults and adolescents, the working group recommended that patients aged 12 years and above be enrolled in such trials.

HIV/AIDS⁹

Many people infected with HIV have a near normal life expectancy due to substantial improvements in HIV therapeutics over the past 20 years. Cancer is now a leading cause of mortality in people with HIV, however most oncology studies exclude this population. This working group recommended that HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes should be included in cancer clinical trials unless there is a specific rationale to exclude such patients – for example, if there is reason to believe that the investigational drug might interfere with control of HIV infection, which may be the case with some immunomodulating agents. In the absence of a rationale for exclusion, HIV-related eligibility criteria should be straight-forward and focus on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions such as opportunistic infections other than historically low CD4 and T cell counts, and status of HIV treatment. Healthy HIV-positive patients that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication.

Organ Dysfunction¹⁰

This working group began by discussing the types of organ dysfunction that were likely to drive most clinical trial exclusion criteria. They decided to focus on kidney, heart, and liver dysfunction, as well as exclusion based on a prior, alternate cancer history. The group conducted analysis of these criteria from a large, representative dataset that included a cohort of nearly 13,000 patients newly diagnosed with breast, colon, lung, and bladder cancers from 2013-2014. The analysis, as well as review of the literature, helped the group determine which of the organ dysfunction criteria to prioritize for development of recommendations. Because the dataset included only newly diagnosed patients, it is possible that other exclusionary criteria should also be considered, but the group decided to focus on the organ performance status that raised the most challenge for patient participation. The group prioritized a focus on renal function because the rates of exclusion based on typical hepatic and cardiac function tests would not have raised a problem with participation in the newly diagnosed patients. The group concluded that renal function criteria should be based on creatinine clearance rather than serum creatinine levels. The group also proposed liberal creatinine clearance criteria in situations where renal excretion is not a significant component of a drug's pharmacokinetics or when known dose modification strategies can allow safe and effective administration. Conservative criteria remain appropriate for nephrotoxic drugs. Although the group did not recommend changes to the current criteria for hepatic or cardiac function, they did propose that future studies include cohorts of patients with organ dysfunction as well as geriatric patients when appropriate to better define the spectrum of toxicity. This would aid clinicians in decision-making and allow a more realistic description of patient outcomes. The group agreed that exclusions based on prior malignancies should be liberalized –

⁹ Recommendations of the 2016 ASCO-Friends HIV/AIDS Eligibility Criteria Working Group (K Dunleavy, G Isom, RF Little, BW Miller, A Noy, M Rudek, K Schwartz, TS Uldrick, J Wang, J Zeldis). In preparation for publication.

¹⁰ Recommendations of the 2016 ASCO-Friends Organ Dysfunction Eligibility Criteria Working Group (SM Lichtman, P Cortazar, L Fehrenbacher, RD Harvey, NA Rahman, N Rosch, D Smit, M Thompson, D Walker). In preparation for publication.

both in terms of the timing and types of prior malignancies, as well as current malignancies that are not life-threatening in the short term.

Implementation

Through the course of working group discussions, potential benefits and risks of expanding eligibility criteria were identified (Table 1). As previously stated, the primary purpose of eligibility criteria is to protect the safety of patients presumed to be at a higher risk of experiencing an adverse event. Thus, significant concerns are that use of broader criteria may put some patients at risk, and that the development of an effective drug could be jeopardized if a serious adverse event occurs in a patient population that is inherently sicker. Inclusion of some patients may require additional screening/monitoring or the engagement of additional expertise to manage safety issues specific to that patient population. This would help to mitigate risk in these patients but would also increase trial cost and complexity. In some cases, working groups concluded that it would be appropriate to include a traditionally excluded patient population as a part of the general trial population, while in other situations, working groups recommended that certain patient groups be included as a separate cohort within a trial or analyzed separately from the general trial population. Either of these options would again present additional operational considerations and cost to drug sponsors; however, they may also provide data in an underrepresented population that could potentially be included in a drug label and used to differentiate a drug from others in its class. Potential study design options that can be considered to address these concerns and potentially mitigate risk are provided in Table 2. Some options are similar to biomarker-based stratification designs that have been used to evaluate efficacy and toxicity in biomarker-positive and -negative patients. These designs may facilitate label inclusion of safety or efficacy information in the expanded population if sufficient data is collected to draw meaningful conclusions; however, discussion with regulators will be necessary to determine the best approach for each situation. We anticipate that current efforts to expand eligibility in several clinical trials will help to demonstrate the feasibility and that future FDA guidance, particularly with regards to safety reporting, will assist sponsors in designing more representative trials.

Following publication of the current working group recommendations, future efforts will include data-driven efforts to identify other opportunities to safely broaden clinical trials, including evaluation of potential opportunities to adjust requirements around drug washout periods, use of concomitant medications, and inclusion of geriatric patients. One goal will be to create standardized and consistent language for trial protocols to facilitate electronic data collection and searches of clinical trials. Another goal will be to develop metrics to monitor uptake of these recommendations. Outreach to institutional review boards will be critical to ensure that patient safety is appropriately balanced with access to investigational therapies. Ultimately, the goal of this initiative is to change the culture such that sponsors and investigators include patients unless there is a compelling rationale not to, rather than the current default to exclusion. Given the significant interest in and enthusiasm for this effort from many in the cancer community, we believe this goal can be achieved for the benefit of all stakeholders.

	Patients and Physicians	Sponsors/Investigators
Benefits	Earlier access to investigational agents, expanded trial and treatment options	Ability to generalize to “real-world” patients, and may reduce post-marketing requirements.
	More complete safety data, which can inform clinical use and enable safe delivery if/once investigational agent becomes commercially available	Faster accrual
		Identification of potential safety issues during clinical trials may facilitate early development of mitigation strategies, enabling broader uptake after approval
Availability of efficacy data can inform weighing of commercially available treatment options	Efficacy in traditionally understudied population could potentially be included in drug label and provide a differentiating factor between drugs of same class	
Risks	Limited data from small cohorts may not be adequate for clinical decision-making	More variability in outcomes – may require larger sample sizes and inferences may not be as precise
	Patients that are inherently sicker may have higher risk of experiencing an adverse event due to the drug or disease	Potential safety concerns – may require separate cohorts or analysis plans and early stopping rules for excess toxicity
		May complicate attribution of adverse events - consider randomization and data from other drugs in class
Additional screening or imaging needs in some situations may incur additional costs to patients	Increased costs associated with additional cohorts, statistical requirements, additional testing or special expertise to manage specific patient needs	

Table 2: Potential Trial Designs and Considerations
Early Phase Trials
<p>Add an expansion cohort restricted to a specific patient population (e.g., a pediatric population, patients with poor performance status, or patients with active brain metastases).</p> <ul style="list-style-type: none"> Maximum tolerated dose, dose-limiting toxicities, pharmacokinetics may be assessed separately in that population Serious safety issues could prompt the cohort to be closed without compromising the entire drug development program. Results in early phase can inform the decision as to whether and how to include (or not) the patient population in later phase trials
Later Phase Trials
<p>Expand eligibility criteria to include a specific patient population (may be appropriate for prior malignancies or patients with HIV) and include these patients in primary analysis</p>
<p>Allow broad enrollment while restricting primary analysis to narrower patient population</p> <ul style="list-style-type: none"> Protects integrity of trial while enabling data collection in broader populations Data may be helpful to inform safe clinical use in “real-world” patients
<p>Expand trial eligibility to include a specific patient group but stratify randomization where one strata includes patients who would not meet traditional eligibility to ensure balance of these patients across treatment arms.</p> <ul style="list-style-type: none"> May be appropriate when early-phase data shows that special subset can tolerate drug but only at a lower dose, or when life expectancy is shorter in special subset
<p>Consider adaptive designs where trial is expanded or restricted based on data collection early in the trial and recommendations from a Data Safety Monitoring Board</p>
<p>Initiate a separate cohort or companion protocol restricted to a specific patient population</p> <ul style="list-style-type: none"> Similar to expanded access protocols and may only include safety monitoring

Optimization of Exploratory Randomized Trials

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Summary

In recent years, the field of oncology has benefitted from the development of several highly effective new therapies for some forms of cancer. These therapies may demonstrate profound treatment effects that are apparent in early phase clinical trials, necessitating expedient clinical trial approaches that move beyond the traditional stepwise drug development paradigm. These approaches must maintain rigor while improving efficiency to ensure that truly effective drugs can quickly reach patients in need without compromising patient safety. Different approaches may be needed for different scenarios. This panel will address potential paths forward when unexpectedly large improvements in overall survival (usually included as a secondary endpoint) are observed in early phase randomized studies, a scenario that is occurring with increasing frequency. Because these are exploratory trials, primarily initiated to guide “go/no-go” decisions in product development, they are typically not designed with the necessary statistical rigor for definitive assessments of clinical benefit. Therefore, using these trials as the basis of a regulatory decision without further study may present challenges. However, only using the data for a “go/no go” decision and initiating a separate randomized phase 3 trial may also be problematic depending on how compelling the exploratory trial results were as well as the level of unmet need in the disease under study. We will provide recommendations for the optimal conduct of early phase randomized trials, potential frameworks that can be put in place prospectively for the controlled expansion of exploratory trials, and statistical approaches that can be used by sponsors or FDA reviewers to help interpret the results in the absence of pre-specification and determine how to proceed in the event of unexpected but promising survival signals.

Exploratory Randomized Trials

Although exploratory trials are often single-arm studies, in some cases randomized trials are employed early in development with the objectives of providing proof-of-concept or generating hypotheses. In these trials, the patient population under study may be limited for safety reasons or to improve the chance of detecting an efficacy signal. The requirements for the trial’s operating characteristics such as power and Type I error (concluding that a drug has a certain effect, when it, in fact, does not) may also be less restrictive than in later stage trials, or may not even be pre-specified. There may be multiple looks at the data, potentially introducing bias, and informal interim analyses with no planned adjustments to avoid inflation of the Type I error rate. In our scenario, compelling survival outcomes may be observed, but survival is not the primary endpoint and is rather a secondary endpoint. In fact, a variety of endpoints may be specified to assess pharmacological activity and tolerability and to provide early evidence of efficacy with respect to clinical or patient reported outcomes, typically with no plans to account for multiplicity due to the numerous outcomes in place. In general, these “looser” operating characteristics are accepted for exploratory trials, with the assumption that clinical benefit will be rigorously assessed in later phase trials.

Consequently, if unexpected and potentially exceptional survival signals are observed in an exploratory randomized study, these issues can lead to difficult decisions about whether to expand the ongoing trial, initiate a subsequent phase 3 trial, or seek regulatory approval. Options available to sponsors could include:

Traditional approach:

1. Use the exploratory data results solely for a “go/no go” decision and initiate confirmatory trials.

Alternative approaches:

2. Expand the exploratory randomized trial, and if the survival benefit is maintained, seek regulatory approval.
3. For exceptional survival data in exploratory randomized trial, submit for regulatory approval, and potentially initiate a phase 3 confirmatory study at the same time.

There are many factors to consider as sponsors determine how best to proceed with unexpected data that includes both statistical and non-statistical issues.

Statistical Approaches for Interpretation of Unexpected Findings

In instances where there is little to no pre-specification in the exploratory randomized trial and an unexpectedly large improvement in overall survival is observed, sponsors and the FDA can be faced with the challenging scenario of interpreting the results. We will discuss a potential statistical model that can be useful in these scenarios. This is an adaptation of a previously published Bayesian approach which accounts for the clinical significance of the results and for the fact that the survival results were unexpected in a phase 2 trial and often not specified as the primary endpoint for analysis.¹ Bayesian approaches can be very useful in looking across multiple endpoints, analysis times, or studies. These factors are not accounted for in the calculation of a “p value”.

Instead of a p value, the tool described here provides a posterior probability that the treatment effect (treatment relative to control) exceeds a minimal clinically significant threshold. For survival in oncology studies that threshold might be a 20% to 30% relative reduction in the hazard of death but will depend on the disease and line of therapy. The posterior probability depends on the observed treatment effect in the clinical trial, the size of the trial, and on the prior probability distribution of the treatment effect (i.e., the likelihood of different treatment effect sizes one would expect before seeing the results of the clinical trial). It is the prior distribution which enables one to express the fact that an extreme treatment effect on survival is unexpected for a phase 2 trial with a PFS or response endpoint. The prior distributions have decreasing effect on the posterior probabilities as the sample size of the trial increases, and in the example case studies discussed below, the results are not critically dependent of the prior distribution.

The model we have investigated is based on the estimation of an unknown hazard ratio (HR) for treatment on survival. An HR of 1.0 means no treatment effect on survival and an HR of 0.75 represents a 25% reduction in the hazard of death by treatment. The prior probability of the null hypothesis of no treatment effect on survival is denoted by $1-\theta$. For an early phase 2 trial of a drug of unknown efficacy, one would generally set this null prior probability to be .90 or some suitably large figure. The prior distribution when the null hypothesis is false is based on a standard deviation parameter τ as described in the Appendix.

To compute the posterior probability that an observed difference in survival is clinically significant, one must specify the survival results of the trial, θ , τ , and the threshold for clinical significance (e.g. 25%

¹ Simon R. “[Clinical Trials and Sample Size Considerations: Another Perspective]: Comment.” *Statistical Science*. 2000 15(2): 103-5.

reduction in hazard of death). In our simulations, we have summarized the trial results for survival by indicating the observed HR and the total number of deaths observed in the trial. For details on computing the posterior probability of a clinically significant treatment effect, see the Appendix.

It is important to note that this model helps to interpret the level and confidence of evidence in trials with unexpected results, but it does not alleviate issues related to robustness of results, sensitivity analyses, uncontrolled interim looks, and trial conduct.

Application of the Bayesian Statistical Approach to Real-World Case Studies

Iniparib is an inhibitor of the enzyme poly ADP-ribose polymerase (PARP). This example is chosen because it is a well-known example where preliminary trial results indicated a significant survival advantage which generated considerable enthusiasm. However, follow-up studies failed to confirm this effect and, in fact, demonstrated that iniparib did not inhibit PARP at clinically relevant doses. Early approval based on the initial phase 2 results would have put patients at risk by exposing them to an ineffective drug.

In a phase 2 open-label, randomized study of patients with metastatic triple negative breast cancer iniparib combined with chemotherapy improved the rate of clinical benefit from 34% to 56% ($P=0.01$) and the rate of overall response from 32% to 52% ($P=0.02$).² The addition of iniparib also prolonged the median progression-free survival from 3.6 months to 5.9 months (HR for progression, 0.59; $P=0.01$) and the median overall survival from 7.7 months to 12.3 months (HR for death, 0.57; $P=0.01$). A subsequent randomized phase 3 trial enrolled 519 women who had previously received at least two rounds of chemotherapy. This trial was designed with overall survival and progression-free survival as co-primary endpoints and was unable to demonstrate significant improvements in these endpoints.

We applied the statistical model described above to determine how it might have influenced decision making based on the phase 2 results. The total number of deaths was not reported but was estimated to be approximately 73 from the confidence interval given for the HR. From that value and the reported HR, the Bayesian analysis was performed using $\theta=.9$ and $\tau=1$. The resulting posterior probability distribution for the true HR for survival is shown in Figure 1. For any HR on the x axis, the y axis shows the posterior probability that the x-axis value is the true HR. An HR value of 1.0 corresponds to no treatment benefit on survival. A vertical line is drawn at 0.70 as a potential threshold for clinical significance; that is an HR < 0.70 would represent a clinically significant treatment effect on survival. The area under the curve to the left of the vertical line is the posterior probability that the treatment effect is clinically significant. In this case that area is 0.71 which may indicate that additional data is needed to ensure the treatment effect on survival is clinically significant. If we use a threshold of clinical significance of 0.75, the area under the curve to the left of the x-axis point HR=0.75 is 0.82. Thus, even with a threshold of clinical significance of 0.75, the data is not strongly convincing that there is a clinically significant treatment effect on survival. The posterior probability of the null hypothesis that iniparib has no effect on survival was 0.044 as can be seen by the point at an x-axis value of 1.0. The posterior probability of the null hypothesis is however not very robust to changes in the model parameters, and we do not recommend using it for decision making in this context. A posterior probability of .82 that the HR for survival is less than .75 may not be sufficiently

² O'Shaughnessy J, Osborne C, Pippen JE, et al. "Iniparib plus chemotherapy in metastatic triple-negative breast cancer." *N Engl J Med.* 2011 364:205-14.

strong to support the conclusion that the treatment is effective to a clinically significant degree. Consequently, this approach as part of the evaluation of the study would not have suggested consideration of approval of the drug without a follow-up phase 3 trial. This use of this approach would have been appropriate to guide decision making in this example.

Olaratumab is a platelet-derived growth factor (PDGF) receptor alpha blocking antibody. Olaratumab received fast track and breakthrough therapy designation, priority review status, and accelerated approval for its use in soft tissue sarcoma (STS). This example illustrates a study where there was highly significant improvement in survival outcomes, a secondary endpoint, in an early phase trial when progression-free survival was the primary endpoint. Though the study was not necessarily designed to be a pivotal trial, it did lead to its approval.

Data came from a randomized phase 2 trial involving 133 patients with multiple subtypes of metastatic STS.³ Patients were randomized in a 1:1 ratio to receive either combination therapy comprising of olaratumab and doxorubicin, or the standard of care treatment of doxorubicin monotherapy. Patients in the combination treatment arm had a median overall survival of 26.5 months, compared with 14.7 months for those treated with doxorubicin monotherapy (HR 0.46; P=0.0003). In contrast, progression-free survival was extended by only 2.5 months in the olaratumab arm (6.6 months versus 4.1 months). Though the primary endpoint of the study, a 50% increase in progression-free survival, was met, it was not significant by investigator assessment (HR 0.67; P=0.0615) or independent radiological review (HR ratio 0.67; P=0.1208).

To evaluate how the statistical model described above might have influenced decision making, data from the phase 2 trial were evaluated using an HR of 0.46 and 91 observed deaths (Figure 1). A vertical line is drawn at a true HR of 0.70 which might correspond to a minimal clinically significant effect. The Bayesian analysis was performed and the posterior distribution of HR for survival is shown in Figure 1. The area under the curve to the left of 0.70 is approximately 0.95. This means that there is a 95% posterior probability that the true HR is 0.70 or less indicating that the evidence is convincing and supports the FDA decision. If the line were drawn at 0.75, representing a lesser reduction in survival, the posterior probability to the left of that would be 0.98.

The posterior distribution was computed based on an assumption that the prior probability of no treatment benefit was 0.90; so the survival effect was unexpected. However, the data was sufficiently strong that with 91 deaths the high prior probability of no treatment effect is overridden by the data. We also used the parameter $\tau=1$ for the standard deviation of the treatment effect under the alternative. The results were little changed however if we used $\tau=2$ or 0.5.

³ Tap WD, Jones RL, Van Tine BA, et al. "Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomized phase 2 trial." *Lancet*. 2016 388:488-97.

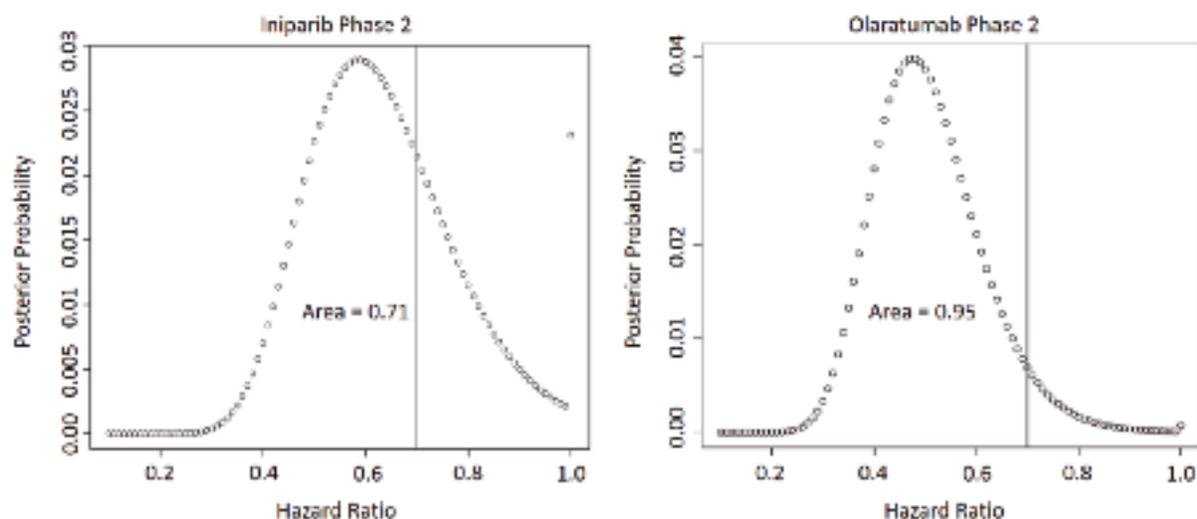


Figure 1. Statistical model evaluating data from phase 2 trial data of iniparib and olaratumab. For any HR on the x-axis, the y-axis shows the posterior probability that the x-axis value is the true HR. An HR value of 1.0 corresponds to no treatment benefit on survival. A vertical line is drawn at 0.70 as a potential threshold for clinical significance; that is an HR < 0.70 would represent a clinically significant treatment effect on survival. The Bayesian analysis was performed and the posterior probability calculated as the area under the curve. For iniparib, there is a 71% posterior probability that the true HR is 0.70 or less indicating that additional evidence may be needed to sufficiently support the conclusion that the treatment is effective to a clinically significant degree. For Olaratumab, there is a 95% posterior probability that the true HR is 0.70 or less indicating that the evidence is convincing, but would need to be considered as part of the evaluation of the entire study.

