On Tuesday, April 2, 2013, the National Comprehensive Cancer Network® (NCCN®) held the *NCCN Oncology Policy Summit: Evolving Policy Issues in Oncology – Revisiting Biosimilars and Molecular Testing* at the National Press Club in Washington, DC. Stakeholders gathered to examine how biosimilars and molecular testing in oncology, two topics addressed in 2011 by NCCN Work Groups and at NCCN Policy Summits, have changed. The Summit included discussion of the current status of these areas, review of the newest guidance documents and regulatory requirements, examination of payer viewpoints and practices, and discussion of where the oncology community is headed on these two important issues. The program, moderated by Clifford Goodman, PhD, of *The Lewin Group*, consisted of two short presentations and two roundtable discussions with vigorous discussion and audience participation.

Biosimilars

The morning session, focused on biosimilars, started with an overview of the milestones of biosimilars development from James Hoffman, PharmD, MS, BCPS, Medication Outcomes & Safety Officer, St. Jude Children's Research Hospital. In 2006, the first biosimilar was approved in Europe. While several legislative proposals were introduced from 2006 to 2008 in the United States, these efforts did not produce any tangible results. On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act, which contains a subtitle, "The Biologics Price Competition and Innovation Act of 2009" (BPCI Act), that establishes an abbreviated approval pathway for biological products that are demonstrated to be "highly similar" (biosimilars) to, or "interchangeable" with, an FDA-licensed biological product.[1] In February 2012, the FDA released its draft guidance on the development of biosimilars in the form of three separate guidance documents, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product", "Scientific Considerations in Demonstrating Similarity to a Reference Product", and "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." The introduction of biosimilars in the United States is of great interest to many different stakeholders as they have the potential to impact the cost of innovator biologics which accounted for 55% of cancer drug expenditures in 2011, totaling $157 billion.[2]

Dr. Hoffman reviewed key consensus statements, recommendations, and challenges identified by the NCCN Biosimilars Work Group in 2011 and highlighted areas of concern still surrounding biosimilars—safety, tracking, naming, substitution practices, and provider education. Dr. Hoffman also touched upon the role of state pharmacy boards and pending state laws regarding substitution of biosimilars. When biosimilars were first being considered, most stakeholders were thinking about them at the federal level and what legislation and guidance federal organizations would provide. Now the issue is very much

[1] Federal Register, Volume 75, No. 192, Tuesday, October 5, 2010, page 61497.
[2] Doloresco F, Fominaya C, Schumock GT, et al. Projecting Future Drug Expenditures – 2011. Am J Health Syst Pharm 2011;68:921-932.

coming to the state level with state legislatures starting to evaluate this issue and look at the substitution process that should occur with a biosimilar. They are specifically looking at the pharmacist's role in dispensing a biosimilar product and what communication should occur to a patient, the prescribing physician, and other stakeholders.

The introductory presentation was followed by a roundtable discussion moderated by Dr. Goodman. Panelists, including Jeff Allen, PhD, Friends of Cancer Research; Stan Bukofzer, MB, BCh, MMed, Hospira; Leah Christl, PhD, US Food and Drug Administration (FDA); Dr. Hoffman; Richard Markus, MD, PhD, Amgen; Lee Newcomer, MD, MHA, UnitedHealthcare; Marjorie Shapiro, PhD, FDA; and Andrew Zelenetz, MD, PhD, Memorial Sloan-Kettering Cancer Center, discussed a variety of issues surrounding biosimilars development and clinical use.

With the potential exposure of patients to the same drug multiple times over a lifetime, the topics of interchangeability and substitution were discussed in great depth. There is at the moment no FDA guidance on interchangeability, but according to Dr. Christl, it is something the FDA is working to develop. Dr. Bukofzer commented that safety concerns around switching between biosimilars and innovator drugs should hold for switching between all biologics as there is inherent variability in both lots of an innovator drug and different innovator drugs that are used to treat the same indication.

