FDA Addresses Compounding at Outsourcing Facilities

In a statement released on March 23 by the U.S. Food and Drug Administration (FDA), FDA Commissioner Scott Gottlieb, MD, announced steps to implement elements of the Drug Quality and Security Act (DQSA) and section 503B of the Federal Food, Drug, and Cosmetic Act that are intended to limit bulk drug substances that can be used by outsourcing facilities in compounding. The FDA announcement accompanied the release of a policy document (draft guidance) that details the agency's intention to develop a list of bulk drug substances for which there is a clinical need (the 503B bulks list). The draft guidance was described as a part of a comprehensive policy framework. The document, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act," follows the January release of the agency's compounding policy priorities plan, which included a draft memorandum of understanding between the FDA and states.

Gottlieb reviewed the importance of compounding for patients with specific medical needs. "We're fully committed to implementing the DQSA requirements in a way that preserves access to compounded drugs for patients who have a medical need for them, while protecting patients from poor quality or otherwise unsafe compounded drugs that could cause them serious harm," he said.

The announcement noted that outsourcing facilities are subject to more stringent FDA oversight than traditional pharmacy compounders and can compound drugs in 1 of 2 ways: (1) the facility may start with an FDA-approved drug and alter it; or (2) the facility may start compounding from a bulk drug substance (usually when something about the appropriate FDA-approved drug product makes it inappropriate or unsafe for a specific patient or subset of patients). Gottlieb noted that the second approach is more complex and associated with higher risks of errors or contamination. He also noted that in some cases drugs compounded using bulk substances "can undermine the drug approval process by reducing the incentive for drug manufacturers to seek approval of brand or generic drugs."

Among the elements of the new guidance highlighted by Gottlieb were: (1) the FDA's intention to interpret the statutory language "bulk drug substances for which there is a clinical need" to mean a clinical need or reason for an outsourcing facility to compound a drug product using a bulk drug substance (instead of the FDA-approved drug as the source); and (2) factors proposed for use in evaluating relevant bulk drug substances.

"As the agency further refines what we intend our policies to be on this important topic, we know that stakeholders will, through the public comment process, bring competing concerns to our attention. We look forward to engaging stakeholders during this process," said Gottlieb.

U.S. Food and Drug Administration

New Research Framework for AD

A new framework designed to develop a biologically based definition of Alzheimer disease (AD) modeled on measurable changes in the brain was announced on April 10 by the National Institute on Aging (NIA) and the Alzheimer's Association. A description of the framework appeared on the same date in *Alzheimer's & Dementia*. In an associated NIA press release, the joint sponsors indicated their expectation that the framework would "facilitate better understanding of the disease process and the sequence of events that lead to cognitive impairment and dementia." The construct is envisioned as enabling researchers to study AD from its earliest biologic underpinnings to outward signs of memory loss and other clinical symptoms. The framework was the result of multiple consultations and investigations and will be updated as new knowledge becomes available.

The framework is relevant in clinical trials and may be used for observational and natural history studies as well. This "common language approach" may be helpful in harmonizing the ways in which different stages of AD are measured and validated, increasing comparability and confidence in cross-study data significance.

"In the context of continuing evolution of Alzheimer's research and technologies, the proposed research framework is a logical next step to help the scientific community advance in the fight against Alzheimer's," said NIA Director Richard J. Hodes, MD. "The more accurately we can characterize the specific disease process pathologically defined as Alzheimer's disease, the better our chances of intervening at any point in this continuum, from preventing Alzheimer's to delaying progression."

The research framework builds on the 3 stages (preclinical, mild cognitive impairment, and dementia) of AD originally adopted in NIA diagnostic guidelines in 2011 and enhances these with the addition of a biomarker-based disease continuum. The groups of biomarkers initially targeted are β-amyloid (A), tau (T), and neurodegeneration/neuronal injury (N). The framework incorporates these into 8 biomarker profiles and corresponding categories that could be used to group research patients: (1) A-T-(N)-, normal AD biomarkers; (2) A+T-(N)-, AD pathologic change; (3) A+T+(N)-, AD; (4) A+T+(N)+, AD; (5) A+T-(N)+, AD and suspected non-AD pathologic change; (6) A-T+(N)-, non-AD pathologic change; (7) A-T-(N)+, non-AD pathologic change; and (8) A-T+(N)+, non-AD pathologic change. These biomarker profiles can be grouped in 3 categories: normal AD biomarkers (1), AD continuum (2–5), and

non-AD pathologic change (6–8). The focus in this framework is on biomarker identification and pathologic processes that can be measured in vivo with imaging technologies and cerebral spinal fluid samples, also incorporating a grading system for cognitive impairment.