Additional Factors to Consider When Interpreting Findings from an Exploratory Trial

As sponsors navigate these various options, factors other than statistical analyses will also need to be considered, such as the strength of evidence from the phase 2 study, the feasibility of restarting enrollment once preliminary results are known, the role of an independent monitoring committee in triggering further enrollment, and potential drifts in patient population due to expanding the number or location of study sites. Additionally, recruitment for a subsequent study may be difficult, once the early trial's results are publicly available. Other issues critically important include chemistry, manufacturing, and controls (CMC) readiness and the adequacy of the safety database.

Standard considerations around the interpretation of results from any randomized clinical trial, such as those described in ICH E9, apply across all trials in general.⁴ Several considerations are highlighted here as particularly relevant in the context of observing an unexpectedly large benefit in survival in an exploratory randomized study. The extent to which many of these can be adequately addressed will help determine the interpretation of the strength of the results, and hence help determine the best appropriate path forward.

⁴ Guidance for Industry: E9 Statistical Principles for Clinical Trials.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm023137.pdf> (accessed Oct. 31, 2016)

Potential sources of concern in the design, conduct, analysis, and interpretation of the results include:

- Multiplicity due to overall survival typically being a secondary endpoint, multiple interim analyses; other possible sources of multiplicity such as multiple arms, statistical methods for analyzing the data, and the primary analysis population
- The robustness of the survival results, in view of the likely small sample size of an exploratory study, especially as it relates to potential imbalances in important prognostic factors, the impact of post-discontinuation anti-cancer therapy, and the ability to evaluate consistency across subgroups
- The conduct of the study, including the level of blinding, the sufficiency of the description of the process and procedures for examining data, including informal and formal analyses, and whether crossover to the experimental therapy has been allowed

In contrast to confirmatory trials, exploratory trials often have less pre-specification allowing for more flexibility in the design and conduct of the study. This is often appropriate depending on the specific objectives of the study, the extent to which the safety and efficacy of the experimental treatment is understood, and the extent of ongoing biomarker evaluation. However, flexibility in the design and conduct of these studies can pose challenges to evaluating the results in a regulatory approval setting.

There is benefit in sponsors considering the incorporation of some standard features found in confirmatory trials when designing, conducting, and analyzing exploratory randomized studies. The addition of some pre-specification and rigor around the timing and assessment of interim analyses or the planned timing of the final overall survival analysis can often bring additional scientific rigor with little downside. Furthermore, recently observed faster-than-expected enrollment in studies (e.g., checkpoint inhibitor trials) coupled with the time lag on obtaining survival data may make it necessary to add language that allows extended enrollment if early efficacy results are quite favorable to help reduce delays in global protocol amendment.

Opportunities for Prospective Planning and Trial Expansions

In instances where there is a promising benefit in overall survival but the data is not quite strong enough or requires additional patient populations before submission for regulatory approval, a trial expansion may be one approach to efficiently collect more evidence and data. The points to consider in the section on “Additional Factors to Consider When Interpreting Findings from an Exploratory Trial” are applicable both to the original study (in terms of whether it provides a solid basis for expansion) as well as to the design of the expansion. It is also important to note that having a prospective plan in place does not guarantee positive data; it simply improves the ability to appropriately interpret the data.

Adaptive designs that prospectively incorporate a trial expansion, using appropriate statistical methods to control the Type I error rate are available and are described in the extensive literature on this topic. These designs are valuable in the context of designing a Phase 2/3 study. Few exploratory studies are designed in this way, and it would not be desirable or feasible to design all randomized phase 2 exploratory studies in this manner. However, trials for new classes of drugs that have shown exceptional promise in early exploratory settings in terms of objective tumor response (e.g., immune checkpoint inhibitors), may warrant greater consideration for provisions to be in place at the start of the trial.

Some pre-planning around potential outcomes, associated decisions, and resultant actions into the protocol can be beneficial in terms of reducing the need for protocol amendments and improving the understanding

of the operating characteristics of the study. At this stage of development though, maintaining the ability of the sponsor to also incorporate ongoing, and maybe unexpected, learnings from this trial and external data will continue to be important.

A major concern in regards to unplanned adaptations in clinical trial design or conduct during the trial is the loss of control over Type I error rates. As a starting point, it is worthwhile to consider the simplest case of expanding the trial (either in terms of number of patients or number of events) to collect additional overall survival data in the same patient population as defined by the protocol. In the context of this paper, it is assumed that a large overall survival has been observed in the original (unexpanded) study, and what might be defined as an unexpectedly large effect, is also likely to be statistically significant at the 5% level. With a statistically significant effect on overall survival acting as a gate-keeper, a study expansion in the same population would not inflate the Type I error rate above the standard 5%. Methods to assess the evidence, such as the interpretation of the p-value (and point estimate), from the expanded trial with reference to an even higher bar for remarkable results (such as that outlined in the Bayesian statistical approach above as guidance) will then need to be evaluated.⁵ In instances where the threshold for statistical significance is not met, it may be desirable to increase patient follow-up time or recruit additional patients. However, in scenarios where statistical significance is not met but is still promising, it may be necessary for sponsors to have some pre-specification in place prior to unblinding (e.g., number of overall survival events to collect if the trial were to proceed) and to utilize adaptive methods to ensure statistical validity is maintained.^{6,7}

Expansion from a study that made significant alterations to the patient population based on results might be more challenging and could lead to significant bias. This could be somewhat mitigated if the study was originally designed to evaluate the populations—for instance, a study designed to evaluate in a specific biomarker positive and negative population, and subsequently dropping the biomarker negative population for the expansion.

Further, expansion based on data collected from a study with insufficient quality is also a concern. Making alterations to the choice of study endpoints, patient populations, or treatment allocations based on unblinded interim results may lead to biases toward favorable study outcomes or add unwanted variability to the study characteristics. A framework designed with operating characteristics that permit trial expansion or potential drug approval depending on the outcome of the exploratory trial may help minimize uncertainty in the assessment of the results of these types of trials.

A template for pre-specified expansion could include options to modify inclusion/exclusion criteria to increase generalizability of data within a single trial, or the template could allow for adaption of specific trial features, if warranted based on accumulating data, without starting a new trial. Additionally, it could include options to increase the follow-up time and the sample size possibly through expanding the number and geographic spread of trial sites. This framework could guide the development and use of pre-specified triggers for expansion in the event of observing a surprising survival benefit, the statistical considerations

⁵ Gao P, Liu L, Mehta C. "Exact inference for adaptive group sequential designs." *Stat Med*. 2013 Oct;32(23):3991-4005.

⁶ Denne JS. "Sample size recalculation using conditional power." *Stat Med*. 2001 Sep;20(17-18):2645-60.

⁷ Müller HH, Schäfer H. "Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches." *Biometrics*. 2001 Sep;57(3):886-91.

necessary for a robust analysis, and the operating characteristics necessary to minimize uncertainty in the results in these types of trials.

Conclusions

Oncology drug development is benefiting from improved research capabilities and techniques that help to better identify appropriate patient populations for clinical trials. Thus, scenarios where unexpectedly large improvements in overall survival observed in exploratory randomized studies are becoming more frequent as our scientific understanding continues to advance. New therapies have necessitated the need for innovative clinical trial designs and expedient pathways for drug approval. It is clear that full pre-planning for registration for every early phase trial is not feasible or even possible because exploratory trials need to be able to have a reasonable sample size for the phase of development; be able to address multiple exploratory objectives; and if needed, evolve in response to the data being generated. However, both sponsors and the FDA can be better equipped to handle and evaluate trials with unexpectedly large improvements in overall survival. It is important to get the most information from data collected in these trials. Therefore, we have provided considerations for sponsors to consider at the design and conduct stages and for both sponsors and the FDA to use to help evaluate these types of results, which include a Bayesian analysis approach to assist with decision-making.

Appendix

Proposed Model:

- δ = log hazard ratio for survival
- δ takes any value ≤ 0
- Prior probability $\delta=0$ is $1-\theta$
- Prior probability density for any value $\delta<0$ is θ times a folded normal $N(0,\tau)$ distribution
- Trial survival results summarized by the maximum likelihood estimate of δ denoted δ' and by the total number of deaths, D , observed in the trial.
- The standard error of δ' is approximately $s=2/\sqrt{D}$
- The posterior probability that $\delta=0$ can be written $\Pr[\delta=0|\delta']=c (1-\theta)\phi(\delta'; \text{mean}=0, \text{sd}=s)$ where c is a normalizing constant and ϕ denotes the density function for the standard normal distribution.
- For any $\delta<0$, the posterior probability that the log hazard ratio is δ can be written $c \phi(\delta'; \text{mean}=\delta, \text{sd}=s) \theta 2\phi(\delta; \text{mean}=0, \text{sd}=\tau)$
- The normalizing constant c is determined by computing the posterior over a grid and forcing the posterior values to sum to 1.
- We considered a result to be conclusively clinically significant if the posterior probability that δ is less than the threshold for clinical significance was at least 0.90
- We found that for studies of 25 total deaths or more, the results were rather insensitive to θ
- With 25 or 50 total deaths, results are convincing for clinically significant treatment effect on survival if the nominal p value for survival $p \leq .001$
- With 100 total deaths, a nominal $p \leq .0001$ is necessary for the results to be convincing for a clinically significant treatment effect on survival. A given p value corresponds to a smaller treatment effect as the sample size increases. Hence, larger studies require smaller p values to be clinically significant.

A Century of Medical Product Regulation: The Historic Framework for Personalized Medicine in Oncology



Personalized Medicine in Oncology

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A Century of Medical Product Regulation: The Historic Framework for Personalized Medicine in Oncology

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Progress in personalized medicine is currently taking place within a system of governmental regulation that was largely created before the term was even coined. Today's regulatory framework, directed primarily by the Food and Drug Administration (FDA) and a handful of other federal and state agencies, was created incrementally over the course of the 20th century to meet various public health needs, from the thalidomide crisis of the 1960s to the HIV/AIDS crisis of the 1980s and 1990s. As various regulatory gaps were filled over time, a complete system of regulation encompassing pharmaceuticals, medical devices, and diagnostic technologies emerged. This system, although comprehensive, was not designed by Congress with personalized medicine in mind, and thus it may be time to rethink how regulatory authorities are structured.

Here we provide a brief overview of the legislation that created the regulatory framework overseeing products in personalized medicine with the hope of improving understanding of why things are the way they are and how they might change to better align with the future needs of an advancing field.

Progress in personalized medicine today is taking place within a system of governmental regulation that was largely created before the term was even coined.

The Creation of the FDA and Drug Regulation *Pure Food and Drugs Act (1906)*

The law that created the nation's first drug regulations was the 1906 Pure Food and Drugs Act, signed by Theodore Roosevelt after years of campaigning by progressives to address widespread medical fraud and food contamination. The leading advocate for reform was Harvey Wash-

ington Wiley, Chief Chemist in what is now the Department of Agriculture, who was among the first to champion the role of government in protecting the public from abuses in the market. One such abuse was the marketing of "patent medicines," drugs that made lofty health claims but whose ingredients were withheld from doctors and patients. A series of articles in *Collier's* magazine published in early 1906 exposed the ingredients of many of these "secret formula" medicines, showing that common remedies contained narcotics while others contained nothing but water and alcohol.

To address concerns about unknown ingredients in patent medicines, the 1906 Act introduced drug labeling requirements, but only for certain substances such as alcohol and opiates; all other ingredients were permitted to continue to be withheld from consumers. Additionally, the law prohibited "misbranding" of drugs, but the Supreme Court in *United States v Johnson* (1911) ruled that misbranding did not apply to false therapeutic claims, a decision that significantly diminished the impact of the legislation, as assertions that drugs were cure-alls went uncontested. Moreover, it would not be until the 1960s that false therapeutic claims were effectively curtailed by the FDA. The 1906 Act was primarily about policing fraud, not assuring drug safety; nothing in the law could prevent harmful drugs from entering the market.

Food, Drug and Cosmetic Act (1938)

Significant action to overhaul the 1906 Act did not begin until 1933, when a bill was drafted that would extend misbranding provisions to advertisements, require labels to display all ingredients, not just addictive ones, and, most importantly, require drugmakers to submit evidence that their products were safe before selling them. FDA officials made the case for increased regulation with an exhibit that came to be known in the press as the "Chamber of Horrors," a collection of the most egregious safety issues associated with drugs that highlighted dangers that were currently beyond the reach of the law. Although these efforts drew attention to reform,

a public health crisis was the primary impetus for passage of new regulations. In 1937 the antibiotic sulfanilamide, having been combined with the solvent diethylene glycol, killed over 100 people, many of them children. Congress, seeking to prevent future tragedies, passed the Food, Drug and Cosmetic Act, which was signed by Franklin Roosevelt on June 15, 1938.

The 1938 Act established premarket review of safety for new drugs, changing the FDA's position from responding to harm to attempting to prevent it.¹ It also led to the creation of a scientifically minded pharmaceutical industry, given its requirement that drug makers produce evidence about the effects of their products.² However, like its predecessor, the 1938 Act had flaws that would need to be addressed by future policymakers. The first was that only safety, not both safety and effectiveness, was required to be demonstrated. The closest it came was to tweak misbranding language from the 1906 Act to include false therapeutic claims, but these were dealt with in the courts, an inappropriate forum to assess the merits of a drug. The second flaw was that applications for approval became effective automatically after 60 days, leaving the FDA only 2 months to decide if a drug was safe.¹

Kefauver-Harris Amendments (1962)

FDA officials, well aware of the limitations of the 1938 Act, began to lobby members of Congress and draft legislation in the late 1950s to address gaps in oversight.³ These efforts coincided with a series of hearings on pharmaceutical monopolies and price fixing led by Senator Estes Kefauver of Tennessee. A number of proposals emerged from this spike in attention on the FDA, but, much like the 1938 Act, congressional action only took place in the wake of public outcry. A front-page article in the *Washington Post* in the summer of 1962 told the story of how an FDA official, named Francis Kelsey, refused to give a positive opinion on a drug called thalidomide, an act that came to be viewed as heroic after the drug, often used to treat morning sickness, was found to have caused hundreds of birth defects in children in Western Europe. The story reminded the public of the importance of drug safety laws, while also lifting the reputation of the FDA as a protector of public health, embodied in the maternal persona of Francis Kelsey.³

The 1962 Kefauver-Harris Amendments to the 1938 Act, passed shortly after the thalidomide incident, made 2 major changes to drug regulation. First, they overturned the automatic approval provision of the 1938 Act, revising the existing premarket *notification* system into a premarket *approval* system in which the FDA now held veto power over new drugs entering the market.¹ This provision inaugurated FDA's gatekeeping power,

requiring all new drugs to pass through the FDA on the way to market. Second, drugs now had to demonstrate evidence of effectiveness as well as safety, dramatically increasing the amount of time, resources, and scientific expertise required to develop a new drug.

The concept of 3 phases of experiment emerged in the wake of the new law and was adopted by the FDA, becoming the default method for studying medicine in humans ever since.

Birth of the Modern Clinical Trial System

To be implemented, the 1962 Amendments required interpretation of the legislative text, which stated effectiveness had to be derived from "substantial evidence" in "adequate and well-controlled investigations." Drug-makers looked to the FDA to lay the ground rules for how they should conduct their experiments, and as a result, the FDA's interpretation of concepts like "efficacy" played a central role in shaping how clinical trials would be conducted moving forward. The concept of 3 phases of experiment emerged in the wake of the new law and was adopted by the FDA, becoming the default method for studying medicine in humans ever since.

Filling Regulatory Gaps: Biologics, Devices, and Diagnostics

Slightly over 20% of consumer spending in the United States is on products regulated by the FDA. Past Congresses have given the FDA authority to regulate a spectrum of other medical products beyond food and drugs, from biologics to in vitro diagnostics. However, the creation of today's regulatory framework took place slowly over the course of the 20th century, with separate categories of products coming under government oversight incrementally as technology advanced. Periodic adjustment to the FDA's governing statute continues to occur as science evolves and new types of products come on the market.

Biologics

The first regulations concerning biologics actually preceded the 1906 drug law by 4 years; in 1902 the Biologics Control Act required purveyors of vaccines to be licensed and gave the Hygienic Laboratory—renamed the National Institutes of Health (NIH) in 1930—authority to establish standards for the production of vaccines. Regulation of vaccines and other biologic products would be housed in the NIH until 1972, when it was

transferred to the FDA. In 1944, the Public Health Service Act expanded regulation of biologics to the products themselves, not just the bodies that manufactured them, but standards for effectiveness equivalent to those for drugs were not imposed until the move to the FDA in 1972. Biologics are currently overseen by the Center for Biologics Evaluation and Research at the FDA, which exists alongside parallel centers for drugs and devices. An internal reorganization of the FDA in 2004 resulted in the transfer of regulation of some therapeutic biologics, including monoclonal antibodies, to the Center for Drug Evaluation and Research, allowing for the streamlining of oversight of many cancer agents.

Devices

Medical devices first came under government regulation in the 1938 Food, Drug and Cosmetic Act, although, as the law's name reveals, they were not yet considered a separate category of product, defined instead under the term "drug." The 1938 Act provided the FDA with authority to take legal action against the

Long before the "10 years, \$1 billion" figure was attached to drug development there was a general view that new drugs appeared rather slowly and patients suffered as a result, especially those with deadly diseases.

adulteration and misbranding of medical devices, although it did not contain a premarket notification provision for devices, as it did for drugs.⁴ When the 1962 Kefauver-Harris Amendments were passed, there were rumors that Congress would consider a companion bill requiring premarket approval for medical devices shortly thereafter. However, it took 15 years for comprehensive legislation to be passed. The 1976 Medical Device Amendments created an alternative regulatory approach that involved classifying devices according to risk and strengthened the provisions of the 1938 Act to include premarket review of those devices that fell into the high-risk category.

Diagnostics

In implementing the 1976 Medical Device Amendments, the FDA was required to conduct an inventory and classification of all existing devices to fit products into risk categories that would then inform whether a device needed to undergo the premarket review pro-

cess. The FDA classified in vitro diagnostics (IVDs) as medical devices, and many IVDs that have become central to personalized medicine, such as pharmacogenomic tests, fall into FDA's highest risk category. A separate category of tests, called laboratory developed tests (LDTs), were not initially regulated by FDA but rather the Centers for Medicare & Medicaid Services acting under the Clinical Laboratory Improvement Amendments of 1988. The FDA has claimed jurisdiction over all tests, both IVDs and LDTs, but has exercised enforcement discretion with regard to the latter until very recently, when it proposed extending oversight to LDTs.⁵ As laboratory medicine has increased in complexity, a greater number of LDTs are being considered high-risk tests due to their role in diagnosing disease and steering treatment decisions.

Spurring Innovation and Patient Access

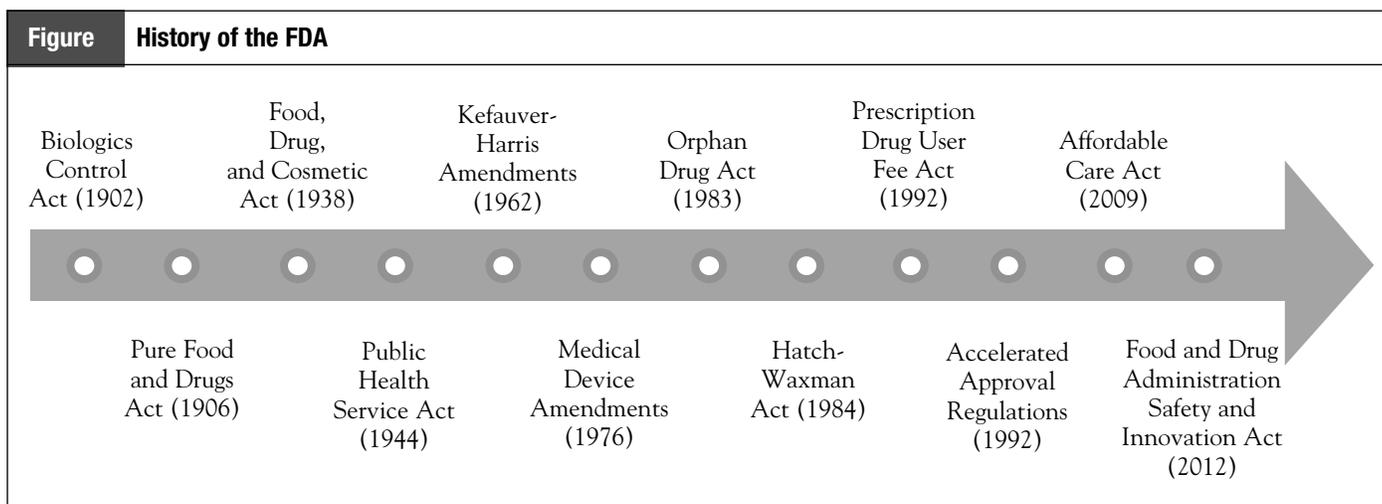
Long before the "10 years, 1 billion dollars" figure was attached to drug development, there was a general view that new drugs appeared rather slowly and patients suffered as a result, especially those with deadly diseases. In the 1980s and 1990s, upon the urgings of patient groups and observers who felt more could be done to bring drugs to patients quickly, policymakers passed a series of bills and administrative reforms that promoted patient access to new drugs.