While interchangeability is important, the FDA is currently focused on the demonstration of biosimilarity. Dr. Christl noted that, "For a biosimilar, you're not asking the biosimilar applicant to reprove safety and efficacy. You're asking them to demonstrate that the molecule that they have is highly similar analytically and has no clinically meaningful difference from that reference product they're comparing to." The FDA is encouraging sponsors to come in early with significant analytical data packages to support biosimilarity. It was suggested that the stronger the analytical studies the less need there will be for clinical studies, with the exception of pharmacokinetic (PK) and pharmacodynamic (PD) studies. This may seem counter-intuitive to many stakeholders like physicians that will want to see clinical studies before utilizing the biosimilar. In regards to clinical data and more specifically PK/PD data, it was suggested that PK/PD data will be needed for each indication for where a drug might be used because of differences in diseases and how a drug is metabolized in each disease state.

An audience question broached the subject of efficacy of biosimilars and how physicians could be sure of the efficacy of a biosimilar if only limited efficacy data are needed for FDA approval. Dr. Shapiro explained the obstacles biosimilar manufacturers have surpassed to get to the point of clinical use and questioned, "But basically if the foundation of that demonstration of similarity is really strong, then I come back to the question, why would you think it would behave differently?" Stakeholders will need to trust and put faith in the analytical data supplied to the FDA and the ability of the FDA to evaluate data packages. The ability to monitor effectiveness and track adverse events were concerns also raised by both panelists and audience members. It was explained that effectiveness data along with adverse events can be tracked through claims data and other data sources in order to further evaluate biosimilars once they have been approved. Dr. Markus explained that Amgen has a large safety group that does survey claims databases routinely to look for data on their own products.

The uptake and costs of biosimilars were also reviewed by the panel. In regards to acceptance and uptake, the panelists noted that safety, including immunogenicity, will be the first consideration, followed by cost. Dr. Hoffman noted that acceptance and use of some biosimilars like growth hormones will likely occur sooner because of their "simpler" nature and use in non life-threatening situations. The panelists also agreed that because the large majority of early biosimilars will primarily be used in hospitals and clinics, the uptake should be quicker than if they were distributed to patients at the local pharmacy level.

Dr. Newcomer noted that payers would welcome any intervention that lowers costs, including biosimilars. Payers have the potential to encourage the uptake of biosimilars by only reimbursing for the lower priced biosimilar or reimbursing it at the same rate as the innovator, despite its lower acquisition cost. The panelists debated the importance of a biosimilar being labeled interchangeable in order to see price competition and cost savings. Dr. Markus suggested that true price competition will come with having several high quality biosimilars to choose from that may or may not be deemed interchangeable. The question as to how many competitors are needed to see real cost savings went unanswered, however. Dr. Zelenetz shared a different opinion – "To me interchangeability is the greatest, simplest way to get to that cost savings because it goes out of the hand of the writing practitioner and into the hands of someone who actually does a better job of caring about costs and that's the pharmacist." Dr. Zelenetz was referring to the use of P & T Committees in hospitals and health systems that determine formularies and therapeutic interchange. If a P&T Committee decides a biosimilar is therapeutically equivalent, all prescriptions for the drug will be filled with the biosimilar. Dr. Newcomer expressed the opinion that if the FDA deems a biosimilar interchangeable, P&T Committees will spend little time debating the merits of the biosimilar and will make the switch on their formularies automatically. P&T Committees have strong influence at the organizational level and will be able to impact the uptake of biosimilars. In private practice, physicians are not governed by P&T Committees and will need to make their own decisions to utilize biosimilars. The uptake of biosimilars may be slower in the private practice setting, but specialty pharmacies have the ability to encourage and require the use of biosimilars outside the hospital setting.

Extrapolation and off-label use of biosimilars were discussed briefly by the group. The panelists agreed that biosimilars will be used off-label as most cancer drugs are and their use will be extrapolated across the indications that the originator is approved for. Dr. Christl commented, "It is incumbent on the sponsors to support extrapolation." Dr. Bukofzer stressed the importance of pharmacovigilance surveillance systems that can adequately pick up any issues that might occur in extrapolated or off-label uses as soon as possible.