"We have to focus on biological or physical targets to zero in on potential treatments for Alzheimer's," said Eliezer Masliah, MD, director of the Division of Neuroscience at NIA. "By shifting the discussion to neuropathologic changes detected in biomarkers to define Alzheimer's, as we look at symptoms and the range of influences on development of Alzheimer's, I think we have a better shot at finding therapies, and sooner."

The creators emphasized that the framework is intended for research purposes only, requiring further testing before it could be considered for general clinical practice. The original article describing the framework is available at http://www.alzheimersanddementia.com/article/S1552-5260(18)30072-4/fulltext.

National Institute on Aging
Alzheimer's Association

Molecular Reclassification of DLBCL

In a new study, researchers identified genetic subtypes of diffuse large B-cell lymphoma (DLBCL) that could explain why patients with the disease do or do not respond to treatment. The study, led by researchers in the Center for Cancer Research (CCR) at the National Cancer Institute (NCI), with additional authors from several institutions around the world, was published online on April 11 ahead of print in *The New England Journal of Medicine*.

"These findings are the culmination of 2 decades of research at NCI and elsewhere, advancing our understanding of the effect of DNA mutations and gene expression on lymphoma biology and outcome," said NCI Director Ned Sharpless, MD. "This refined molecular classification will be instrumental in predicting prognosis and tailoring therapy for patients with DLBCL going forward."

For several years 2 major subgroups of DLBCL, arising from different cells of origin and with different patterns of gene activity, have guided research and treatment. Patients with activated B-cell–like (ABC) DLBCL have a much lower survival rate than those with germinal center B-cell–like (GCB) disease. In both groups, subsets of patients experience disease relapse after treatment. "The first question we wanted to tackle was whether there were other molecular features of the tumors that could help us explain why some people were well served by chemotherapy," said Louis M. Staudt, MD, PhD, of the NCI CCR, who led the new study. "And the second, related question was, if we could understand who was not responding well to treatment, could we understand the genetics of these tumors to suggest new potential therapies beyond chemotherapy? The answer to both questions was 'yes.'"

The investigators performed a multiplatform analysis of genomic alterations and gene expression on tumor samples from 574 patients with DLBCL. This analysis identified 4 prominent genetic subtypes that share a group of genetic aberrations. Patients with 2 of the subtypes (BN2 and EZB) respond well to treatment, whereas those with the other 2 (MCD and N1) do not. Some of these subtypes can be found in both ABC and GCB subgroups, so a patient could, for example, have ABC DLBCL, the gene expression profile with a lower survival rate, but the disease could also have the BN2 genetic subtype that responds well to chemotherapy.

"This shows we've gone beyond where we were," said Staudt. "Before, even with our most advanced molecular diagnosis, we would have said all ABC tumors are the 'bad' type and they need to be treated aggressively. Now we can implement this kind of classification and say that even if a patient has the 'bad' ABC type, they have the 'good' genetic type, BN2. So there's a much better chance of chemotherapy curing the disease."

Data from the study will be shared through NCI's Genomic Data Commons to make it available for future research. Although the new findings relate to current treatment, Dr. Staudt said he and his colleagues hope the new molecular classification will be used in clinical trials to provide evidence that may allow treatment to move away from chemotherapy toward more targeted therapies with fewer side effects. Research is already underway in this area. The results of a phase 2 clinical trial published in 2015, for example, demonstrated that patients with ABC DLBCL were more likely to respond to the targeted therapy drug ibrutinib than were those with GCB DLBCL. "The goal is to find the right drug for the right person at the right time," said Staudt. "And we feel this genetic understanding of diffuse lymphoma is a step forward in precision therapy."

National Cancer Institute