Drugs for Rare Diseases

One of the first pieces of legislation to promote innovation in the pharmaceutical industry was the Orphan Drug Act of 1983, passed in response to concerns that companies lacked incentives to develop drugs with limited commercial value. Primarily intended for rare diseases, the law has since been applied to many development programs for biomarker-enriched cancer populations, such as EGFR- and ALK-positive lung cancer. Under the Orphan Drug Act, Congress defines a rare disease or condition as affecting fewer than 200,000 people in the United States or for which there is no reasonable expectation that the sales of the drug treatment will recover the costs.⁶ Drugs that are designated as orphan products benefit from 2 years' additional marketing exclusivity (7 years vs the standard 5 years), federal grants to conduct clinical trials, and tax credits for clinical development costs. The orphan designation has been granted widely in the field of oncology, with one report finding that 27% of all orphan approvals between 1983 and 2009 were for cancer drugs.⁷

Generics and Biosimilars

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman



Act for Senator Orrin Hatch and Representative Henry Waxman, gave rise to the modern generic drug market. It was designed with 2 purposes in mind: 1) to preserve incentives to develop new drugs, and 2) to make low-cost generics widely available. The Act offset an unintended consequence of the 1962 Kefauver-Harris Amendments that greatly increased clinical development time, which in turn shortened the remaining patent life of medicines once they entered the market. The Hatch-Waxman Act “restored” some of the lost patent life, thereby increasing financial incentives to develop new drugs. In addition, the Act made it possible for manufacturers of generic products to apply for approval without demonstrating safety and effectiveness, requiring only that generics are shown to be the “same” as and bioequivalent to brand name products.⁸

These dual aims of enhancing innovation and expanding patient access were also reflected in the Biologics Price Competition and Innovation Act of 2009, which Congress created to promote competition in the biologics market once products go off patent. The complexity of biologic products prevents them from being replicated in the same fashion as small molecule drugs, so instead of demonstrating bioequivalence, the law requires evidence of “biosimilarity,” defined as the absence of clinically meaningful differences between the biosimilar and the reference product. The first biosimilar approval in the United States was in March 2015, and a number of other products are currently in development, although many developers are anticipating further guidance from the FDA on how to best demonstrate biosimilarity.

Speeding Review and Development Times

Major changes to drug policy took place in response

to the HIV/AIDS crisis of the 1980s and 1990s. The accelerated approval regulations, instituted in 1992, made it possible for drugs intended to treat serious or life-threatening diseases to be approved more quickly on the basis of surrogate end points. Drugs that receive ac-

The Hatch-Waxman Act gave rise to the modern generic drug market. It was designed with 2 purposes in mind: 1) to preserve incentives to develop new drugs, and 2) to make low-cost generics widely available.

celerated approval must show evidence of improvement over available therapy based on a surrogate end point that is reasonably likely to predict clinical benefit.⁹ These regulations, which changed approval standards, were initially brought about by administrative rulemaking rather than legislation—accelerated approval was not codified in statute until 2012. Accelerated approval has been used most widely in the field of oncology, with one-third of all oncology approvals between 2002 and 2012 approved via the accelerated pathway.¹⁰ Oncology has benefited most from this program largely due to the identification of numerous surrogate end points that can reasonably predict survival, such as progression-free survival and response rate.

Also taking place in 1992 was passage of the Prescription Drug User Fee Act (PDUFA), which has lent consistency and predictability to drug review times. Twenty years earlier in 1971, critics of the FDA coined

the term “drug lag” to describe instances in which new medicines were made available in Europe prior to the United States. The drug lag became a perennial talking point among critics of the agency as evidence of regulation impeding patient access. In 1980, a report published by the General Accounting Office disputed this narrative, attributing backlogged new drug applications to inadequate resources. Rather than increase direct appropriations to the FDA, policymakers settled on a “user fee” program, wherein the pharmaceutical indus-

Each PDUFA reauthorization has presented an opportunity to pass additional legislation related to the FDA, and in recent years, such add-ons have focused on promoting innovation in the pharmaceutical industry.

try would provide funds to hire additional FDA reviewers in return for assurances of timely reviews of new drug applications. PDUFA had an immediate impact, speeding up review times and allowing the FDA to consistently meet its 10-month goal for standard reviews and 6-month goal for priority applications.¹¹ Due to the program’s success, additional user fee programs have been established for generic drugs, medical devices, and biologics. The law has a sunset clause, requiring it to be reauthorized every 5 years to allow user fees to be renegotiated based on the FDA’s performance in meeting review timelines. Each PDUFA reauthorization (there have been 5 so far) has presented an opportunity to pass additional legislation related to the FDA, and, in recent years, such add-ons have focused on promoting innovation in the pharmaceutical industry.

The most recent reauthorization of PDUFA took place in 2012 and was accompanied by a series of reforms to the FDA intended to spur innovation and speed drug development. The authorizing law, called the Food and Drug Administration Safety and Innovation Act (FDASIA), created a new method, called the breakthrough therapy designation, for the FDA to speed the development of certain drugs. To receive the designation, a drug must be intended for a serious or life-threatening disease and early clinical evidence (usually from phase 1 or 2 trials) indicates that the drug may provide a substantial improvement over available therapy. Designed as a way for the FDA to expedite the development of drugs that have the potential to be transformative, the breakthrough therapy designation

confers increased communication with high-level FDA officials who can provide advice on development programs and the most efficient path forward. The designation has been granted to over 100 drug development programs, and over 30 have been approved, with more than one-third of approvals for anticancer agents.

Also included in FDASIA was a provision that created the patient-focused drug development initiative at FDA, which brought patients together in disease-specific meetings to share their experiences with FDA officials. The goal of the initiative is to use this “patient experience data” to inform clinical trial design, end points, and risk-benefit calculations to better reflect patient needs. Two oncology-specific meetings have already been held for lung and breast cancer patients, and another is planned for neuropathic pain associated with peripheral neuropathy in 2016.

Looking Forward

The current regulatory framework, although comprehensive, came about in a piecemeal fashion through a patchwork of laws granting the FDA authority to regulate various new types of medical products. As a consequence, the agency’s structure is oriented around the products it regulates and is divided into multiple centers, each devoted to oversight of a different product. While this structure has allowed for an aggregation of product-related expertise, it does not fully reflect the current multimodal approach to medical care. In the field of oncology, for example, therapeutics are being developed using genetic information with increased frequency, a trend that involves the concurrent use of drugs and molecular diagnostics. In its current form, the FDA is not optimally positioned to address the coordinated use of a spectrum of technologies and interventions common in medical practice today.

Thus, rather than maintaining a product-oriented approach to regulating new treatments, the FDA should adopt a patient-centered orientation to reflect the current multimodal approach to patient care. This should include an organizational realignment at the FDA based on major disease areas. Housing functions and expertise according to disease areas would better reflect how products are used in practice and would enhance collaborative interactions and streamline administrative processes. Such a patient-oriented realignment will also allow for enhanced interactions with patients and the external biomedical community who already approach disease states holistically rather than by product type. Increased staffing and resources that go beyond the review functions should be provided to support this type of realignment at the agency to ensure optimal implementation and long-term success.

Conclusion

Over the course of the 20th century and into the 21st, a system of regulation was established for a broad spectrum of medical products. Although crises were typically the immediate instigator of new laws, advancing science

The FDA in its current form is not optimally positioned to address the coordinated use of a spectrum of technologies and interventions common in medical practice today.

and the development of new technologies were what shaped the content of reform efforts. In some cases, changing science enabled policymakers to explore ways of making the development process more efficient, as was the case for the accelerated approval regulations, which stemmed from an understanding of surrogate end points, and the breakthrough therapy designation, which was inspired by dramatic improvements seen in early-phase trials. In other cases, policies clearly shaped the subsequent conduct of science, such as the Kefauver-Harris Amendments, which inaugurated the concept of phased drug development, and the Orphan Drug Act, which stimulated the development of tools to evaluate drug efficacy in small populations.

Recent reform efforts have similarly focused on ways to promote scientific advances with legislation. As

noted above, each reauthorization of the PDUFA has enabled lawmakers to consider legislation related to medical product regulation. Members of the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor and Pensions are currently weighing a host of proposals that may be coupled with the 6th PDUFA. This will present a new opportunity to assess the current regulatory framework, and if Congress determines it necessary, to make adjustments. ♦

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Regulatory Watch: Impact of Breakthrough Therapy Designation on Cancer Drug Development



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REGULATORY WATCH: Impact of Breakthrough Therapy Designation on Cancer Drug Development

Introduction

The breakthrough therapy designation, established in 2012 by the US Congress to expedite the development of drugs that show promising early clinical evidence of benefit over available therapies, has been granted to more than 100 drug development programmes so far. Over 30 such drugs had been approved by the US Food and Drug Administration (FDA) by the end of 2015, of which more than one-third are anticancer agents. Here, we present an analysis of the impact of the breakthrough designation on key metrics for anticancer drugs, such as review time, development time, pivotal trial phase and use of additional regulatory pathways.

Methods

Study Sample

We compared characteristics of all new oncology drugs approved with a breakthrough therapy designation and all new oncology drugs approved without a breakthrough therapy designation from January 1, 2013 to December 31, 2015 using publicly available information provided on the internet database Drugs@FDA. Our population included twelve new molecular entities (NMEs)/new biological products that previously received breakthrough therapy designation and seventeen NMEs/new biological products that did not receive the designation.

Review and Development Times

Review timelines vary depending on whether a drug receives priority review or if a drug was approved under the FDA's Program for Enhanced Review Transparency and Communication, which involves an extension of a 60-day filing period to the six-month review clock for priority reviews and the ten month review clock for standard reviews. Due to this variability, we analyzed how much time elapsed between approval and the review goal date, rather than total review time. To measure clinical development times, we counted the number of calendar days between submission of an investigational new drug (IND) application and submission of a new drug application (NDA). IND and NDA submission dates are typically available in medical reviews, the former appearing in "Section 2.5: Summary of Presubmission Regulatory Activity Related to Submission." Three

drugs reviewed in this study (obinutuzumab, ceritinib and afatinib) did not have IND dates listed in medical reviews; dates were requested from sponsors.

Expedited Approval Mechanisms

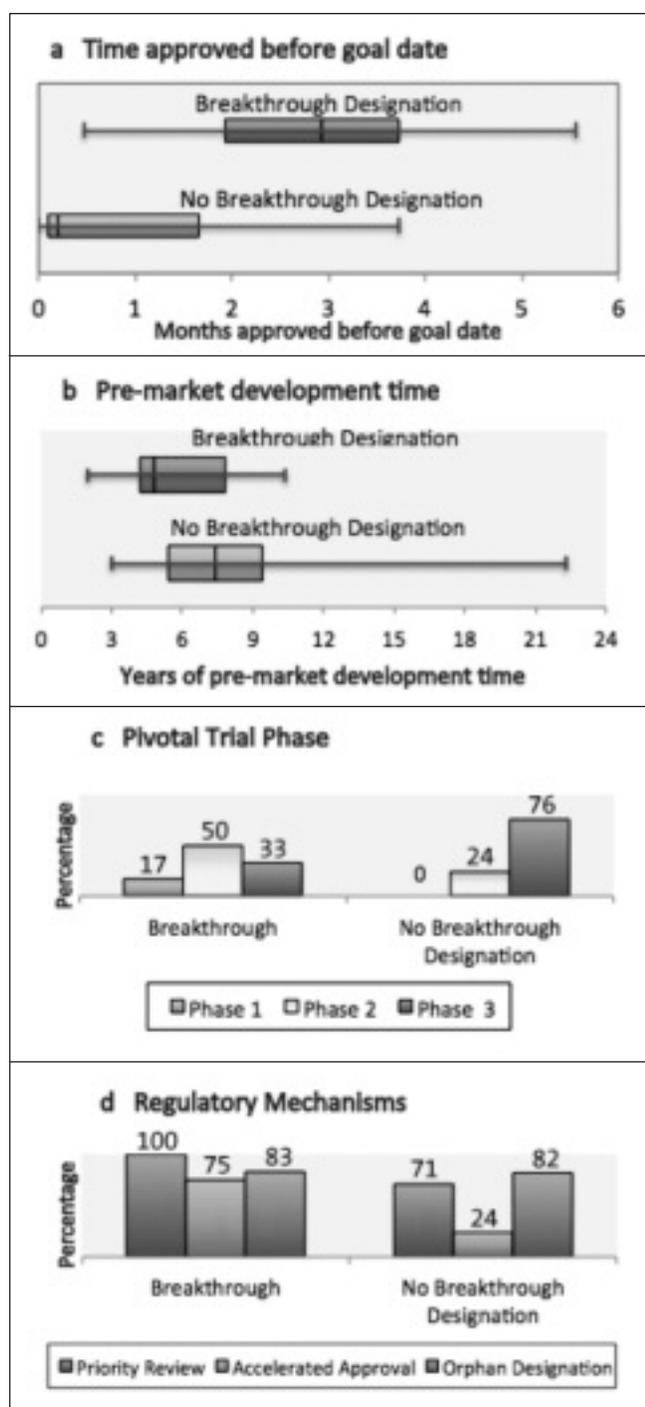
The FDA has additional programs to expedite the development and review of drug development programs: accelerated approval, priority review and fast track. These programs are widely used in oncology. Fast-track designation was not assessed in this report due to its substantial overlap with the breakthrough therapy designation. The accelerated approval pathway allows drugs to be approved on the basis of surrogate endpoints and requires post-market trials to confirm clinical benefit. FDA's orphan designation provides incentives for manufacturers to develop drugs for rare diseases. Priority review is granted at time of submission and shortens the review clock to six months plus a 60-day filing period.

Phase of Pivotal Trial

We determined pivotal trial phase from medical reviews; pivotal studies were either identified as such in reviews, or discussed in depth as the primary basis for efficacy findings. We found that two-thirds of breakthrough-designated drugs were approved based on pre-Phase III trials. A few examples underline this trend. Two breakthrough drug development programs^{1,2} were approved based on expanded Phase I studies, highlighting a potential paradigm shift toward gathering information about efficacy early in the drug development process. In another instance³, the FDA agreed to review Phase II data as the primary basis of an approval decision given the magnitude of benefit observed, despite the fact that the Phase II study was not originally designed as a pivotal trial. The FDA requested that a blinded independent central review be conducted, as well as additional sensitivity analyses to guarantee the robustness of the data.

Results

Drugs with breakthrough designation were typically approved well ahead of their Prescription Drug User Fee Act (PDUFA) goal dates (median 2.9 months before) compared with those without the designation (median 0.2 months), a difference of nearly 3 months (Fig. 1a).



Pre-market development time, calculated as the number of years from submission of an investigational new drug application (IND) to submission of a new drug application (NDA) or biologics license application (BLA), was considerably shorter among approved breakthrough-designated drugs (median 5.2 years) than non-designated drugs (median 7.4 years), a difference of 2.2 years (Fig. 1b).

Of the 12 approved oncology drugs with breakthrough designation, 8 (66%) were approved based on Phase I or Phase II data. By contrast, 4 of 17 (24%) of drugs without breakthrough designation were approved on the basis of Phase II data, and none on the basis of Phase I data (Fig. 1c).

All of the drugs with breakthrough designation received priority review (100%, 12 of 12), compared with nearly three-quarters of drugs without the designation (71%, 12 of 17). Use of the accelerated approval pathway was more varied, with three-quarters of breakthrough-designated drugs approved via accelerated approval (75%, 9 of 12) compared with less than one-quarter of non-designated drugs (24%, 4 of 17). Orphan designation was very common among both groups (Fig. 1d).

Discussion

In summary, among novel anticancer agents approved by the FDA between 2013 and 2015, we found that drugs with breakthrough designation reached the market more quickly than those without the designation owing to faster pre-market development and review times. We also found that considerably more breakthrough-designated drugs were approved via the accelerated approval pathway than non-designated drugs, and that breakthrough-designated drugs were more often approved on the basis of Phase I or Phase II trials. Thus, we conclude that the breakthrough designation is helping to speed patient access to innovative new cancer treatments. We also conclude that, owing to the large number of accelerated approvals among breakthrough-designated drugs, the FDA is more willing to take measured risks in approving drugs that show early evidence of substantial improvement over available therapy.

Owing to the large proportion of breakthrough-designated drugs that received accelerated approval, it can only be stated that drugs that have received a breakthrough designation have had a shorter median pre-market clinical development time, not total development time. This is because development is not over at the time of approval for drugs approved via the accelerated approval pathway, for which the FDA requires post-market confirmatory trials. In addition, the data set is small, necessitating caution in drawing conclusions on the extent to which breakthrough designation decreases pre-market clinical development time. Nevertheless, the data presented here provide preliminary evidence of the positive impact of the breakthrough therapy designation in oncology.

Supplemental Table | Novel anticancer agents approved by the FDA between 2013 and 2015***Breakthrough Designation***

Drug	Approval Date	PDUFA Date	Development Time (days)	Orphan?	AA?	Priority?	Pivotal Trial Phase
Obinutuzumab	1-Nov-13	20-Dec-13	1536	yes	no	yes	3
Ibrutinib	13-Nov-13	28-Feb-14	1754	yes	yes	yes	2
Ceritinib	29-Apr-14	24-Aug-14	1180	yes	yes	yes	1
Idelalsib	23-Jul-14	6-Aug-14	2016	yes	no	yes	3
Pembrolizumab	4-Sep-14	28-Oct-14	1541	yes	yes	yes	1
Blinatumomab	3-Dec-14	19-May-15	2773	yes	yes	yes	2
Nivolumab	22-Dec-14	30-Mar-15	2954	yes	yes	yes	3
Palbociclib	3-Feb-15	13-Apr-15	3809	no	yes	yes	2
Osimertinib	13-Nov-15	5-Feb-16	724	no	yes	yes	2
Daratumumab	16-Nov-15	9-Mar-16	2838	yes	yes	yes	2
Elotuzumab	30-Nov-15	29-Feb-16	3285	yes	no	yes	3
Alectinib	11-Dec-15	4-Mar-16	1374	yes	yes	yes	2

No Breakthrough Designation

Drug	Approval Date	PDUFA Date	Development Time (days)	Orphan?	AA?	Priority?	Pivotal Trial Phase
Pomalidomide	8-Feb-13	10-Feb-13	3436	yes	yes	no	2
Ado-trastuzumab	21-Feb-13	26-Feb-13	2460	no	no	yes	3
Radium Ra 223 dichloride	15-May-13	14-Aug-13	1821	no	no	yes	3
Dabrafenib	28-May-13	30-May-13	1102	yes	no	no	3
Trametinib	28-May-13	3-Jun-13	1572	yes	no	no	3
Afatinib	11-Jul-13	15-Jul-13	3212	yes	no	yes	3
Ramucirumab	21-Apr-14	23-Apr-14	3312	yes	no	yes	3
Belinostat	3-Jul-14	9-Aug-14	3311	yes	yes	yes	2
Olaparib	19-Dec-14	3-Jan-15	2712	yes	yes	yes	2
Lenvatinib	13-Feb-15	14-Apr-15	3453	yes	no	yes	3
Panobinostat	23-Feb-15	24-Feb-15	3933	yes	yes	yes	3
Dinutuximab	10-Mar-15	10-Mar-15	8164	yes	no	yes	3
Sonidegib	24-Jul-15	26-Sep-15	2139	no	no	no	2
Trabectedin	23-Oct-15	24-Oct-15	5167	yes	no	yes	3
Cobimetinib	10-Nov-15	11-Nov-15	1563	yes	no	yes	3
Ixazomib	20-Nov-15	10-Mar-16	2291	yes	no	yes	3
Necitumumab	24-Nov-15	2-Dec-15	2174	yes	no	no	3

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Examining Manufacturing Readiness for Breakthrough Drug Development



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*White Paper***Examining Manufacturing Readiness for Breakthrough Drug Development**

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INTRODUCTION

In July 2012, Congress passed the Advancing Breakthrough Therapies for Patients Act as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). Section 902 of FDASIA provides for designation of a drug as a breakthrough therapy “if the drug is intended alone or in combination with one or more other drugs, to treat

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serious or life-threatening diseases or conditions and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies (1).” Breakthrough designation is a mechanism that the U.S. Food and Drug Administration (FDA) can grant to sponsors to expedite the development of these promising therapies.

As part of the program, the FDA and sponsor collaborate in a dynamic, multi-disciplinary, resource-intensive process to determine the most efficient path using an “all hands on deck approach” involving senior managers and experienced review staff and more frequent and interactive communications (2,3). The objective is to expedite design and review of the clinical development program so that trials are as efficient as possible, and the number of patients exposed to potentially less efficacious treatment is minimized. As a consequence, clinical development timelines involving the traditional three distinct phases could be reduced from 7–10 to 3–5 years.

The shorter clinical development programs will have significant impact on product and process development timelines requiring the manufacturing organization to reconsider traditional approaches to product and process development and undertake their own resource-intensive, cross-functional team approach to ensure a sustained supply of safe and efficacious product at the time of approval. To ensure success, the manufacturing organization should have good communications with the clinical organization to facilitate identification of potential candidates for breakthrough designation early and help gate or accelerate the appropriate Chemistry, Manufacturing, and Controls (CMC) and current Good Manufacturing Practice (cGMP) development activities. It is important to understand that breakthrough drug development programs are resource intensive; sponsors need to be selective about which programs to take forward and ensure management support. Moreover, a collaborative, cross-functional approach between development, commercial, and regulatory operations, with early and robust discussions, is essential to ensure successful development and launch of a breakthrough drug product.