The group considered how biosimilars will be labeled to indicate biosimilarity and interchangeability. The FDA has not yet decided how these items will be included on drug labels, although the present European model is to include this information on the label. In addition to labeling, the group discussed the use of the *Orange Book* to make therapeutic equivalence evaluations for chemical drugs. Dr. Christl acknowledged that an equivalent to the *Orange Book* may be needed in the future for biologics.

The roundtable concluded with panelists sharing their thoughts on what will ultimately lead to the comprehensive uptake of biosimilars. They agreed that clinical and practical experience, technological advances for characterizing biologics, education of providers and patients, and big data that support use and show any adverse events will be the factors that encourage the uptake of biosimilars and ultimately bring biosimilars to all stakeholders.

Molecular Testing

The afternoon portion of the Summit concentrated on molecular testing. Molecular testing in oncology serves many roles, including risk assessment, disease diagnosis and classification, prognostication, response prediction, toxicity prediction, and dose determination. As interest in personalized medicine continues to increase for stakeholders, including patients, providers, industry, and government organizations, there has been a steady increase in the development of molecular tests[3], with increasing interest in the development of LDTs and companion diagnostics, and the related search for clinically meaningful molecular biomarkers. Mark Kris, MD, Chief, Thoracic Oncology Service, Memorial Sloan-Kettering Cancer Center, started the session by explaining how the treatment of lung cancer has evolved and changed due to the advent of molecular testing. Dr. Kris reviewed types of biomarkers and the technological advances that have helped move the field along. He highlighted the role pathologists play in molecular testing. According to Dr. Kris, pathologists are the legal and moral guardians of tissue samples and they have the experience to catalog, store, analyze, prioritize and run molecular tests. Pathologists should lead the advancement of molecular testing while being supported by other physicians. Dr. Kris concluded with predictions of where the molecular testing field will be in 10 years. These predictions included, but were not limited to, more validated targets with available biomarkers and therapies, as well as more comprehensive, cheaper, and faster multiplex testing for all targets at diagnosis.

Pam Germain, MBA, Roswell Park Cancer Institute; Ellie Guardino, MD, PhD, Genentech; Lawrence Jennings, MD, PhD, College of American Pathologists; Dr. Kris; Elizabeth Mansfield, PhD, FDA; Doug Moeller, MD, McKesson Health Solutions; and Dr. Newcomer, participated in a follow-up roundtable discussion. The group reviewed the challenges for the broader integration of molecular testing into oncology practice, development of laboratory developed tests (LDTs), companion diagnostics, and coding and reimbursement of molecular testing.

The cancer community is moving from a one-size-fits-all practice to a much more personalized approach that utilizes molecular testing. Dr. Guardino discussed the huge upside of molecular testing for patients. Patients may receive more efficacious treatments and in turn have a better quality of life. Appropriate use of molecular testing can also make care more cost-effective for both patients and payors. Despite the advent of technology and molecular tests, a learning curve still exists for physicians and education is needed. Physicians need to understand what tests are available, when they should be used, who should receive the tests, how to interpret results, and how to measure the value, both clinically and financially.

[3]There are approximately 2,000 tests available, including oncology and non-oncology tests, with an estimated 1,000 new tests per year[3]

Technological advances have brought down the cost of sequencing the entire genome to approximately $3000 according to Dr. Moeller. While the cost per test is going down, the number of tests being run is going up. As the price goes down and more tests are run, lots of mutations can be tracked, but pathologists and physicians often do not know if, and what, the clinical significance of the mutation is. It was suggested that it is best to collect the information now and go back retrospectively and examine outcomes and mutations to find correlations. The group also discussed the varying impact of mutations on a single gene. Not all mutations are created "equal". Some may be pathogenic while other mutations on the same gene are benign.

Dr. Moeller explained that the complexity is not so much in the actual testing, but in the interpretation and reporting of results. Dr. Jennings expressed confidence in the laboratories conducting the testing as they are accredited and monitored through proficiency testing and laboratory inspections. Criteria for clinical laboratories include qualification of instruments, qualification of reagents, validation, and monitoring. The group examined the merits of the Clinical Laboratory Improvement Amendments (CLIA) and their effect on molecular testing. Dr. Mansfield stated that CLIA is really a minimum standard that measures the quality of laboratory operations and is not an overarching regulatory scheme for molecular testing. Several panelists agreed that CLIA was not meant to handle the complexity of testing we are seeing today. An additional complicating factor in molecular testing is the inherent heterogeneity in tumor samples. Heterogeneity can lead to incorrect typing of a tumor and is a complicating factor in determining treatment based on molecular testing results. This is an area that needs continuous consideration and improvement.