In March of 2015, Friends of Cancer Research (Friends) convened a group of industry and FDA stakeholders familiar with developing breakthrough drugs to explore options,

manufacturers of small molecule and biologic products have for front-loading certain critical manufacturing activities to speed development of breakthrough therapy drugs. This expert group also explored options for science- and risk-based approaches to mitigating the potential risk of having less CMC information at the time of launch *versus* the benefit of having these innovative new products available to patients sooner. The considerations captured in this white paper outline approaches that sponsors have taken to successfully manufacture breakthrough products as well as new approaches that aim to further explore potential efficiencies in bringing breakthrough products to market. These ideas were presented at a public forum, convened by Friends, on June 10 in Washington, DC, in an effort to seek broad feedback on the recommendations put forth to expedite rate-limiting steps in CMC and cGMP for products demonstrating high clinical benefits while ensuring an adequate supply of safe and efficacious product at the time of approval (4).

BREAKTHROUGH DEVELOPMENT PROGRAMS MAY PUT CMC/GMP ACTIVITIES ON CRITICAL PATH

Timelines for completing CMC/GMP activities for a breakthrough product will be driven by the design of the clinical development program for the breakthrough product. Each development program will vary depending on the complexity of the product, how soon accelerated CMC development activities begin, availability of platform technology, relevant prior knowledge, and timing of designation. If the breakthrough designation is granted at an early development stage following promising preliminary clinical data, some of the phase III CMC-enabling activities may need to be accelerated. On the other hand, if a breakthrough designation is granted to a product in late stage development, the challenges for manufacturing readiness may be less burdensome but may also need to be addressed in a more compressed time frame. While drugs approved under the breakthrough pathway still need to meet statutory requirement for product quality, safety, and efficacy, balancing risk to product quality and availability for patients is critical. Therefore, development of breakthrough drugs necessitates risk-based approaches to product and process development, commercial readiness, and regulatory filings, with a focus on a reliable supply of quality product available to meet and sustain market demand. To this end, conventional timing for certain activities may be shifted, with some activities starting sooner, some completing later, and others potentially deferring post-filing (*e.g.*, some aspects of process optimization). Additional activities (*e.g.*, increased testing) may also be warranted based on the overall risk of the breakthrough product coupled with available supporting data.

MANUFACTURING CONSIDERATIONS FOR BREAKTHROUGH DRUG DEVELOPMENT

Some critical product and process characterization activities could be addressed earlier and may facilitate manufacturing readiness for breakthrough products. While the considerations below may aid in introducing efficiencies into the development process, they are not intended to be prescriptive, rather reflective of best practices based on prior experiences or discussions, and rely on establishing early and robust communications with the FDA to ensure suitability with the specific development

program. Where appropriate, molecule-specific recommendations are noted for consideration.

In General

- Selection of the best molecular candidate for development based on physical-chemical properties and the pharmacokinetic (PK) profile for small molecule drugs or screening for and engineering out, where possible, hot spots for degradation or undesired modifications for biologic drugs
- Ensuring the fit of candidate molecules into the manufacturer's platform for drug substance (DS) and drug product (DP) and related processes to improve speed and robustness
- Front-loading activities to address non-platform behavior and/or unusual product and process characteristic
- Assessing Critical Quality Attributes (CQAs) earlier and front-loading method validation activities for them
- Incorporating preliminary quality target product profile (QTPP) and bridging in the development of clinical service dosage forms for early clinical studies (*i.e.*, phase I), which may generate data to support a breakthrough designation (*e.g.*, identification of whether enabling formulations are needed to support rapid development)

Biologics

- Use of cell line and vector constructs for which significant prior knowledge/platform knowledge is available (*e.g.*, viral safety aspects), with the clone selected for phase I studies, ideally carrying through to commercialization, thus minimizing any comparability concerns arising from cell line changes; appropriate methods should be used to establish clonality
- Assuring preliminary cell line stability for launch should be demonstrated (*e.g.*, limit of *in vitro* cell age validation)
- Design and use of host cell protein assays that are comprehensive in their coverage and can be used for multiple products (from the early stages of development and all the way through commercialization)
- Performing sequence variant analysis early in development and on aged cells to understand and control potential cell line variability

Small Molecules

- Early identification of the most thermodynamically stable salt form
- Gaining concurrence on final market image (color, shape, size, and package for tablets) prior to formal stability batches or develop a bridging plan (*i.e.*, color change)
- Early CMC risk assessments to support prioritization of experimental studies
- Evaluation of genotoxic impurities: Impurities, impurity controls, and the establishment of Regulatory Starting Materials (RSMs) are related elements of the drug

substance manufacturing process. With less time to optimize the drug substance process as compared to a traditional development program, it may be necessary to invest more time in negotiation of impurity specifications and designation of RSMs with the FDA. As appropriate, commitments may then be made to reevaluate these elements after launch when the process can be further optimized

Various CMC/GMP development strategies that might facilitate breakthrough drug development are discussed below. In addition, a table from the European Federation of Pharmaceutical Industries Association (EFPIA) Technical Development and Operations Committee (TDOC) Briefing Paper (5) (Annex 2) is included to provide additional examples of opportunities available that might be considered to accelerate traditional CMC approaches for drug development and manufacturing to ensure early access to patients. These proposed strategies will be supplemented with examples (Annex 1) of actual experiences that companies have had working with FDA to implement some of these approaches for expediting approval of breakthrough drug products.

Process and Formulation Development Considerations

Expedited clinical development programs for breakthrough therapy products will shorten the time available to optimize phase III and commercial manufacturing processes. This will necessitate prioritization of development efforts on process reliability over yield and cost of goods. As a result, process and formulation optimization may need to be deferred to post-approval; if it can be determined, there is no impact on patient safety or product availability. Some activities that might be considered to speed development activities include the following:

- Launching commercial processes with limited experience, but sufficient data to ensure that the process can reliably produce a drug to meet the expected quality safety and efficacy profile and optimize post-approval
- Using data from development material or the clinical supplies, with adequate comparability data to support material from initial commercial process lots, may be needed
- Consider delaying intermediate hold time studies and instead doing straight through processing and scheduling of intermediates to speed process development
- Lock the phase I/II drug product formulation and optimize post-approval to avoid need for bioequivalence studies
- If efficacy is indicated in phase I clinical studies, in oncology patients, sponsors may want to strive for a commercial dosage form to be used in the pivotal phase II clinical program
- For biologic products, optimize cell line development early and carry through phase III and commercial production
- For small molecule products, the focus should be on the active pharmaceutical ingredient (API) and excipient attributes impacting formulation and DP manufacturability and performance
- Consider close alignment on linkages in control strategies (e.g., particle size distribution impact on dissolution for small molecule drugs) and overarching themes that might apply to both biologics and small molecule drugs (e.g., moisture sensitive API)

Manufacturing Scale and Launch Site Considerations

- Determine, as soon as possible, launch sites for DS and DP, clinical *versus* commercial
- Clinical manufacturing facilities, used for launch, would need to meet the same quality/GMP expectations as commercial manufacturing facilities
 - Key differences for consideration may be:
 - Cleaning verification *versus* cleaning validation
 - Multi-product manufacturing, including investigational compounds with limited safety data
 - Considering dedicated product contact equipment and/or use of disposables to minimize concerns may be useful. Disposables may also assist with cleaning validation issues
- Gaining concurrence on comparability strategy/protocol for post-approval site changes in advance may lend confidence to manufacturer's ability to ensure sustained supply post-launch, particularly when expediting launch upon initial approval
- If using a contract manufacturing organization (CMO) for DS/DP, ensuring there is capacity to allow rapid scale up and to support commercial volumes will be critical
- Consider decoupling drug substance and drug product qualification lots (e.g., using clinical DS for DP qualification), when feasible to save time on the critical path to licensure
- Pivotal clinical studies could be performed with material from different scale and/or site than is intended for long term commercial production (e.g., studies originally expected to be phase II studies could be used as pivotal studies)
- Scaling-up phase III clinical lots to commercial scale for launch with bridging comparability study

Process Validation Considerations

Process characterization/process validation (PC/PV) studies impacting patient safety must be complete prior to filing. In addition, sufficient process characterization data from clinical and pilot scale lots should be completed to assure process capability and reliability for providing commercial product supply at launch until further PC/PV activities are completed. The following approaches could be considered for discussion and agreement with FDA.

- Due to the likelihood of having limited manufacturing experience at commercial scale, the number of full-scale validation lots at the time of filing may be lower than a typical application
- Determining if clinical DS could be used for DP process validation, through early alignment with FDA on starting materials (e.g., small molecule products) is critical
- Leveraging process and product platform knowledge (e.g., for monoclonal antibodies) with appropriate justification to speed development
- Leveraging life cycle validation principles, "continued verification"
 - Using development experience/smaller scale batches in Process Performance Qualification (PPQ) strategy
 - Identifying whether some PC/PV studies could be

- deferred, such as process linkage studies or chromatographic resin reuse at full lifetime
- Considering concurrent validation approaches, based on the FDA Compliance Policy Guide, CPG Section 490.100 (6), for orphan drugs to allow for product distribution concurrent with release of each conformance batch (e.g., batch specific release option). This could enable launch from a commercial site with limited number of batches but is dependent on manufacturer ensuring trust:
 - Prior demonstration of manufacturing consistency for clinical process material
 - A validation protocol for commercial material and at least one executed batch record at time of filing
 - Robust Quality Systems able to effectively manage Corrective and Preventive Actions (CAPAs) and change management

Analytical Development Considerations

Analytical method development strategies for front-loading of analytical understanding to balance more limited process robustness and support future comparability exercises may include

- A focus on high priority assays, including but not limited to potency for biologics and content, impurities, and dissolution for small molecules to ensure suitability for control system
- Involving commercial quality control (QC) in assay design during development and co-validating, if possible
- Using qualified rather than fully validated methods for internal release and stability testing of qualification lots and completing validation before commercial release
 - This approach presents a business risk, if problems arise in validating a method, and should be accompanied with a backup plan requiring retesting lots and/or implementing alternative methods
- Launching from a clinical site with clinical QC release and transferring to commercial site post-launch

Control Strategy Considerations

Control strategy, based on limited manufacturing experience, but ensuring patient safety and efficacy, may consider,

- Launching with a provisional control system that ensures consistent product and upgrading the control system post-approval with more manufacturing experience and completion of process validation, such as
 - Filing with an expanded monitoring program with more tests initially, more assay controls, and justify elimination of some tests post-approval as more knowledge is accumulated
 - Filing with broader in process controls (IPC) and product specification acceptance criteria at launch and re-evaluating post-approval for specifications that are linked to process consistency
 - Filing with preliminary critical process parameters (CPPs) and CQAs

- For small molecules, considering all available data, including (1) dissolution profiles and other critical analytical results, i.e., impurities, solubility, disintegration, etc. during development, (2) ensuring stability specifications are justifiable, if requested by the FDA, and (3) considering sunset specifications for some parameters (e.g., polymorphism)
- Utilizing enhanced modeling techniques, where possible to support conclusions
- Managing second-generation processes through a life cycle approach in the post-approval lifecycle management plan (PALM), which may contain a network of comparability protocols to facilitate life cycle improvements to the product and process
 - For critical aspects, consider submitting draft P.2 section (gaps in data sets) for early FDA review and concurrence

Stability Data Considerations

Accelerated development timelines may limit availability of real-time stability data, thus launching with reduced real-time stability for commercial material may require

- Leveraging stability from early development and clinical batches when formulation remains unchanged and product comparability is demonstrated
- Using forced degradation and stress studies to provide additional supporting and comparability data
- Providing the stability protocol for commercial material
- Gaining FDA concurrence and committing to provide more real-time confirmatory data during review and post-approval
- Enhancing temperature monitoring and control of the product during shipment may be considered until shipping validation studies have been completed

Pharmaceutical Quality System (PQS) Alignment with BT Product Development Considerations

PQS requirements must be adhered to for breakthrough product development while providing appropriate flexibility to accommodate accelerated activities for breakthrough product development timelines. Thus, the accelerated development PQS strategy for each product will be unique, as it depends on the timing of the BT designation,

- Flexibility, based on molecule, available product, and platform knowledge will be required
- Only those activities with no impact on patient safety or product supply should be considered to be deferred
- A quality risk assessment must be applied to all activities that will be deferred, and the rationale, and controls needed to ensure deferred activities are completed documented
- Some activities that are normally completed prior to license application may need to be deferred and submitted:
 - Post-submission, complete at inspection
 - Post-inspection, prior to approval
 - Post-market commitments
- The manufacturing readiness plan can be used for developing internal filing and inspection readiness checklists to ensure all deferred activities are completed or addressed

- Any PQS deferrals must be documented in a manufacturing readiness plan and monitored to ensure completion

BALANCING RISK OF LESS CMC DATA AT TIME OF FILING *VERSUS* PATIENT BENEFIT

In spite of front-loading certain critical product and process characterization activities, it may not be possible in the limited timeframes available to complete all CMC/GMP activities at the time of filing and launch of a breakthrough product. To address this possibility, manufacturers should develop a manufacturing readiness plan, which aligns the timeline for completing the manufacturing activities with those of the clinical development program. This plan should address all manufacturing sites and their suitability and readiness for development and launch of the breakthrough product, the design and implementation of critical characterization tools, the validation approach for process and methods, stability data to support adequate expiration dating for the product, and delineation of responsibilities for the development and commercial teams in addressing these issues. Where gaps exist in completing certain activities, a risk assessment should be performed, addressing the availability of less CMC information at the time of filing and product launch *versus* patient benefit. This should be coupled with a risk mitigation plan to address these risks either prior to launch or through the use of a post-approval life cycle management plan.

The manufacturing readiness plan and risk assessment should form the basis for discussion and agreement with FDA prior to filing the marketing application. As part of this plan, below are several proposed examples of CMC/GMP activities that may be considered as incomplete at the time of filing and launch of a breakthrough drug product:

- Process validation with fewer than the standard number of full-scale manufacturing runs
- Process characterization, *e.g.*, long duration elements like resin reuse, validation of intermediate process hold times, or extending limit of *in vitro* cell age for life cycle management of a biologic product
- Available real-time stability data on commercial product
- Validated transfer to commercial manufacturing site/scale, though some level of assurance will still be necessary regarding transfer for biologics
- Provisional control system that ensures consistent product with need to upgrade post-approval
- Reliable process capable of meeting initial product demand with need to optimize process yield and performance post-approval
- Phase I/II formulation for launch with potential need to optimize post-approval

A fundamental assumption is that risk assessments demonstrate that having less data at the time of filing and launch of a breakthrough product will not compromise patient safety or product supply. Completion of any deferred CMC activities should be documented in a comprehensive PALM that is part of the marketing application and contains detailed timelines, deliverables, and types of regulatory filing to be completed post-approval.

FLEXIBILITY IN TYPE AND EXTENT OF MANUFACTURING DATA FOR MARKETING APPROVAL OF BREAKTHROUGH DRUG

FDA approval standards for marketed drugs require demonstration of substantial evidence of effectiveness, safety, and product quality. FDA's expectation for pharmaceutical quality is the same for all drugs. However, FDA regulations for orphan drugs do allow for flexibility and scientific judgment in applying approval standards, in terms of the amount and type of data needed for a particular drug to meet the statutory standards. This rationale is stated in FDA's final guidance on Expedited Programs for Serious Diseases (2) which states that the "FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain components (*e.g.*, stability updates, validation strategies, inspection planning, manufacturing scale-up)." Open and transparent discussions with FDA on balancing (and mitigating) risk of less CMC/GMP information at the time of filing *versus* patient benefit should take place prior to filing the marketing application.

SPONSOR/FDA INTERACTIONS DURING DEVELOPMENT AND REVIEW OF BREAKTHROUGH DRUGS

In addition to a risk-based, front-loaded development plan undertaken by the manufacturer to expedite rate-limiting steps in CMC/GMP for breakthrough drug products, the agency can work with manufacturers on risk-based solutions that facilitate expedited development and review timelines without compromising availability of an adequate supply of safe and effective products for patients. A few areas for consideration are as follows:

- The traditional and time-consuming process of formal meeting requests, scheduling, briefing documents, and written responses may not be appropriate in the environment of an accelerated breakthrough therapy drug development program. More flexible approaches to ensuring information exchange and understanding should be considered to facilitate expediting development and review. Formal meetings should be reserved for more comprehensive program discussions or critical review milestones.
- Soon after receiving a breakthrough designation, manufacturers should work with FDA on a plan for early and active engagement to schedule and conduct meetings during development to reach agreement on best path forward
- Consider designating a CMC/GMP point of contact, within both sponsor and FDA, to triage meeting requests and sponsor questions
- Set up secure email to facilitate information exchange
- Agree upon schedule of important review milestones and turnaround timeframes for information requests
- Discuss use of "negotiated amendment" approach to submit agreed upon data packages during the review, for example:

- Submission of the dissolution method development report and dissolution specification setting strategy for early review by FDA Biopharmaceutics reviewers
- Additional real-time stability data on commercial product
- Additional batch data to support validation
- Discuss rolling submission of module 3 components to enable more rapid access to CMC and facility data to facilitate pre-approval inspection scheduling and conduct; Gain early and frequent access to reviewers *via* teleconferences to resolve questions, avoid delays, and provide clarity on specific concerns
- For small molecules, flexibility on the qualification of regulatory starting materials (RSMs), impurities, and impurity controls, perhaps accepting something on an interim basis with a post-marketing commitment to reevaluate these controls after launch. Impurities and their associated controls, including RSMs, should be considered in light of the clinical indication and the potentially life-saving nature of the drug. It may be necessary for drugs which have not been fully optimized at the time of launch to allow for wider initial controls which can be adjusted and refined as more experience is gained in commercial manufacturing provided product safety and quality will not be impacted

CONCLUSION

Breakthrough therapies offer significant patient benefits, but the reduced timelines introduce significant CMC/GMP challenges for product development as well as resource commitments to align the development and commercial organizations. Each breakthrough drug development program will have different risks and constraints, so the specific CMC/GMP approaches will vary by product and timing of the breakthrough designation. Through careful planning and a thorough understanding, by all parties, of the requirements and timeframes, some activities may be optimized post-approval. Leveraging prior knowledge, platform data, and use of comparability protocols are key considerations for developing a breakthrough drug product. Additional considerations include the use of initial product supply from a clinical process or site, use of supportive stability data from representative pilot scale lots, delaying certain process validation requirements not directly related to patient safety, and consideration of broader product quality acceptance ranges for non-critical quality attributes until further manufacturing experience is gained. As a result, these programs will generate significant post-approval CMC efforts and phase IV commitments to address control system updates, process optimization where needed, and site transfers. The key to success is open and transparent communications with FDA to ensure the development program delivers an adequate supply of safe and efficacious product to patients.

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COMPLIANCE WITH ETHICAL STANDARDS

Author contributions All authors contributed in writing the manuscript.

ANNEX 1

Case studies of actual challenges encountered by sponsors during BT development and flexibilities that were agreed upon with the FDA to ensure product safety and availability at the time of approval.

Biologics

Example no. 1:

Genentech/Roche—Gazyva® (obinutuzumab) is a humanized monoclonal antibody approved for the treatment of lymphoma. Acting as an immunomodulator, it targets CD20, killing B cells. Gazyva was the first FDA-designated breakthrough therapy approved by the U.S. FDA in November of 2013. Breakthrough therapy designation was granted for Gazyva late in the development cycle, just prior to the Biologics License Application (BLA) filing. Because of the late stage of designation as a Breakthrough Therapy, most CMC development activities for Gazyva had been completed

- However, to allow for earlier launch, the FDA encouraged conversion of phase III clinical material to launch material in order to accommodate an early launch (~1 month sooner)
- Detailed assessments of clinical material took place during PDUFA V mid-cycle and late-cycle meetings with FDA and during PAI at the DS manufacturing site
 - Same commercial manufacturing facilities and same scale of manufacture
 - Same manufacturing processes planned (very minor changes)
 - Transition from clinical to commercial CoA (met all commercial specifications)
 - Qualified persons requested written endorsement from FDA to release
- Very supportive interaction with FDA regarding conversion of clinical material to commercial launch material to get this medicine to chronic lymphocytic leukemia (CLL) patients quickly

Example no. 2:

Merck & Co.—Keytruda® (pembrolizumab) is the first PD-1 blocking drug approved by the U.S. FDA, in September of 2014, for the treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. At

the time, breakthrough therapy status was granted to Keytruda®, clinical supplies were only manufactured on a small clinical scale, clinical development was in phase I, and CMC development was stage appropriate, in early stages

- Expediting CMC readiness to meet clinical timelines meant decoupling DS Process Performance Qualification (PPQ) from DP PPQ, enabling almost parallel execution and completion of DS and DP PPQ activities, both of which were rate-limiting to the CMC file. This was enabled by ensuring no significant process changes were implemented between the clinical GMP DS batches used for DP PPQ and the subsequent DS PPQ batches, saving 4–6 months in the development timeline without incurring additional quality or patient safety/efficacy risk
- To meet the projected commercial and clinical demand, an additional drug substance manufacturing site was rapidly brought online prior to BLA filing. Through multiple interactions with the FDA, licensure was sought for two drug substance manufacturing facilities, one that was the initial clinical supply site and, a second larger CMO site (licensure of this site was based on a strong analytical comparability package, the approach and content of which were discussed with the FDA *via* frequent interactions)
- The FDA partnership was critical to rapid resolution of multiple CMC issues, especially since this was Merck's first monoclonal antibody filing with the FDA. During the final stages of the review of the BLA application, the field office site inspections were not synchronized with early action by the review division—this resulted in removal of one of the manufacturing sites from the BLA, which was subsequently submitted for review and approved very rapidly
- In addition to the rapid pace of development of this molecule, along with multiple sites, the dosage form also transitioned from a lyophilized powder for solution for infusion to a liquid vial. This supply strategy was discussed and reviewed with FDA, in advance, resulting in the recent approval of the post-approval supplement for the liquid vial, based on analytical comparability in the previously agreed upon strategy
- A process/product-specific host cell protein (HCP) method for measurement of host cell impurities in the drug substance was not in place at the time of designation. Upon FDA review, a well-characterized commercially available HCP assay, demonstrating appropriate coverage and clearance in the process, was used for initial commercial release. During BLA review, a post-marketing commitment to develop a process/product-specific HCP assay was agreed to. This allowed development, bridging, and validation of this HCP method off critical path to initial approval, ensuring that the interim solution did not pose any patient safety/efficacy risk. Alternatively, inclusion of the process/product-specific HCP assay in the BLA filing would have resulted in a minimum of 6–9-month delay
- The importance of frequent and data-driven interactions with the FDA was critical to the success of CMC development for this drug

Example no. 3:

Bristol-Myers Squibb—Opdivo® (nivolumab) was approved in December, 2014. Opdivo works by inhibiting the PD-1 protein and is intended for patients who have been previously

treated with ipilimumab, for melanoma patients whose tumors express BRAF V600, and for use after treatment with ipilimumab and a BRAF inhibitor. The following flexibilities allowed for development of a complete package:

- Final cell-based bioassay was not available until after PPQ batches
 - Used frozen samples (release and stability) to allow testing following method validation to justify acceptance criteria
- DS process changes allowed for improved robustness and facilitated future transfers to additional sites
 - Introduced modifications to downstream or purification processing steps prior to manufacture of commercial supplies; no change in cell line or upstream process
 - Type B and type C meeting to align on strategy; Provided preliminary comparability data, including Comparison of release and extended characterization analytical data
Side-by-side degradation profile at stress conditions
Full scale in-process control data comparison
 - Able to bridge stability data to allow expiry to be based on studies performed using material from the clinical process
- Endotoxin
 - Low endotoxin recovery observed with original (kinetic) method used for drug substance
 - Type B meeting to align on proposed strategy
 - Changed to gel clot method during BLA review
- Addition of 40 mg/vial presentation with limited formal stability data
 - Same formulation and glass vial as used for 100 mg/vial presentation
 - Type C meeting to align on stability strategy to support proposed expiry

Example no. 4:

Amgen—Blinicyto® (blinatumomab) was approved in December, 2014, to treat patients with Philadelphia chromosome-negative precursor B cell acute lymphoblastic leukemia (B cell ALL). It is a first-in-class bispecific T cell engager (BiTE®) antibody construct that binds CD19 on B cells and CD3 on T cells, inducing a cytotoxic T cell response to kill target B cells. Blincyto received BT designation 2.5 months prior to BLA submission, and accelerated approval (11-week BLA review) was based on phase 2 data for relapsed or refractory B cell ALL

- With a history of multiple sponsors and manufacturing sites and six manufacturing processes, there was
 - No clinical experience with the commercial manufacturing process and limited process experience due to complex manufacturing history
- FDA requested several months acceleration of drug substance contract manufacturing to enable early inspection and faster review
- A dissolution issue with raw material delayed initiation of drug substance manufacturing from the date agreed upon with FDA
 - The FDA agreed to inspect earlier process steps and required a commitment to provide results of raw material investigation and product quality data when available as

well as evidence of existing inventory to supply the market

- The discontinuity in process characterization was addressed by extensive FDA information requests to understand process robustness
- Post-marketing commitments to qualify tests for certain in-process sample types and to complete drug substance and drug product container closure leachate studies allowed for timely submission and approval

Small Molecules

Example no. 5:

Pfizer—Ibrance® (palbociclib) was granted accelerated approval, by the US FDA in early 2015, to treat postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer by inhibiting cyclin-dependent kinases (CDKs) 4 and 6. During commercial scale-up, the manufacturer identified a drop in dissolution performance at the end of each batch. This phenomenon did not occur at smaller manufacturing scale of the drug

- In order to continue uninterrupted supply to the clinical study while this issue was being investigated, a batch cutoff at 85% was instituted by the sponsor to throw away the final 15% of each batch
- The FDA was informed of the issue and agreement was obtained that the 85% cutoff was an appropriate interim measure until a permanent corrective action could be identified
- The applicant identified a set of successful modifications to the encapsulator hopper to improve powder flow and eliminate over-lubrication of the tail end of the batch. Stratified data across multiple batches and strengths confirmed the corrective action was successful
- Ultimately, the 85% cutoff was successfully phased out for the commercial process and all future clinical batches

Example no. 6:

Pharmacy—Imbruvica® (ibrutinib), a first in class, selective, small molecule inhibitor of Bruton's tyrosine kinase (BTK), was granted breakthrough therapy status for three indications in early 2013. Imbruvica® received its first approval under breakthrough therapy designation (BTD) by the FDA on November 13, 2013, for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Subsequently, Imbruvica® was approved by the FDA for three additional indications: the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy, chronic lymphocytic leukemia patients with 17p deletion (under BTD), and for the treatment of patients with Waldenstrom's macroglobulinemia (under BTD). Because BTD was granted at the end of phase 2 clinical studies, development timelines for Imbruvica were shortened by about 12–18 months. CMC development

activities were on the critical path for the NDA submission and commercial launch.

- One of the regulatory starting materials Pharmacyclics proposed was not accepted by the FDA. FDA requested that the regulatory starting material should be separated from the DS by additional synthetic steps. The material which was custom manufactured for Pharmacyclics was therefore designated as an intermediate and the manufacturing process of this intermediate was added to the commercial manufacturing process. The site was rapidly readied for pre-approval inspections
- At the CMC-specific pre-NDA meeting, several key issues were discussed with the FDA and agreements obtained to expedite commercial readiness. Agreement was obtained on regulatory starting materials, impurity qualification strategy, validation strategy, *etc.*
- To meet the compressed timelines for NDA submission and approval, PPQ activities of DP and PPQ of DS were conducted in parallel. This was made possible because no major process changes were implemented between DS manufacturing process used to manufacture the pivotal clinical batches and eventual commercial process
- The commercial DS manufacturing site was different from the site where earlier clinical batches were manufactured. Comparability data of clinical batches to commercial batches was used to support the change. Both clinical process and commercial process used similar control strategy and no major changes to the manufacturing process were made between the two sites
- An alternate more discriminating dissolution method was developed and validated prior to NDA submission. However, available data generated using the new method was limited and not sufficient to propose a specification using this method. A commitment was made to collect additional data using the new method and revise the dissolution specification post-approval
- Responses to FDA queries and request for information during review were completed promptly with turnaround time of 24–48 h
- Labels, cartons, and other launch materials were printed at risk in order to minimize delay in commercial launch after approval

ANNEX 2 (5)

Illustrative Examples of Adaptations of Traditional CMC Development and Manufacturing Approaches for APIs and Drug Products to Ensure Early Access

The following table from the European Federation of Pharmaceutical Industries Association (EFPIA) Technical Development and Operations Committee (TDOC) Briefing Paper (Annex 2) illustrates some expedited approaches which a company may take (MAPPs aligned approach) to ensure early access of medicines for the

Medicines Adaptive Pathways to Patients Initiative (MAPPs) in Europe. Note this table is not intended to be comprehensive and is for illustrative purposes only. Most aspects of the proposals are valid for small molecules/new chemical entities (NCEs) as well as large molecules/biotech products.

Topic	Traditional approach	MAPPs aligned approach
Formulation	Commercial formulation developed and optimized; comparability to pivotal clinical formulation demonstrated in dossier	Use of clinical formulation or limited optimisation of selected market form Where relevant, comparability of launch formulation to pivotal clinical formulation demonstrated in dossier Where relevant/known, planned commercial formulation described and a PACM Protocol to demonstrate comparability to pivotal clinical formulation in the dossier
Packaging	Optimized, based on minimum requirements for protection	Potential for use of “maximum protection pack” to mitigate limited shelf-life
Analytical methods	Developed and validated	Developed and validated
Specification	Established and documented Supported by extensive dataset	Established and documented; possibly broader specifications as little data are available May include more elements than traditional specification due to limited data set and/or some parameters where the data will be reported but acceptance criteria not defined Commitment to update (rationalize) after x time or y batches, based on pre-defined criteria and to reassess the control strategy.
Impurity assessment	Impurities identified, risk assessed and controlled Controlled mainly by process knowledge rather than specification testing	Impurities identified, risk assessed and controlled Higher level of control by specification testing (could include intermediates) may be needed until sufficient data available to support greater reliance on process control
Shelf-life	Shelf-life at launch based upon defined length of stability data on defined batch types/sizes (ICH Q1A) Post-approval extension as further data emerges	Launch product will be supported by (ongoing) stability studies, but ICH-conform data may be limited. Negotiate employment of lean stability strategies (including stress conditions), use of stability models, and extrapolation for supporting shelf-life with competent authorities, enhanced use of scientifically relevant supporting data from earlier batches, and possibly more than one batch annually in ongoing stability Support of adequate shelf-life with use of highly protective packaging/restrictive storage conditions as appropriate to the elicited degradation mechanisms Post-approval strategies will depend on formulation strategy and may also involve novel approaches
Process development	Complete package at filing Process supported by extensive development studies	Partly based on platform knowledge, to be refined as more batches/materials are investigated May be based on proven acceptable ranges (or set points) until data set complete; more reliance on end testing for product release
Process validation	Prospective or continued process verification	Seek regulators’ agreement to a concurrent validation approach, including extended monitoring
Scale of production	Commercial scale	Small commercial scale Scale-up protocol defined

Sites of production	Commercial manufacturing site Existing cGMP clearance or inspection-ready Multiple sites may be included	May be clinical manufacturing site Existing cGMP clearance (possibly only MIA-IMP) Inspection-ready; product history available to support approval of clinical site for commercial launch Site addition PACM Protocol defined
Viral clearance validation	Validated in small scale	If appropriate platform data are available: include such data in dossier, validate in small scale prior to launch, and agree mechanism for provision of data to competent authorities
Inspection of facility	GMP certificate available for commercial use of the facility	Acceptance of GMP certificate for IMP manufacture or, where facilities are outside the EU, the acceptance of QP Declaration for imported API/product
Cleaning method	Established	Established
Cleaning validation	Validated	Appropriate analyses on batch-wise basis and and/or concurrent validation
DMFs (where used)	Submitted in close conjunction with MAA	Negotiate early submission/pre-assessment to mitigate risk of landing on critical review path

ANNEX 3: ABBREVIATIONS

API	active pharmaceutical ingredient
BT	breakthrough therapy
CAPA	corrective and preventative actions
CMC	chemistry, manufacturing, and control
CPP	critical process parameters
CQA	critical quality attributes
DP	drug product
GMP	good manufacturing practices
IPC	in-process control
MAPPs	Medicines Adaptive Pathways to Patients Initiative
PAI	pre-approval inspection
PALM	post-approval life cycle management plan
PC/PV	process characterization/process validation
PC/PV	process characterization/process validation
PK	pharmacokinetic
PPQ	process performance qualification
PQS	pharmaceutical quality systems
PQS	pharmaceutical quality systems
RSM	regulatory starting materials
QC	quality control
QTPP	quality target product profile

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Use of FDA-Approved and Laboratory-Developed Tests in Advanced Non-Small Cell Lung Cancer: Results of a Retrospective Market Analysis



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Use of FDA-Approved and Laboratory-Developed Tests in Advanced Non-Small Cell Lung Cancer: Results of a Retrospective Market Analysis

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A variety of molecular tests are currently in use to detect oncogenic driver mutations in patients with non-small cell lung cancer (NSCLC), particularly in those with advanced-stage adenocarcinoma.¹⁻⁴ For some time, molecular testing in the United States has been complicated by the regulatory environment, which is currently divided between the FDA and the Centers for Medicare & Medicaid Services (CMS).⁵ Tests regulated by the FDA and CMS are often used for the same purpose and in patients with the same condition, which has raised concerns that the different regulatory standards of each agency may introduce an unknown degree of variability into clinical practice.⁶

In October 2014, the FDA announced its intention to extend oversight of diagnostics to include LDTs due to the increasing complexity of LDTs and their growing role in guiding treatment decisions.

The FDA has historically regulated molecular tests manufactured and sold as kits by diagnostics companies, whereas CMS has overseen tests made and used within a single laboratory, called laboratory-developed tests (LDTs).⁵ In oncology, tests regulated by the FDA are typically called “companion diagnostics” owing to the agency’s practice of approving targeted therapies and diagnostics concurrently. The FDA approval process is designed to ensure that individual tests are accurate, reliable, and clinically valid, whereas CMS regulation under the Clinical Laboratory Improvement Amendments (CLIA) is designed to assure that tests are properly performed, largely through the oversight of laboratory personnel and procedures. Although all tests are under its jurisdiction, as a matter of policy the FDA has not

actively regulated LDTs since the start of the medical device program in 1976. At the present time, companion diagnostics undergo rigorous premarket review by FDA, whereas LDTs generally do not.

In October 2014, the FDA announced its intention to extend oversight of diagnostics to include LDTs due to the increasing complexity of LDTs and their growing role in guiding treatment decisions.⁷ In a *Federal Register* notice, the FDA stated that over 11,000 LDTs are currently used in practice.⁸ Yet, to date, it remains unclear how frequently LDTs are used compared with available FDA-approved tests to guide the use of targeted therapies.

We attempt to estimate the extent to which LDTs are used in NSCLC patients with advanced-stage adenocarcinoma, a setting in which molecular testing for 2 specific alterations is considered standard of care and recommended by major clinical guidelines.^{9,10} Testing for ALK gene rearrangements and epidermal growth factor receptor (EGFR) mutations is recommended so that patients with these genetic abnormalities can receive effective treatment with targeted agents.

Material and Methods

Study Sample Design

A universe sample frame of NSCLC-treating oncologists was created by sourcing Symphony Health Analytics’ 2014 insurance claims activity for all oncologists in the United States for both the 162 series of lung cancer ICD9 codes as well as the claims activity related to prescribing lung cancer-targeted therapies (erlotinib, afatinib, crizotinib, and ceritinib). By combining both sources, we identified 10,184 oncologists with activity related to the care of lung cancer patients. To ensure that the physicians targeted for this research would have the required minimum number of patients to participate, we further limited this sample to those with at least 3 unique lung cancer patients in all of 2014. This

reduced the list of oncologists to 8129, thus serving as the sample frame for this survey. All 8129 NSCLC-treating oncologists were invited to participate in the survey by e-mail or postal mail. Oncologists were eligible to participate if they personally managed at least 5 NSCLC patients per month and diagnosed at least 1 NSCLC patient in the past 12 months. A total of 221 oncologists responded to the survey and 153 met eligibility criteria and completed the survey. Participants were offered an industry standard honorarium as compensation for their time in completing the survey. The survey was administered online and was fielded from April 8, 2015, to September 14, 2015.

Data Collection

A questionnaire was developed to collect anonymized information on patients with stage IV NSCLC in the United States. We developed and pretested this instrument through interviews and consultations with 13 NSCLC-treating oncologists before launching the survey online. In the online survey, physicians were asked to randomly select between 3 and 8 stage IV NSCLC patients from their list of patient charts. To ensure random chart selection, oncologists were asked to choose patients whose last names began with a random selection of letters. Patient charts were required to have been active in the practice within the past 12 months to be eligible for inclusion in the study. The anonymized information collected for each patient chart consisted of the following: background information (age, weight, gender, ethnic origin, concomitant conditions, insurance type, smoking status), the year NSCLC was diagnosed, information about the genetic test (which test was used, when and in which setting was it performed, and what was the outcome of the test), and type of treatment patients subsequently received. The 153 oncologists who participated in the survey provided information for 765 patients in total. All patient chart audit data collection fields were Health Insurance Portability and Accountability Act compliant and contained no patient identifying information.

Data Analysis

All survey data were analyzed in aggregate, and the individual identities of the survey respondents were blinded to the study authors. Data were analyzed in total and split per histological subtypes. Other dimensions such as the type of setting, geographical region, patients' ethnic origin, insurance types, and smoking status were used to segment the analysis. The key element in the analysis was to determine, for each patient, whether a molecular test was used to identify *EGFR*

KEY POINTS

- A number of molecular tests are currently used to detect oncogenic driver mutations in patients with NSCLC
- In October 2014, the FDA announced its intention to extend oversight of diagnostics to include LDTs
- It remains unclear how frequently LDTs are used compared with available FDA-approved tests
- LDTs and FDA-regulated tests are often used in the same setting, raising the concern that an unknown degree of variability may exist between tests for the same intended use
- Steps should be taken to mitigate uncharacterized variability between tests used in the same clinical setting

and/or *ALK* alterations, and if so, whether the tests used were LDT or FDA approved. To that end, approval status of tests was determined from FDA's publicly available list of approved companion diagnostics at the time of the survey. At the time of the survey there was no FDA-approved *ROS1* test for NSCLC. Therefore,

The key element in the analysis was to determine, for each patient, whether a molecular test was used to identify *EGFR* and/or *ALK* alterations, and if so, whether the tests used were LDT or FDA approved.

all *ROS1* tests performed were qualified as LDT. Furthermore, in many instances, oncologists surveyed did not know what type of test was performed. In instances where the information was not provided by the oncologists, we followed up with the pathology lab of the relevant treating center and obtained the information by phone. We followed up with pathology labs from 96 centers and clarified the type of test for 340 of 659 *EGFR*-tested patients and for 288 of 562 *ALK*-tested patients. Data presented in this paper include the information obtained through the phone follow-up.

Ethics, Consent, and Permissions

Data for this work were obtained through market research, and no experiment on humans has been carried out. As such, there was no institutional and/or licensing committee involved in approving the experiments, and

no need for informed consent from the participants, as stated in national regulations (HHS.gov; US Department of Health & Human Services; www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102). This survey was done in accordance with market research guidelines such as the ones edited by the Council of American Survey Research Organizations.

Statistical Analysis

Clustered logistic regression was performed to assess whether respondent characteristics (practice setting, practice ownership, geographic region) correlated with use of an FDA-approved test. Clustering of patient records was done according to each oncologist's group of patients.

Although clear guidance was provided to ensure randomization of patient selection, it cannot be ruled out that some respondents might have focused on their most recent patients, or those who have been tested.

Limitations

It should be noted that this survey has a number of limitations. First, this survey focused on oncologists, and not pathologists. The purpose of the research was to evaluate the frequency and type of testing performed and identify whether any differences in testing status were associated with patient characteristics such as age, weight, gender, ethnic origin, concomitant conditions, insurance type, smoking status, etc. We believe that oncologists are best suited to access this type of information. Topics relating to reasons for not testing a patient, number of alterations assessed (single genetic test vs next-generation sequencing), or reasons for using one type of test versus another, may largely fall with the pathologist and were outside the scope of the research. Second, our study was not designed to address the comparative outcomes of patients tested with LDTs versus FDA-approved tests. Third, while we assume that participation in the survey was random and represented basic interest and knowledge in this disease area, the potential for bias in the set of responders versus nonresponders does exist. Due to the methodology, a true response rate cannot be calculated for this survey. Physicians were invited by email or postal mail, and they voluntarily self-screened based on knowledge, interest, and experience level in treating this condition. They had the opportunity to respond to the survey invitation by logging on to the online survey. As it is unknown how many physi-

cians successfully received, reviewed, and self-screened for this survey invitation, the true response rate is unknown. Fourth, as with any survey, our findings may be influenced by response bias of the survey respondents. Although clear guidance was provided to ensure randomization of patient selection, it cannot be ruled out that some respondents might have focused on their most recent patients, or those who have been tested. Despite the potential for bias, we believe the data presented here are valuable as they represent real-life data and are usually not obtainable on a large scale. Additionally, a portion of patient records (and associated pathology reports) did not include information on the type of test used to detect lung cancer mutations and had to be excluded from further analysis (72 [14.5%] of patients tested for *EGFR*; 79 [16.5%] of patients tested for *ALK*). And last, *KRAS* testing rates, which predict resistance to *EGFR*-targeted therapy, were not evaluated because the study design predated inclusion of *KRAS* testing practice recommendations and guidelines.

Results

Participants

The sample of responding physicians was split across practice setting (19% academic, 24% community, 58% private) as well as geographic region and practice ownership (Table 1).

Patient Characteristics

A total of 765 patients with stage IV NSCLC were reviewed in this study. The demographic characteristics of this group are presented in Table 2. Histological subtype split was as follows: 579 (76%) of patients had adenocarcinoma, 147 (19%) had squamous cell carcinoma, and 39 (5%) had other type (including large cell and NSCLC not otherwise specified). Distribution by practice setting was as follows: 445 (58%) of patients were followed in privately owned clinics, 181 (24%) in community-based centers, and 139 (18%) in academic medical centers. Fifty-two percent of patients were male, and 61% were aged 65 years or older.

Overall Test Rate

Among the 579 patients with adenocarcinoma, 550 (95%) and 489 (84%) were tested for *EGFR* mutations and *ALK* rearrangements, respectively (Table 3). Other genetic alterations (*BRAF*, *MET*, *HER2*, *RET*) were tested at lower frequencies, with one exception being *ROS1* gene fusion testing at 28% of adenocarcinoma patients.

Use of FDA-Approved Tests

Of the 550 adenocarcinoma patients tested for

Table 1 Characteristics of Physicians Who Responded and Completed the Patient Chart Review		
Type of Setting	No.	%
Academic center	29	19
Community-based center	36	24
Private clinic	88	58
<i>Grand Total</i>	<i>153</i>	<i>100</i>
Region		
Midwest	28	18
Northeast	37	24
South	61	40
West	27	18
<i>Grand Total</i>	<i>153</i>	<i>100</i>
Practice Ownership		
Physician-owned	91	59
Hospital-owned	59	39
Other	3	2
<i>Grand Total</i>	<i>153</i>	<i>100</i>

EGFR mutations, 496 (90%) were diagnosed or tested following the first FDA approval of an *EGFR* test for lung cancer on May 14, 2013. Seventy-two patients had an unknown test type and were excluded from further analysis. Of the remaining 424 patients, 55 (13%) received an FDA-approved test and 369 (87%) received a LDT (Table 4).