Dr. Goodman turned the discussion to the coverage, reimbursement and billing of molecular tests. Dr. Newcomer explained that he is looking for analytic validity, clinical validity, and clinical utility when considering whether to cover and reimburse for a molecular test. When pressed further, Dr. Newcomer said they will consider a molecular test in the same way as a new drug and consider the totality of the evidence. "You've got to have the evidence to show that the test actually does have value." Dr. Newcomer also expressed frustration over the coding system for molecular tests and shared an example. In his example there was a genome with 300 elements, but only 4 had evidence supporting their use. Dr. Newcomer pointed out they will only pay for the 4 proven elements and would need to figure out a fair price taking into consideration the cost-effectiveness of running the tests at the same time and the decreasing price of technology.

Ms. Germain explained that the stacked coding system is being phased out as CMS and the American Medical Association are introducing single CPT codes for molecular diagnostic tests. They have thus far introduced new codes for both oncology and other disease areas. Ms. Germain gave an example for EGFR – a single code will replace six different codes, some in multiples. The idea of these new codes is that a payer will actually know what test they are being billed for. Dr. Newcomer expressed some concerns with the new system still not being adequate. He explained that while a test for KRAS may have one code in this new system, there may still be a thousand different kinds of KRAS tests. "So it's still a KRAS test, but underneath that, there could be a lot of variation." This large variation in the methodology of tests also equates to a large variation in the cost of each test, with the payor still left unsure of how much to pay for the test.

To figure out appropriate reimbursement for these new codes relevant to oncology, Medicare asked for input from the 11 PPS-exempt cancer centers, but CMS decided as of January 13, 2013, they were not ready to publish a fee schedule. CMS determined that the Medicare Administrative Contractors (MACs) should create fee schedules around the country. Two MACs have developed fee schedules, but they are very different from each other. One is based on gap-filling methodology while the other is based on cross-walking. Neither model was endorsed by panelists.

Dr. Moeller discussed a collaboration between McKesson and the American Medical Association that will introduce Z-code identifiers for corresponding molecular pathology codes in the AMA's CPT code set. This collaboration is based on the McKesson Diagnostics Exchange that was created in conjunction with the Medicare Administrative Contractor Palmetto. Within the Exchange, 3,000 distinct tests have been registered and Dr. Moeller estimated there are currently more than 20 registered versions of KRAS and 14 versions of BRAF. Dr. Newcomer equated the Z-codes to NDC codes for pharmaceuticals – they can tell you who the manufacturer is, what processes were performed, the name of the test, and the analyte used. Connecting Z-Code Identifiers with CPT codes will provide payers with additional details about the tests they are paying for, more efficient contracting, and tracking of outcomes on specific tests.

Two audience comments focused on the pricing of molecular tests. One audience member questioned what private payers will do with the prices Medicare has set thus far as they do not seem to be well thought out or well-calculated. Dr. Newcomer explained that as a temporary fix, UnitedHealthcare based their reimbursement on the predominant regional contracts, but they would like to use Z-code identifiers and negotiate a price for each specific test. Another audience member shared concerns that the current pricing by various MACs is not transparent. Dr. Jennings shared that the College of American Pathologists submitted to CMS what they believed to be reasonable pricing, but they were largely ignored. The panelists agreed that a rational, transparent and fair reimbursement system for molecular testing is still needed.

The roundtable concluded with panelists sharing their thoughts and ideas on what will ultimately lead to molecular testing being part of mainstream oncology care. The panelists thought greater collaboration across stakeholder groups, greater amounts of clinical information and improved access to this information, a rational reimbursement strategy, greater knowledge transfer, appropriate infrastructure, and improved understanding of the biology of all kinds of cancer are the main factors that will bring molecular testing to the mainstream of oncology.