We performed a similar analysis for adenocarcinoma patients tested for *ALK* rearrangements. Of the 489 adenocarcinoma patients tested for *ALK*, 478 (98%) were diagnosed or tested on or after August 26, 2011, the date of the first drug-diagnostic approval for NSCLC with detected *ALK* rearrangement. Excluding 79 patients with unknown test type, 204 (51%) patients received an FDA-approved test while 195 (49%) were tested with an LDT (Table 4).

Statistical Analysis

The characteristics practice setting, practice ownership, and geographic region were evaluated for correlation with use of an FDA-approved test. None of the characteristics reached nominal statistical significance ($P < .05$) for use of either an FDA-approved *EGFR* or *ALK* test.

Discussion

This study was undertaken to evaluate the prevalence of molecular testing in lung cancer, as well as the use patterns of tests overseen by different regulatory

agencies. Although much has been written about the rate of molecular testing in oncology and in lung cancer specifically, little is currently known about the relative use of FDA- versus CLIA-regulated tests (the latter are

The high rate of overall testing observed in this study is consistent with other findings in the literature and supports the claim that molecular testing is now a routine part of advanced lung cancer treatment.

referred to as LDTs in this article). This study seeks to address that gap by viewing lung cancer as a case study, owing to the diversity of testing options that exist in that setting. Findings from this study will help inform the debate over how best to structure regulatory oversight of molecular testing in the future.

The patient chart review conducted in this study revealed that a large proportion of patients with advanced lung adenocarcinoma underwent molecular testing for *EGFR* mutations and *ALK* rearrangements in accordance with major clinical guidelines.^{9,10} The high rate of overall testing observed in this study is consistent with other findings in the literature¹¹⁻¹³ and supports the claim that molecular testing is now a rou-

Table 2 Demographic Characteristics of Stage IV Non–Small Cell Lung Cancer Patients

Characteristics	Total Sample (N = 765)	
	No.	%
Sex		
Female	394	48
Male	371	52
Age groups		
18-39 years	18	2
40-64 years	282	37
65+ years	465	61
Geographic region		
Midwest	149	19
Northeast	169	22
South	305	40
West	142	19
Type of practice		
Academic center	139	18
Community-based center	181	24
Private clinic	445	58
Ethnic origin		
Caucasian	499	65
African American	139	18
Asian	69	9
Hispanic	48	6
Other	10	1
Histological subtypes		
Squamous cell carcinoma	147	19
Adenocarcinoma	579	76
Other type	39	5
Smoking status		
Current smoker	187	24
Past smoker	363	47
Passive smoker	33	4
Never smoked	175	23
Unknown	7	1

Distribution of study population across 7 factors of interest. Information on 765 patients was provided by 153 responding physicians.

tine part of advanced lung cancer treatment. Moreover, the finding that *ROSI* was the third most commonly tested biomarker is not surprising given the fact that

ROSI has been recognized as a potential therapeutic target for some time¹⁴ and was approved as a target for crizotinib in March of 2016.¹⁵

This study also found that testing was more commonly performed with LDTs than with FDA-regulated tests for *EGFR* mutations and was evenly split between LDTs and FDA-regulated tests for *ALK* rearrangements. The high rate of LDT use may be caused by a number of factors. First, clinical guidelines are not prescriptive about specific testing platforms. It remains unknown whether there is any quality trade-off associated with the use of many commonly used LDTs in place of FDA-regulated tests in settings where both exist, and both FDA-regulated tests and LDTs are generally considered acceptable so long as proven test methodologies are used.¹⁶ Second, many LDTs became available prior to the introduction of FDA-approved alternatives. This was the case, for example, with tests for *EGFR* mutations in lung cancer, where the first *EGFR*-targeted therapy was approved several years prior to FDA clearance of an *EGFR* test, leading to the introduction of

This study also found that testing was more commonly performed with LDTs than with FDA-regulated tests for *EGFR* mutations and was evenly split between LDTs and FDA-regulated tests for *ALK* rearrangements.

LDTs¹⁷ for *EGFR* prior to the approval of the cobas *EGFR* Mutation Test. As a result, physicians may have developed comfort and familiarity with the LDT prior to the availability the FDA-approved test. Third, many tumor biopsies provide limited tissue for testing, which may encourage the use of assays that detect multiple biomarkers simultaneously, none of which are currently FDA-approved for use in lung cancer. This study did not collect information on the cost of tests, and we cannot speculate on whether cost plays a role in the decision to use an FDA-regulated test or an LDT.

There are pros and cons to the widespread use of LDTs. On the one hand, LDTs may offer rapid technical advances and facilitate innovation in molecular testing and have been demonstrated in some cases to offer advantages beyond existing FDA-regulated alternatives.^{18,19} On the other hand, concerns exist that LDTs are not currently subjected to premarket review by the FDA and thus are not required to meet the same evidentiary standards as FDA-regulated tests. Additionally, LDTs have in at least some instances been

Table 3 Mutation Test Rate for Stage IV Non–Small Cell Lung Cancer Patients

Mutation type	Total Sample (N = 765)		Adenocarcinoma (n = 579)	
	No.	%	No.	%
EGFR mutation	659	86	550	95
ALK rearrangement	562	73	489	84
BRAF V600E mutation	38	5	32	6
MET amplification	40	5	30	5
ROS1 rearrangement	181	24	162	28
HER2 mutation	31	4	23	4
RET rearrangement	25	3	19	3
Other	35	5	25	4

Table 4 Use of FDA-Approved vs Laboratory-Developed Tests in Non–Small Cell Lung Cancer Stage IV Adenocarcinoma Patients

Mutation types	EGFR Mutations (n = 424)		ALK Mutations (n = 399)	
	No.	%	No.	%
FDA-approved test	55	13	204	51
Laboratory-developed test	369	87	195	49

Rates of EGFR and ALK testing of stage IV adenocarcinoma patients using FDA-approved and laboratory-developed tests. Analysis was conducted such that test use was measured only when an FDA-approved version of the test was available. Therefore, EGFR data are for patients who were tested after May 2013, and ALK data include patients who were tested after August 2011. Regression analysis was performed to assess whether geographic region or type of practice were correlated with use of an FDA-approved test, and neither of the characteristics reached nominal statistical significance ($P < .05$).

reported to perform poorly, as noted in a report of case studies released by the FDA.²⁰ This study does not seek to address the relative quality of LDTs and FDA-regulated tests, but rather the relative frequency of use.

Owing to the large number of tests currently in use, some of which have been subjected to premarket review by FDA while others have not, there exists the potential for wide variability in test performance and claims.²¹⁻²³ As demonstrated by this study, LDTs and FDA-regulated tests are often used in the same setting, raising the concern that an unknown degree of variability may exist between tests for the same intended use.

Steps should be taken to mitigate uncharacterized variability between tests used in the same clinical setting. Further evaluation of the relative performance of tests intended to measure the same alteration is needed to identify cases in which different tests may not provide comparable results. ♦

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Conflict of Interests

Authors declare no conflicts of interest.

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Blueprint for Breakthrough: Exploring the Utility of Real World Evidence (RWE)

Conference White Paper

5th Annual Friends of Cancer Research & Alexandria Real Estate Equities Conference

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Goals

Friends of Cancer Research (*Friends*) and Alexandria Summit will convene a multi-stakeholder meeting to include industry, real world evidence (RWE) vendors, FDA, academics, researchers, patients, advocacy organizations, and other vested stakeholders with the expressed intent of developing consensus toward the potential use of RWE in the regulatory setting. The following report, developed by a work group aims to build consensus in the following three areas which, will be presented on June 16th, 2016 to solicit public input and further refine content:

- 1) Identify disease and drug candidates in oncology as potential case studies,
- 2) Develop regulatory strategies for optimal use of RWE in oncology, and
- 3) Outline potential pilots in oncology that could be used for clinical evidence generation to support regulatory decisions.

Background

With bringing innovative medicines to patients in a timelier manner, there is great interest in designing clinical trials with adaptive features that make studies more efficient, more likely to demonstrate an effect of the drug, more informative, and better able to capture the totality of clinical evidence.¹ Advancements in our ability to build learning systems and improve data collection, so as to link clinical priorities and measurable outcomes, are beginning to inform clinical studies with respect to how patients are treated, should be treated, and wish to be treated with these new therapies in the real world. Thus, an opportunity exists to learn from current efforts to collect, interpret, and apply real world evidence to drug development.

Real World Evidence

RWE refers to evidence generated from data collected outside the traditional clinical trial setting, such as electronic health records (EHRs) including patients treated on- and off-label, pragmatic clinical trials, patient registries, patients treated through expanded access, administrative claims, surveys, and mobile health-generated data (e.g., smartphones, wearables, internet and social media). RWE is thought to better reflect the general population and the care they receive, given that enrollment in clinical trials is often limited to patients with specific baseline characteristics, with often restricted eligibility. Therefore, high quality RWE can provide different, and at times broader, estimates of the safety and effectiveness of therapies than certain traditional clinical trials with narrow eligibility criteria.

While randomized controlled trials (RCTs) are the gold standard for minimizing sources of potential bias, RWE may have utility in certain scenarios. Particularly, in the case of a drug where the effect size is likely to be significantly larger than any confounding factors that might occur and where confidence in the original efficacy data is relatively high,² such as for a therapy designated as a Breakthrough Therapy. While there may be concerns regarding data quality, owing to factors such as missing information and non-systematic data collection, information gathered from EHRs can allow for data to be collected on more patients, in an unselected patient population and more rapidly than traditional phase 4 trials designed to meet post-market requirement and commitments. Thus, in cases of transformative treatments, the question of whether it would be feasible and sufficient to confirm clinical benefit in the real world setting warrants serious consideration.

Breakthrough Therapy Designation

The Breakthrough Therapy Designation (BTD) was created in 2012 as a way to expedite the development of drugs for serious conditions with a large unmet medical need. Breakthrough Therapy designation decisions are based on preliminary clinical evidence demonstrating a substantial improvement over existing therapies. The designation and subsequent actions are primarily designed to maximize efficiency in the clinical development regulatory review processes for potentially transformative new medicines. An additional goal of the designation is to minimize the number of patients that are exposed to a less efficacious treatment throughout the entire development process, including the post-market setting. Drugs intended to treat a serious or life-threatening condition for which there is a large unmet medical need can receive accelerated approval by demonstrating a large effect on a surrogate or biomarker endpoint, e.g., tumor response, reasonably likely to predict a clinical benefit. Drugs approved using a surrogate endpoint generally

¹ Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics. 2010 (version 1).

² Simon R et al, Clin Pharmacol Ther. 2015. 97(5):502-7.

require further evaluation to confirm clinical benefit where there is uncertainty in the relationship between the surrogate endpoint and the clinical benefit, or the observed clinical benefit and ultimate outcome. In the case of an expected substantial improvement in overall survival, as with drugs granted BTB, there may be loss of equipoise for conducting a randomized trial with a less effective therapy for confirmation of clinical benefit following accelerated approval. This raises the need for alternative approaches such as the use of RWE for confirmation of clinical benefit for highly active anticancer therapies such as those granted BTB.

Pragmatic Trials

In addition to traditional models for clinical trial designs, which may not always be practical, adaptive clinical studies that more closely reflect routine medical care represent opportunities to better understand novel therapies in the real world setting. Pragmatic clinical trials (PCTs), which leverage existing clinical infrastructure, are designed to test interventions in everyday clinical settings to maximize therapeutic applicability and generalizability. Although PCTs are defined by FDA as being randomized studies, there are notable examples of nonrandomized pragmatic trials as well. For example, the Targeted Agent and Profiling Utilization Registry (TAPUR) Study,³ launched in March 2016 by ASCO, is a nonrandomized pragmatic trial intended to collect data on the safety and efficacy of approved therapies in other disease settings. However, even with careful planning, such as with validation studies examining sensitivity, specificity, positive and negative predictive values to ensure the data needed to measure safety and effectiveness are captured reliably, it may still be challenging to identify confounding factors that impact study results and generalizability.

Challenges and Considerations

Technological advancements and the growing use of EHRs have facilitated collection of patient data outside of clinical trial settings, and hold potential to further inform patient care, supplement current clinical trial methodologies, and speed drug development. Although real world data (RWD) collection, like other data collection efforts, has challenges with variable data quality, heterogeneity in collection mechanisms, and privacy concerns, among others, a lot of progress has been made in this area recently. Several outstanding challenges that limit full implementation of RWE are highlighted in Table 1.

TABLE 1: Challenges that limit full implementation of RWE.

Data sources	EHRs (i.e., labs data, claims/billing codes, etc.) from academic, hospital, and community oncology sources, and registries, that may include patient reported outcomes (PROs), from patient advocate organizations and others.
Potential variables needed	The minimum information base includes: Diagnosis (International Classification of Disease (ICD) codes; dates of initial and advanced diagnoses; Disease staging; Dates and sites of metastases); Histology; Radiology and pathology reports; Treatment dates (start/stop, for prior and subsequent treatment), CPT codes; Labs (test date, result date, test name, result with units, and normal ranges); Demographics (e.g., smoking status); Biomarker status; Gene sequencing; Performance status; Medication and administration (date, drug, dose, routine, and units); Adverse events report/collection (Grade 3+ or serious adverse events only); Outcomes (e.g., date of death, other endpoints). Additional unique variables will need to be considered depending on the questions.
Data standards	Regulatory trials have adopted Clinical Data Interchange Standards Consortium (CDISC) data standards, however, universal data standards are still being developed within the EHR infrastructure. Similarly, electronic data capture (EDC) systems have become standardized, with fewer proprietary systems requiring extensive validation. ⁴ Among various hospital settings, there may still be variability in software for electronic records management, though a trend towards commercial systems, e.g., EPIC, has been observed.

³ <https://clinicaltrials.gov/ct2/show/NCT02693535>

⁴ Guidance for Industry - Part 11, Electronic Records; Electronic Signatures, establishes the United States Food and Drug Administration (FDA) regulations on electronic records and electronic signatures (ERES). Title 21 CFR Part 11 Section 11.1 (a).

Processes for data merging vs. established third party aggregators	While there is no established internal process to merge RWD sources, a number of third party organizations have begun doing this in oncology (e.g., Flatiron, USO) and beyond oncology (e.g., Humedica). The Flatiron dataset, for example, comprises longitudinal, patient level EHR data and incorporates data from both structured and unstructured EHR data streams.
Challenges/ considerations related to data merging	Variability of data sources, different EHR platforms, different site adaptations of platforms (e.g. custom workflows and proprietary logic, structured and unstructured data collection), high level of ambiguity and complexity in the data concepts (e.g. clinical, financial), lack of interoperability, and complexities associated with data merging, mapping, normalizing, while not insurmountable, requires significant programming and informatics work to prepare research ready datasets. Linking or tracking the same individual across different EHR and disparate RWD platforms is also an important consideration to fully capture the care of a single patient who may appear in more than one RWD source.
Structured, unstructured and missing data challenges	There can be significant variation across EHR systems/providers especially with respect to data collected via structured vs. unstructured parts of an EHR (e.g., some capture disease stage, others do not). It is estimated that half of critical variables for oncology-focused RWE are in unstructured documents ⁵ thereby requiring technology-enabled ⁶ or manual chart review (although Natural Language Processing is also under evaluation). Structured data include data points that are organized in a predefined manner, such as dropdown fields, and unstructured data may include free text from a physician note or a scanned pathology report. Derived variables such as “lines of therapy” and “real-world progression” can supplement RWE datasets; these are generated by combining structured and unstructured data elements using pre-defined business rules. Since each variable comes from a different potential source, the reliability and validity of variables should be described. In addition, missing data, an issue encountered in clinical trial reports as well, will need to be addressed regardless of structured or unstructured data collection.
Challenges/ considerations related to variable extraction processes	Data quality, missing variables, methods applied to extract unstructured content; audit trails are variable depending on EHR system. Hospitals have different extraction systems, heterogeneity in IT capabilities, and data captured by clinicians. Working with an oncology EHR data aggregator would be the simplest mechanism to leverage existing processes that map data from additional providers and present the data in different formats. This would ensure less variability and easier extraction. However, issues such as limited access to broad populations limit the ability to extrapolate results broadly. Ideally, EHR fields could be adjusted for specific data collection as per provider.
Challenges/ considerations related to defining endpoints	Each clinical endpoint, including hard endpoints (e.g., OS), surrogate endpoints (e.g., PFS), and other clinically meaningful endpoints (e.g., RR) have different challenges with respect to collection, reliability, and recording precision in EHR. Discussion and agreement with the appropriate regulatory agency is necessary. Can we quantify tumor shrinkage by mining radiology reports? Will tumor shrinkage require qualification with the same precision as the standard RECIST criteria? Should we integrate clinician assessment of the patient with radiologist assessment of scans into summary variables reflecting tumor burden? Would time to next therapy or time to treatment failure as assigned by the treating physician be reasonable proxies for efficacy? Treatment decisions may be hard to capture (e.g., endpoints used for treatment modification, choice of therapy, etc.). What additional work with EHR providers may be necessary to adjust the records if those are to be used for purposes other than primary billing? How will we determine if endpoints assessed through real-world data are reliable, valid, and meaningful?
HIPPA/ informed consent issues	Informed consent will likely be required due to the need for identifiable information for data linkages, AE reporting, etc. As such, patient level and physician data would be available for auditing. Information from EHRs does not currently have patient consent and would likely involve new processes and policy changes. While it may be possible to obtain consent for registries, these studies are monitored and may not be totally

⁵ Berger, ML et al, Future Oncology, 2016. 12(10) : 12674.

⁶ Liede A et al, Clin Epidemiol. 2015. 7:441-8.

	reflective of RWE. While broad consent will be difficult to obtain, future trials using EHR may require prospective consenting with a clear explanation of the information gathering intent.
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Data Quality and Utility

Significant challenges remain with combining, organizing, and analyzing data from various information sources, including EHRs, insurance claims, biosensors, genomics datasets and patient-reports. Yet interest in using RWE in the assessment of drugs and other clinical interventions remains high. Programs like Sentinel and PCORNet, which aggregate multiple data sources, are relying on claims and EHR-based information to collect large amounts of health data to drive research, including comparative effectiveness. The value of EHR is further evidenced by the American Society of Clinical Oncology (ASCO) launch of the CancerLinQ™ system designed to improve patients' outcomes and quality of life based on EHR data. To date, however, it remains unclear whether such data could be suitable for regulatory purposes. Provided proper standards and methods of collecting, validating, and analyzing real-world data exists, RWE may support a number of activities that impact drug development and delivery.

Questions regarding RWD quality:

- What data quality elements need to be considered and should they differ by data source (e.g., EHRs)?
- How should various databases (community versus academic) with respect to extractability of relevant fields be considered?
- How should quality be reported (e.g., data completeness, variable reliability, variable validity, sources of variables, data provenance) and presented for review? What thresholds need to be reasonably considered for these categories?
- What details should be captured with respect to cohort selection when generating RWE?
- What additional analyses need to be done to generate RWE (i.e., sensitivity analyses)?

Questions regarding RWE use:

- What aspects of efficacy need to be captured with RWE in addition to addressing safety concerns? How best to consider the most appropriate endpoints and outcome measures for various intended uses?
- What requirements are needed for safety reporting based on RWD collected in a trial using EHR? Any specific regulatory advice considering that the drug is marketed? What additional reporting is needed in EHR beyond physicians' reports in their daily activities, according to Good Clinical Practice? Why and under what circumstances?
- How do data requirements change for differing regulatory use cases (e.g., post-market commitments, label expansion, improving dose selection, and defining safety in broader populations)?
- How do we accommodate changing data characteristics and needs for RWD over time?
- What specific adjustments (if any) need to be made to the EHR recordings to allow data transfer to the FDA?

Whereas multiple comprehensive EHR platforms collecting health information (i.e., EPIC) already exist, the individual modules vary by disease specialty and are frequently proprietary and not interoperable. Thus, it is pertinent to initially determine whether any of the collected information could be tested to meet a regulatory threshold.

- Do data fields vary with study design? If so, could these be grouped?
- What data fields are needed to address a study question?
 - Demographics
 - Diagnosis (data, test, treatment and length of treatment)
 - Efficacy outcome(s); therapy changes; subsequent treatments
 - Co-morbidities
 - Toxicities and side-effects
 - Other
- Could the above questions be tested in advance of a pilot to determine feasibility/data extraction, such as designing a simple randomized non-interventional study?

Case Studies

Taking the above challenges into consideration, the work group reviewed scenarios where RWD has been collected and identified opportunities to apply this evidence towards answering specific clinical questions in routine clinical care. The following case studies, while broad in scope, are intended to illustrate possible uses for RWE collection.

Safety (Ceritinib) – In 2014, the FDA approved ceritinib (Zykadia) for the treatment of patients with anaplastic lymphoma kinase-positive (ALK⁺) metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. Anecdotal patient reports suggested that taking ceritinib with food may improve gastrointestinal (GI) tolerability but may lead to increased systemic exposure of the drug. The observed safety data led to a post-market commitment⁷ to evaluate a lower dose of ceritinib taken with a meal that potentially improves GI tolerability. Furthermore, during FDA's review of ceritinib, the FDA noted signs and symptoms of pancreatitis (pancreatic enzyme elevations in addition to gastrointestinal symptoms) in several cases, but there was only one case of investigator-reported pancreatitis occurring in a supportive clinical trial.⁸ Exploration of RWD following approval of ceritinib could have provided additional information on the safety profile of the drug and its association with pancreatitis.

Furthermore, RWD collection on ceritinib use including: dose interruptions, dose modifications (with and without food), concomitant medications, GI toxicity, diarrhea, therapy duration, other adverse events, may contribute to the enhanced evaluation of an appropriate dose of the drug in the post-market setting.

Treatment Sequencing (Ramucirumab) – Docetaxel has been one of the standards of care for the treatment of second line metastatic NSCLC regardless of histology. In December 2014, ramucirumab (Cyramza) was approved in combination with docetaxel for patients who have progressed on a platinum based combination therapy and have received an EGFR or ALK based therapy if indicated. In October 2015, two new immunotherapies, nivolumab and pembrolizumab were approved in the second line (or higher) NSCLC setting; they have already showed significant clinical benefit. These agents may be used in different lines of treatment for these patients; indeed, they are even sometimes being utilized prior to chemotherapy.

While there is no rationale that the safety of ramucirumab plus docetaxel will be affected by prior treatment of an immune checkpoint inhibitor, approval was based on clinical trials conducted before immune checkpoint inhibitors entered the market. Formal clinical trials can test the impact of sequencing on the safety and efficacy profiles of these therapies, yet such trials can be time and cost prohibitive and further complicated by the fact that new treatments will potentially be approved during the course of the study. Overall, it is difficult to study all of the permutations of treatment sequence, especially in a landscape where the available options are changing yearly. RWE can potentially be a practical solution. Thus, collecting RWD on patient characteristics, safety, and mortality in patients with advanced NSCLC receiving treatment with ramucirumab plus docetaxel as well as PD-1 inhibitor, in any treatment setting using even a limited patient pool of approximately 100 patients that meet the criteria of the study population, may facilitate determination of appropriate treatment sequencing.

Orphan Drug Application (Denosumab) – On September 12, 2013, FDA granted orphan drug status for the use of denosumab (XGEVA) for the treatment of hypercalcemia of malignancy (HCM) based on results of a study conducted with EHR data from oncology clinics.⁹ This represents the first-time ruling by the FDA for orphan drug designation based primarily on RWE. The RWE was provided because the published medical literature on HCM ranged from <1% to 30% depending on tumor type and studies were mainly from single institutions or focused on a single tumor type.¹⁰

The RWE featured in the orphan drug application (ODA) was based on analysis of the Oncology Services Comprehensive Electronic Records (OSCER) database (established by Amgen for observational research, today powered by Flatiron Health), which captures outpatient data for a representative sample of more than 569,000 cancer patients treated at 52 community- and hospital- affiliated oncology practices (565 clinics) from 2004 forward. The widespread adoption of EHR by community oncology practices makes this a valuable tool for observational studies in oncology. Specifically, EHR, which captures routine laboratory results (i.e., serum calcium and albumin values), were used to estimate the

⁷ Leong R et al, J Clin Oncol 33, 2015 (suppl; abstr 2574).

⁸ Khozin S et al, 2015. 21(11):2436-9.

⁹ Gastanaga VM et al, Cancer Medicine (in press) 2016. 51(13) : 1704B.

¹⁰ Basso U et al, Curr Med Chem. 201.

prevalence of HCM by tumor type (confirming findings in the literature) and grade, and describe trends over a recent time period (2009–2013) including the use of bone resorptive therapies (intravenous bisphosphonates [pamidronate and zoledronic acid] and denosumab). Additionally, EHR analyses also provided described renal impairment among patients with HCM, and survival for a subset of patients with vital status via external data linkage.

Indication Expansion (Vemurafenib) – On August 17, 2011, the FDA approved vemurafenib (Zelboraf) tablets for the treatment of patients with unresectable or metastatic melanoma with the BRAF^{V600E} mutation as detected by an FDA-approved test. The major efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free survival (PFS). While less common in NSCLC, BRAF mutations do make up between 1 and 3% of patients predominantly in adenocarcinoma with a history of smoking. A histology-independent phase 2 basket study observed vemurafenib activity in NSCLC.¹¹ Determining whether additional data on BRAF patients in NSCLC can be extracted from EHRs may help build the case for an expanded indication without the need to confirm through a traditional clinical trial.

Indeed, supplementing patients' data from the Basket trial with about 40-50 patients with data on real world response rate, duration of therapy, prior treatment, and safety may be sufficient describe patient responses in BRAF V600E Mutation-Positive NSCLC.

Confirmatory Studies (Crizotinib) – In August 2011, FDA granted accelerated approval to crizotinib (Xalkori) for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive. Full approval was contingent on the completion of two phase 3 randomized clinical studies in treatment-naïve (N=343) and in previously treated (N=347) ALK⁺ NSCLC. Full approval was granted November 2013, based upon PFS results from the trial in treatment-naïve patients. A sNDA label update for the second phase 3 study in previously treated patients was approved September 2015. In 2016, crizotinib received BTM for the ROS1-positive development program and the sNDA application for patients with ROS1-positive disease was granted Priority Review and received approval in March 2016.

In retrospect, and in the context of breakthrough activity of crizotinib in the selected patient population, would a RWE study have been appropriate as a confirmatory study for ALK⁺ NSCLC? Following crizotinib approval, a retrospective real world cohort study was conducted in the United States and Canada utilizing medical record review of 212 ALK⁺ NSCLC patients who initiated crizotinib as first or later line therapy¹² This study provided further information on crizotinib use and outcomes of patients and was supportive of the phase 3 clinical studies. For example, response rates seen in the real world cohort study (66% overall; 69% in first line and 60% in second or later line) were similar to the response rates seen in treatment-naïve patients (74%)¹³ and previously treated patients (65%)¹⁴ in the clinical studies. In the real world study, one-year survival rates in first-line patients (85%) from the real world chart review was also similar to the one-year survival rate seen in the clinical study of treatment-naïve patients (84%).¹⁵ These real world data provide support for the benefits of crizotinib in patients with ALK⁺ NSCLC and are in line with data previously reported in clinical studies.

Following the early phase results, could RWD supplement, or replace, traditional requirements for post-market commitments in future development programs? A better understanding of whether real world studies are able to confirm clinical trial results would lend credence to this idea. Ultimately, observations confirming clinical trial findings may provide opportunities for novel trial designs that incorporate real world evidence earlier into development.¹⁶

Pilot Studies

Building on the above examples, this work group considered opportunities for designing prospective pilot studies to assess the feasibility of using RWE to support regulatory decisions. The key goal of this exercise would be to test and validate data collection efforts and identify novel endpoints that correlate with clinical benefit and reflect correlations between clinical practice and trial settings. Possible approaches for developing a pilot study are captured below.

¹¹Hyman DM et al, NEJM. 2015.

¹²Davis KL et al, Presented at 16th World Conference on Lung Cancer, September 6-9, 2015; Denver, CO.

¹³Solomon B et al, NEJM. 2014. 371(23):2167-77.

¹⁴Shaw AT et al, NEJM. 2013. 368(25):2385-94.

¹⁵Solomon B et al, NEJM. 2014. 370(11):988-90.

¹⁶Koehler M et al, Ann Oncol. 2016. In print.

Immune checkpoint Inhibitors in tumors with high rates of mutational burden

Among various tumor types, melanoma and NSCLC patients have been the best responders to immunotherapies, possibly due to the number of somatic mutations present. Indeed, early studies point to an association between tumor mutational load and efficacy. For example, patients with high rates of microsatellite instability (MSI-high), a marker of defective mismatch repair mechanisms, have been observed to respond remarkably well to PD-1 and other immune checkpoint inhibitors. While most fully characterized in colorectal cancer (CRC), clinical reports in other gastrointestinal malignancies, and gynecological cancers among others are increasingly available. A recent report suggested that the objective response rate for the PD-1 inhibitor, pembrolizumab, in CRC was 40% when there was evidence of MSI-high (versus 0%) in patients with proficient mismatch repair. Additionally, 5 of the 7 non-CRC patients studied also responded to treatment.¹⁷ Studies evaluating the link between MSI-high and immune checkpoint blockade are already ongoing and there may be additional biomarkers of mutational burden to better identify responders including, quantifying mutational load or identifying mutations in other DNA repair proteins.

To date, studies have not shown that immune checkpoint inhibitors are safe and efficacious for widespread use in highly mutated tumors. Hence, the clinical rationale for prescribing PD-1 inhibitors for people with evidence of mutational burden, such as microsatellite instability, exists but is insufficient. Based on this rationale, a prospective study of currently approved PD-1 inhibitors in patients with highly mutated tumors, could be addressed in the real world setting.

Determining the feasibility of this pilot would initially require a retrospective analysis of existing databases (e.g., the Flatiron Health dataset plus targeted chart abstraction and linked claims data) to address outstanding questions, such as, testing patterns (i.e., timing, disease state, test type, etc.) and treatment patterns (including toxicities and observed outcomes) in cancers with evidence of mutational burden. Once all the necessary components are identified, building a prospective trial would depend on scoping (i.e., cancer type, study size, etc.), optimizing the biomarker and test use, and ultimately defining mechanisms to measure efficacy.

Proposals for RWE Applications

With numerous advantages to collecting RWD, ranging from supplementing post-market data collection, decreasing costs and development timelines, defining novel outcomes, and minimizing the number of patients exposed to a less efficacious therapy, this working group proposes utilizing RWD with the intent of answering specific clinical questions and, when appropriate, informing product labels, in the following areas,

1. Expanding the safety profiles of a therapeutic,
2. Identifying populations with enhanced benefit/risk for an already approved therapy to inform clinical practice,
3. Piloting studies to determine the potential correlation between feasible real world measures (i.e., time to treatment switching) and more traditional clinical trial endpoints (i.e., time to progression),
4. Building evidence for a supplemental package to expand the indication profile for a therapeutic,
5. Supporting efficacy results observed in clinical trial setting, particularly in areas of unmet medical need, when a new drug shows substantial clinical benefit. Real world studies that are able to support the preliminary magnitude of effectiveness in a larger cohort may be sufficient to serve as post-market confirmation of clinical benefit.

These proposals are intended to guide developers in considering RWD collection during drug development; however, careful consideration and discussions with regulatory agencies will be needed in order to account for any observed outcomes, such as loss of efficacy, within RWD.

¹⁷ Le DT et al, NEJM; 2015. 372(26):2509-20.

Appendix A: Detailed outline for the Ramucirumab case study

Clinical questions to be addressed utilizing RWE	<p>The objectives of this study are to describe patient characteristics, safety and mortality in patients with advanced NSCLC receiving treatment with ramucirumab plus docetaxel (R/D) as well as a PD-1 inhibitor (PD-1) in any sequence. Included patients will be those who received the R/D in any treatment setting as well as a PD-1.</p> <p>Key questions include:</p> <ul style="list-style-type: none"> • What are the demographic, clinical and treatment characteristics for the cohort? <ul style="list-style-type: none"> ○ Demographics: age; gender; race ○ Clinical characteristics: smoking status; ECOG performance status; stage at diagnosis; biomarker status (EGFR; ALK; ROS1; PD-L1; KRAS) time between diagnosis and advanced disease; histology ○ Treatment history: use of systemic and targeted therapies ○ Reimbursement: insurance status • What is the treatment sequencing of R/D, PD-1 and other therapies in this population? • What outcomes are observed when R/D precedes PD-1 vs comes after PD-1? <ul style="list-style-type: none"> ○ What OS is observed?¹⁸ ○ What safety events are observed?¹⁹ <p><i>Proposed Milestones</i></p> <ol style="list-style-type: none"> 1. Feasibility, scoping and study design, presented at the 6/16/2016 Friends/Alexandria Summit meeting on RWE (intention is to present high-level study scope and design) 2. Full analysis and report once the data matures 3. Potential labeling updates based on the outcomes of the study
Included data sources	<p>In order to address these questions, we plan to leverage RWD and specifically EHR data. The proposed data source is the Flatiron dataset, which comprises longitudinal, patient-level EHR data. The Flatiron dataset incorporates the data from both structured and unstructured EHR data streams. For unstructured sources in particular (e.g., physician notes, pathology reports, etc.), Flatiron uses technology-enabled abstraction to curate data points at scale. This enables Flatiron to consistently and accurately pull some of the most elusive clinical details out of the EHR. Each patient record passes through the technology-enabled process, with human review of each data element collected to confirm patient information (such as demographics, diagnosis, stage, histology, etc.). This abstracted information is often missing and/or inaccurate if relying on the structured EHR fields alone. By combining the processed structured and unstructured data, Flatiron can create a longitudinal view of each patient, tracking key events, interactions, and therapies over time. Flatiron's EHR dataset is already annotated with mortality data; No additional linkages are needed to add these variables. The mortality variable represents an amalgamation of internal and external data sources to represent the best understanding of a patient's vital status and date of death. Data is sourced from the EHR as well as obituaries, funeral homes, and other sources. No other data sources are needed, based upon the current scope of the research questions. If needed, the Flatiron EHR data can be linked to healthcare claims data of other sources.</p>
Data merging processes and challenges	<p>Data linkage is not necessary in order to accomplish this project, but would be doable if needed. Flatiron retains the underlying patient identifiers (in a HIPAA-approved manner), and can link directly to external data sources. Because Flatiron maintains access to the patient identifiers required to link patient-level data to external data sources, Flatiron must take extra precautions to ensure linking occurs in a de-identified manner. Flatiron works with a third party de-identification expert to oversee the linking process and confirm that all linked data is certified as de-identified.</p>
Variables needed to address clinical questions	<p>Flatiron will abstract the data variables included in the data model listed below to support the key research objectives. As noted above, Flatiron processes both structured data (i.e., data points that are organized in a predefined manner, such as dropdown fields) and unstructured data (e.g., free text from a physician note or a scanned pathology report). Together, these patient-level data provide a complete view of each patient with resolution at the indication, testing and treatment level.</p>

¹⁸ Since the potential follow up time for PD1 inhibitor therapy is shorter overall, it is likely necessary to restrict the cohort to people receiving therapy for metastatic NSCLC after the date of first approval of PD1 inhibitors in lung cancer in order to reduce bias.

¹⁹ Exact safety events to be confirmed prior to study initiation

Structured and unstructured data variables	<p>Preliminary data model to be confirmed upon formal study scoping with Lilly:</p> <p>Structured Data:</p> <ul style="list-style-type: none"> • Demographics (to be determined based on de-identification requirements) • Diagnosis (ICD9 codes, ICD10 codes and dates) • Visits (date and type) • Labs (test date, result date, test name, result with units, and normal ranges) • Medication Administration (date, drug, dose and units) • Medication Orders (date, drug, dose and units, route) • Insurance • Performance Status (ECOG) <p>Unstructured Data:</p> <ul style="list-style-type: none"> • Date of initial diagnosis • Date of diagnosis of advanced disease: first recurrence or metastasis • Group stage at time of initial diagnosis • Documented history of smoking • Biomarker status: EGFR, ALK, PDL1, KRAS, ROS1 (including testing status, test result, and test date) • Safety events (specific events to be defined in collaboration with Lilly) <p>Derived Data Elements (combine structured & unstructured data elements using clinician-defined business rules):</p> <ul style="list-style-type: none"> • Lines of therapy • Mortality
Challenges/considerations with regard to consistent/reproducible variable extraction process	<p>Flatiron maintains robust QA/QC records to support data credibility and provenance requirements for RWE use cases. Documentation includes:</p> <ul style="list-style-type: none"> • Cohort selection criteria • Overview of the source data, including completeness, inter-abstractor agreement, and kappas for each structured and unstructured variable • Analytic notes • Business rules used to develop each derived variable, including an audit trail of changes <p>Specific data provenance initiatives include, but are not limited to:</p> <ul style="list-style-type: none"> • Fulfillment of HIPAA certification requirements • Secure HiTrust certification • Data freeze and retention processes <p>Flatiron also maintains internal QA/QC processes. For enhanced data captured by Flatiron abstractors from unstructured fields, in particular, Flatiron has developed multiple tools to monitor and measure quality. All Flatiron Health data abstractors are experienced oncology nurses, clinical research associates, or trained tumor registrars and continuous quality monitoring governs the abstraction process. Abstractor reliability scores, designated by kappas, are required to remain within a defined range (specific to the diagnosis and data model for each module) during both initial training and ongoing quality assurance (QA) checks. Furthermore, initial training and testing is conducted on actual EHR records against “gold standard” outputs (as defined by our internal oncologists) to ensure abstractor comprehension of specified data points and policies and procedures prior to initiating “live” abstraction on a set of tasks. Data elements are duplicate abstracted at the start of each new module to confirm agreement and ensure consistency of variable collection. The quality of each variable is monitored on an ongoing basis and medical outliers or edge cases are escalated via a “Review Panel” for adjudication by our Abstraction team leads, QA specialists, and/or medical oncologists.</p>
Endpoints to be defined and associated challenges	<p>Surrogate endpoints are not planned. This study will look at OS and safety. Specific safety events will be defined and scoped in collaboration with Lilly. Flatiron will abstract safety events as documented by the physician in the underlying chart. While Flatiron will be able to provide details around specific safety events that are recorded in the chart, visibility into specificity or severity of each event is sometimes limited. Flatiron has found that physicians typically do not systematically document grading in the chart in the real world; though where available, Flatiron would collect this information. Depending on the specific safety event, Flatiron can collaborate with Lilly to develop proxies for grading based on lab values that are in the structured data.</p> <p>As part of the development process, Flatiron plans to build a quality validation plan in order to assess the quality of the abstracted safety events. This plan will be developed collaboratively with Lilly and/or other key</p>

	stakeholders in order to ensure that the resulting data represent a robust endpoint to support this research question.
Collection of patient level RWD	<p>As of January 31, 2016, we have approximately 80-90 patients in the Flatiron dataset that generally meet the criteria for the study population. Since ramucirumab and PD-1 inhibitors were fairly recently approved, we anticipate that the use of these drugs will increase quickly over time as clinicians become more familiar with them and patients receive successive lines of therapy (e.g., 2nd line and beyond). We are seeing new ramucirumab patients added to our advanced NSCLC dataset at a rate of approximately 10-20 patients per month; New PD-1 patients are being added to our dataset at a rate of approximately 200 per month. Further, we anticipate that time will be needed for safety and survival outcomes to accrue with the population; A minimum of 6 months median follow up is likely needed.</p> <p>Based upon the above, we anticipate that the sample size available for review at a June meeting with Friends of Cancer Research (<i>Friends</i>) is a cohort of approximately 100 patients. Maturing of the dataset beyond June will add patients and longitudinal safety + outcomes data. The exact timeline and implications for sample size will be determined collaboratively with Lilly based upon review of the initial cohort and projections. Upon delivery of the dataset, Flatiron will provide full documentation of data completeness.</p>
HIPPA/informed consent issues, regarding submission of patient level data to regulatory agencies and auditing of individual data. What new processes/policy changes need to be in place?	<p>Deidentified patient level data can be used for this purpose without patient level consent. Flatiron partners with oncology care providers through several software products, in aggregate referred to as OncologyCloud™. Flatiron executes Business Associate Agreements (BAAs) with every cancer specialist using these software products thereby allowing Flatiron to pull a copy of the patient medical record into a central repository for data processing under the TPO exemption of HIPAA. Structured and unstructured data processing renders the main dataset, which is then deidentified and stored separately for secondary research purposes. Flatiron maintains the full patient chart for each patient in Flatiron's network, enabling an adaptive data model and the ability to conduct supplemental abstraction to support studies at any point in time. The Flatiron data repository, data processing approach, and approach to retrospective research is described in a protocol approved by the New England IRB.</p> <p>Flatiron maintains full documentation of the data abstraction processes and quality metrics (as described above), allowing for audits should the need arise. Individual data can be submitted to regulatory agencies (assuming deidentification requirements are met).</p>

Appendix B: Glossary of Terms. The following terms, while still evolving, have defined for the purposes of this white paper here.

Breakthrough Therapy Designation (BTD) - Created in 2012, as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) and intended to: 1. treat a serious or life threatening disease or condition and 2. preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

Electronic Health Records (EHRs) - A digital version of a paper chart that contains all of a patient's medical and clinical history throughout the patient's care and used by providers for diagnosis and treatment.

Pragmatic clinical trials (PCTs) - Are prospective randomized intervention studies that leverage the existing clinical infrastructure and are designed to test interventions in everyday clinical settings to maximize therapeutic applicability and generalizability.

Real World Data (RWD) - Data collected from sources outside of conventional randomized controlled trials – for example, from electronic systems used in health care delivery and to track patient experience with care – are commonly referred to as real-world data

Real World Evidence (RWE) - Evidence derived from the use, benefits and risks of medicines that fall outside the bounds of the classic clinical trial settings, including use of data that is routinely collected in the daily practice of medicine, and thus reflective of the heterogeneous patients seen in real world practice settings.

Examining the Feasibility of Real World Evidence Through Pilot Studies

Conference White Paper

Friends of Cancer Research Annual Meeting

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Summary

Technological advances in data capture are raising the potential that information collected as part of broad care delivery can be used to support the observed clinical benefit of a new drug and supplement post-marketing commitments or label claims for additional indications in rare cancers, where few treatment options exist.

Introduction

Traditional evidence generation for the development of new treatments follows well-established pathways beginning with defining safety profiles, establishing initial efficacy, and expanding to pivotal trials to support regulatory approval. Often pivotal trials rely on randomized controlled clinical trials (RCTs) that provide the most reliable information, through comprehensive designs to control for most sources of bias, regarding the effects of therapeutic interventions. In recent years, biomedical advances have facilitated broader use of alternative evidence collection models, including non-randomized approaches, where RCTs may not be feasible or ethical.¹

While providing mechanisms to comprehensively address the safety and efficacy of novel therapies, these traditional approaches to evidence generation only provide information of relatively homogeneous populations found in clinical trials and needed for regulatory approval, yet, leave many questions unanswered regarding drug effectiveness, tolerability, and treatment heterogeneity in real-world populations. While many new drugs continue to be monitored through systemic post-market evaluation to address certain practical aspects of drug applications, the systemic monitoring of clinical practice has yet to be more broadly applied to other stages of drug development, particularly in oncology.

Additionally, new scientific advancements in drug development have led to the increase in molecularly targeted therapies, which target “subgroups of patients (within the larger population with a given disease) who are predicted to benefit from them.”² The increased specificity and potential for substantially greater benefits over other therapies provide great promise, but also may lead to tension between the regulatory requirements and development resources, including ethics, time, costs, and patients. The Breakthrough Therapy Designation (BTID) program, for example, seek to mitigate some of these tensions by expediting the clinical development of drugs that are intended to treat serious and life-threatening diseases and for which preliminary clinical data indicate that the drug may provide a substantial benefit over available therapies, while minimizing valuable resources. While BTID and Accelerated Approval programs have contributed to the expedited development of many novel therapies, they rely on the need to expand the safety profile and confirm clinical benefit of the drug in other disease settings and/or in the post-market setting.

Real-World Evidence

The growing use of electronic health records (EHRs) have facilitated collection of patient data outside of clinical trial settings, and hold potential to further inform patient care, supplement current clinical trial methodologies, and speed drug development; in general, EHR-derived clinical data, which is a comprehensive collection of a patient’s medical and clinical history, is referred to as “real world data” (RWD). EHRs, along with numerous other data sources including, randomized trial supplements, pragmatic trials, patient registries, administrative claims, surveys, pre-approval access programs, and mobile health-generated data (e.g., smartphones, wearables, social media) all contribute to the broader concept of Real-World Evidence (RWE), referring to evidence generated from data collected outside the traditional clinical trial setting including use of data that is routinely collected in the daily practice of

¹ The role of Non-Randomized Trials for the Evaluation of Oncology Drugs. November 2014.

<http://www.focr.org/sites/default/files/pdf/Non-Randomized%2BTrials.pdf>

² Sherman RE, Li J, Shapley S, Robb M, and Janet Woodcock. Expediting Drug Development—The FDA’s New “Breakthrough Therapy” Designation, NEJM. 2013. 369:1877–1880.

medicine, and thus reflective of the heterogeneous patients seen in real world practice. RWE may better reflect the general population and the care they receive, given that enrollment in clinical trials is often limited to patients with specific baseline characteristics. Therefore, high quality RWE can potentially enable a more generalizable estimate of the safety and effectiveness of therapies than well-controlled clinical trials with narrow eligibility criteria.

RWE may be particularly useful in the case of a drug with a large effect size, such as a BTD, where confidence in the original efficacy data is relatively high. While concerns regarding data quality, owing to factors such as missing information and non-systematic data collection, are substantial, information gathered from EHRs holds the promise of allowing data to be collected on more patients and more rapidly than traditional phase 4 trials, or phase 2/3 trials designed to provide evidence for new indications. Thus, in cases of transformative treatments, the question under what conditions would it be feasible to confirm clinical benefit in new indications in the real world setting and use this evidence to support new label claim, warrants serious consideration.

Real-World Evidence Applications

There are numerous uses and advantages to collecting RWD and applying it as a source of RWE to extend our understanding of the safety and effectiveness of a therapeutic.³ The challenge for studies utilizing RWE, will be to balance the need to ease access to new promising therapies and at the same time provide strong convincing evidence of clinical benefit.

Thus, an opportunity exists to outline approaches and considerations for developing and testing pilot studies that aid in determining the feasibility of collecting and using RWE to provide strong clinical evidence to support regulatory decisions. Pilot projects have opportunities to 1) test data collection systems and identify reliable sources of RWD, 2) assess the feasibility and utility of real-world data, 3) identify novel endpoints that correlate with clinical benefit and reflect correlations between clinical practice and trial settings, and 4) determine other study criterion, such as biomarkers and study size, important for meeting study objectives. Ultimately, such studies can inform regulatory practices, including identifying criterion for label expansion, and improving our understanding of drug performance and clinical trial generalizability.

Exploring RWE Collection: Hypothetical Case Studies

We explore three potential uses for RWE using a hypothetical scenario. In this scenario, the original approval of “Therapy A” was based on a single arm study, which displayed activity similar to a Breakthrough-like product. The drug received either full approval in an indication with a small overall patient population or accelerated approval that was later converted to full approval based on a randomized study in a less sick population. The drug has been available on the market for 1+ years and additional data, including phase 4, investigator initiated studies and RWD, confirms the positive risk/benefit in the approved indication.

Based on this scenario, three case studies are considered below for using RWD could be used to support and expand the safety and efficacy dataset for hypothetical Therapy A. The goal of these approaches is to learn about the utility of collecting real-world data in the specific cases described and determine if the generated evidence that meets a pre-specified data quality standard, could support a label claim for an additional indication or an update to the label considering dosage and/or schedule of approved treatment regimen. Thus, each approach requires a discussion, between the sponsor/investigator and the FDA around determining the appropriate standard for collecting real-world data, which may include observational data, as well as best approaches for combining data from multiple

³ Blueprint for Breakthrough: Exploring the Utility of Real World Evidence (RWE). June 2016. <http://www.focr.org/sites/default/files/pdf/RWE%20-%20Project%20PRE-MEETING%20DRAFT.pdf>

sources, determining the appropriate study sample size, analysis approaches, and data quality expectations.

1. Prospectively-defined collection and review of patient experiences on off-label use (i.e., observational data) for approved agents.

Application: Early phase 1 trials and evidence from a "basket" phase 4 trials, based on 10-15 treated patients, indicates the Therapy A maybe very active in a rare cancer, where no other treatment options are available. To gain access to this drug (off-label), the sponsor requests a meeting with the FDA to review and discuss existing evidence and the ability to collect observational data to supplement the existing limited data obtained in clinical trials.

Determining the feasibility of using observational data as the basis to update the label of Therapy A, will depend on an agreement around the assurance of data quality and necessary documentation, the necessity of conducting an observational study over a traditional single-arm approach, and the ability to define and meet study objectives.

Based on the feedback received, the sponsor conducts analyses using the most relevant endpoints (e.g., physician defined response, time on current therapy, compared to time on previous therapy and/or decrease of pain medication use on current therapy, compared to previous 6 months). If significant activity is observed, sponsors may consider requesting a FDA meeting to discuss the submission of reports and data.

2. Phase 2 randomized trial approach to assess or confirm a robust response rate and continue long-term follow-up in the real-world setting.

Application: In a narrow disease setting, patients have limited treatment options once they exhaust the 3-4 available therapies resulting in unfavorable outcomes. A strong scientific rationale exists that Therapy A could be active in a specific indication (e.g., biomarker defined). A detailed assessment of the activity of Therapy A could be done using a relatively small, approximately 60-80 patients, randomized (2:1) phase 2 study of Therapy A vs. physician's choice. If the patients on Therapy A experience significant response compared to patients on the control arm, who are progressing rapidly, then crossover at the time of progression would be allowed.

Concurrent to the phase 2 study, an observational data collection strategy for the same indication, matching patients on a set of pre-specified baseline characteristics and number of prior therapies, could be employed. The collection of observational data could also be used as a control arm to the phase 2 trial to assess and compare longer-term outcomes (e.g., time on the most current therapy, and even overall survival). The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study design.

3. Pragmatic randomized trial approach leveraging existing clinical infrastructure to test interventions in everyday clinical settings.

Application: Following initial approval of Therapy A, additional clinical experience suggests that a lower dose given more frequently could be just as efficacious and possibly safer than the original dose studied and included in the product label.

Efficacy and safety of the new dose could be assessed by conducting a non-inferiority pragmatic randomized study comparing the two treatment regimens. Following randomization, the data for the study (including patient characteristics, treatment, and outcomes) could be obtained from electronic health records. The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study

design. This approach would allow for assessment of feasibility of both obtaining consent and randomizing patients at sites beyond those typically conducting randomized controlled trials. Given the pre-specified criteria are met, the generated evidence could be used to update the label with information on the new regimen.

The success of these three approaches depends on a rigorous assessment of outcomes within the RWD setting. The assessment process needs to assure reliability, consistency and validity of the outcomes. It maybe also be required that real world data outcomes in the original indication are consistent with the results from the clinical trials in the original indication.

While not captured in the above approaches, RWD collection for Therapy A post-approval may additionally provide information on the safety profile of the drug including: dose interruptions, dose modifications, concomitant medications, additional toxicity and other adverse events, therapy duration, and may contribute to the enhanced evaluation of an appropriate dose of the drug in the post-market setting. Thus, data around patient characteristics, safety, and mortality in patients receiving treatment with Therapy A, in any treatment setting using even a limited patient pool that meet the criteria of the study population, may facilitate determination of appropriate treatment safety, dosing, and sequencing.

Real-World Evidence Considerations

Each approach will require additional considerations and questions to be addressed to determine the appropriate study mechanism. These are summarized in the below table.

Considerations	Questions
Disease setting	<ul style="list-style-type: none"> • Is randomization feasible? • Should rarity be a factor? • Could study enrollment and completion be effected (i.e., inability to accrue patients)?
Efficacy experience	<ul style="list-style-type: none"> • What efficacy data is available? • Is it consistent with a BTID? • Does preliminary information on the activity of the BTID in this specific indication exist?
Safety profile	<ul style="list-style-type: none"> • Is there a well-described safety profile on this therapy? • Are adverse events well described? • Has appropriate dosing and sequencing been determined?
Existing treatment options	<ul style="list-style-type: none"> • Could these serve as a control? • Could alternative treatment options effect study accrual or analysis?
Study outcomes	<ul style="list-style-type: none"> • Which outcomes are appropriate for the study? <ul style="list-style-type: none"> ○ Physician assessed response rate ○ Duration of physician assessed response ○ Decrease in pain medication use as compared to patients previous 6 – 8 months ○ Decrease in medication use to control other disease specific symptoms ○ Duration on previous anti-tumor therapy as compared to duration on the most recent breakthrough therapy ○ Time to switch in therapy (versus control) ○ Overall Survival (versus control) ○ Physician assessed PFS (versus control)
Sample size	<ul style="list-style-type: none"> • What data is already available? • What is the expected sample size, based on factors such as response rate?

Feasibility	<ul style="list-style-type: none"> • Given the above, is the study feasible? <ul style="list-style-type: none"> ○ Can it be enrolled considering disease rarity? ○ What will it take to complete the study (time and resources)? ○ Will control patients agree to be part of this study, or will they look for other treatment options? ○ Where appropriate, is crossover possible? How will the point of cross-over be determined?
Data collection and use	<ul style="list-style-type: none"> • What approaches can be used to minimize bias? <ul style="list-style-type: none"> ○ Data is collected from multiple medical institutions with varying standard practice ○ Gather data for same indication for patients treated with any other therapy as a control arm • Can patient level data be submitted to FDA? • What documentation is available for these data and can any of the source documents be audited?
Benefit/Risk	<ul style="list-style-type: none"> • What are the benefits of this approach compared to other approaches? • Under what conditions would it be preferable to other approaches for labeling claims, i.e., additional indications for BTID? • Are there any legal ethical concerns with the approach? i.e., off-label promotion? • How can the risks for sponsors and the FDA be mitigated? • Can a clinical trial, or pragmatic trial be initiated in the same indication, but in earlier lines of therapy? • Are there conditions under which this approach would be able to support label claim for an additional indication for BTID? <ul style="list-style-type: none"> ○ Outside BTID? ○ Under-represented groups? (e.g. patients with brain metastases, leptomeningeal carcinomatosis) ○ Biomarker selected studies (e.g. selection based on liquid biopsy rather than tissue testing)?

Conclusions

As real-world evidence is increasingly used to support drug development, more research, collaboration, and transparency is needed to improve data capture, quality, and analytics. Already advancements in data capture have expanded opportunities to better incorporate patient experiences and outcomes from routine clinical care into a range of drug development processes that can improve evidence quality used to support decision making. Additional efforts, including legislative proposals and Prescription Drug User Fee Act VI (PDUFA)⁴ negotiations have highlighted these issues as a priority.

The first step in realizing the numerous opportunities offered by real-world data, will be to begin testing the ability of such data to address outstanding questions in drug development. This work group considered possible approaches for designing prospective pilot studies to assess the ability of using RWE to support regulatory decisions. The three approaches outlined above for developing pilot studies are intended guide developers in considering broader data collection to inform the totality of evidence during drug development; however, careful consideration and discussions between sponsors and regulatory agencies will be needed including an agreed upon pre-specified approach, data standards, and considerations that account for any observed outcomes, such as loss of efficacy, within the real-world.

⁴ PDUFA VI Commitment Letter

<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>

About *Friends****PARTNERSHIPS* SCIENCE SOLUTIONS**

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients.

THE POWER OF COLLABORATION

During the past 20-plus years, Friends of Cancer Research (*Friends*) has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible. We've been successful due to our ability to convene the right people at the right time and put forth revolutionary, yet realistic ideas. We are energized now more than ever to continue this critical work with our trusted partners, creating innovative solutions to overcome barriers standing in the way of conquering cancer. Below are highlights of our collaborations and active initiatives.

BREAKTHROUGH THERAPY: A *PATHWAY THAT REWARDS INNOVATION*

When new drugs aimed to treat serious and life-threatening conditions show unprecedented effect in early clinical testing, patients shouldn't have to wait to receive treatment. To address this complex problem, *Friends* worked with partners in advocacy, regulation, drug development, and bipartisan Congressional champions to take the Breakthrough Therapy Designation from an innovative concept, to scientific whitepaper, to federal law in just 13 months. This resulted in the passage of an expedited FDA development program that ensures patient access to revolutionary drugs as quickly and effectively as possible.

- The concept was initiated at our Annual Meeting, with an expert working group which proposed strategies to expedite FDA approval of exceptional drugs intended to treat a serious or life-threatening disease and preliminary clinical evidence suggests it provides a substantial improvement over existing therapies, without sacrificing safety and efficacy standards.
- The program has seen upwards of 450 requests, over 150 designations with more than 50 of those drugs now approved.

LUNG-MAP: A REVOLUTIONARY PRECISION MEDICINE CLINICAL TRIAL DESIGN

Taking a new drug from the initial discovery stage through clinical testing and regulatory review is complicated, expensive, and often inefficient. This is compounded by the fact that trials for new drugs are almost always conducted separately, even when multiple drugs are being developed to treat the same condition. To address these hurdles, *Friends* developed a first-of-its kind collaborative clinical trial.

- The approach, first discussed at our Annual Meeting, is a multi-stakeholder partnership with leadership from the FDA, NCI, Foundation for the NIH, research institutions, patient advocacy groups, and industry collaborating together to develop a new and more efficient protocol for how future clinical trials could be conducted.
- The trial, a biomarker driven multi-drug study in squamous cell non-small cell lung cancer launched in June 2014, now enrolls over 1,000 patients and is open at more than 700 sites across the U.S. with 5 pharmaceutical companies collaborating on a single trial.

CREATING A BLUEPRINT FOR DRUG/DIAGNOSTIC CO-DEVELOPMENT

While cutting-edge drugs have access to special FDA pathways and approval mechanisms, the addition of companion diagnostics that enable their use can complicate the regulatory process. Through our annual “Blueprint” forum, we develop innovative solutions and approaches to address the challenges of drug/diagnostic co-development. Major outcomes of this forum include:

- Identify ways to overcome the challenges associated with biomarker development;
- Facilitate optimal development of diagnostics with breakthrough therapies;
- Develop a regulatory framework for next-generation sequencing as a companion diagnostic;
- Develop standardized approach to increase utilization and sharing of large-scale genetic databases

THE FUTURE OF TREATING CANCER: IMMUNOTHERAPIES

Friends is working to further the field of immuno-oncology through the development of a Policy Advisory Group consisting of a small, but representative group of scientific, clinical, patient, policy, and industry thought leaders. These thought leaders will shape a multi-stakeholder process to pave the way for this exciting new science. In April of 2016, *Friends* became a launch partner of The Parker Institute for Cancer Immunotherapy, with *Friends’* Chair, Ellen Sigal, serving on the institute’s advisory committee.

PATIENT & ADVOCATE REGULATORY EDUCATION

Patient input in the regulatory process is a vital part of the evaluation and approval of new therapies. The FDA structure and process for potential new therapies is complicated and not commonly understood. To best equip advocates to engage with researchers, regulators, and scientists, *Friends* is developing an online-based advocacy education and training program. This will provide a strong foundation of knowledge and act as a venue to connect patients with opportunities to impact drug development.

POLICY PRIORITIES

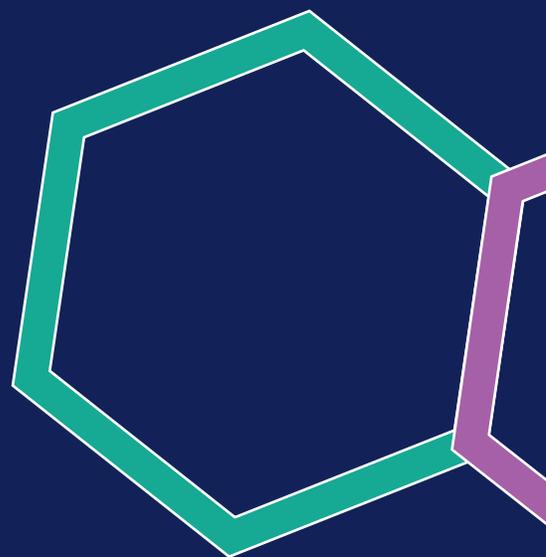
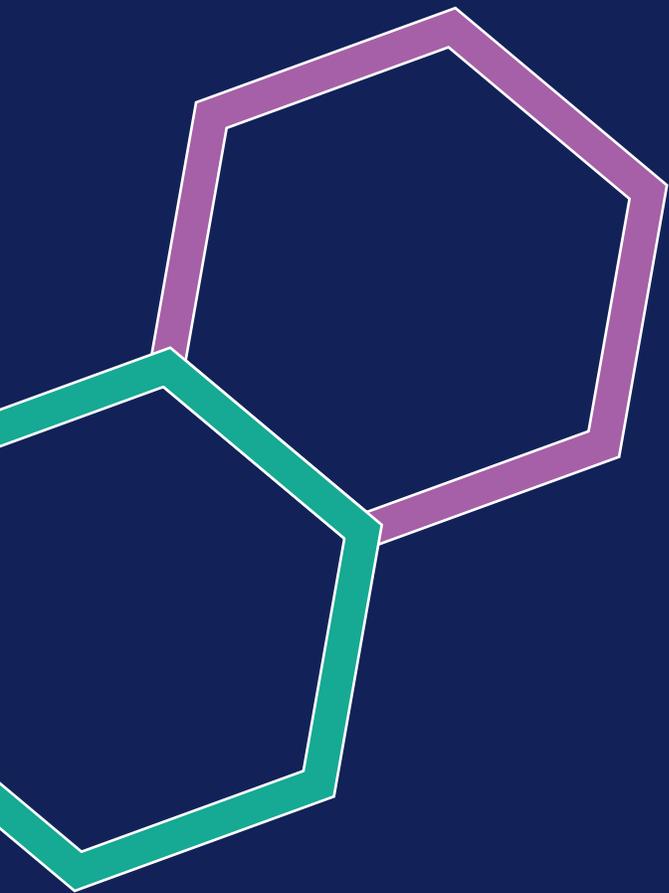
21ST CENTURY POLICIES FOR 21ST CENTURY SCIENCE & INNOVATION

- *Friends* was a primary driver of one of the most significant health-related legislative actions of Congress, the 21st Century Cures Act. The Act passed the House on November 30th by a vote of 392-26 and the Senate by a vote of 94-5, shortly before President Obama signed it into law on December 13, 2016.
- *Friends* developed key sections of the bill that represent substantive changes that will improve outcomes for patients. These sections focus on: creating a framework for patient-focused drug development, improving tools to evaluate and advance precision medicine, expanding FDA flexibility, and enhancing the ability for the agency to attract the best and brightest talent.

CENTERS OF EXCELLENCE: CROSS-CENTER COORDINATION AT THE FDA TO REFLECT CURRENT PATIENT CARE

Congress has not modernized FDA's organizational structure for medical products since the 1970s. The existing regulatory framework has been defined by a "divide and conquer" approach to oversight; separate centers within FDA regulate three major categories of medical products: drugs, devices, and biologics. In order to take advantage of today's advancements in science, drug development, and patient treatment, the FDA's structure needs reorganization to focus its resources and ensure the best outcomes for patients.

- *Friends* put forth a proposal to enhance coordination at the FDA based on specific diseases to reflect 21st Century science and modern medical care.
- Centers of Excellence will build on previous efforts to develop a more disease-oriented approach to product regulation that have demonstrated the positive effect of this type of organizational structure. They will also allow the agency to develop regular cross-center processes to align with and support employee motivation for regulating and delivering safe and effective medical products to treat major diseases.
- Our proposal was adopted by the White House as part of Vice President Biden's National Cancer Moonshot Initiative, and was included in the 21st Century Cures Act, which was recently signed into law.



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