FDA Challenges Sponsors to Create New Approaches to Patient Experience Data

By Bill Myers

The FDA is challenging drug sponsors to come up with their own ideas for identifying and gathering the kind of patient experience data that can bring ordinary people closer to the clinical trial process without sacrificing safety or efficacy.

The agency, in a draft guidance released in late December, is encouraging sponsors to propose new draft guidances that focus on points in a treatment or device’s lifecycle that “could be particularly informed by” patient’s experiences.

Sponsors interested in doing so should think about whether they already have expertise in such areas as patient registries, natural history studies and work coordination between patient advocacy groups and trials officials or regulators, the 12-page guidance states.

According to the FDA, a draft guidance might be helpful if:

- There already is clinical guidance in a disease area, but it doesn’t address the needs of specific subpopulations;
- There’s a methodological guidance — such as adaptive trial designs — but sponsors still need specific ideas for how such methods can be applied to a specific disease or subpopulation; and
- If there seems to be a need for a diseasespecific guidance the FDA hasn’t addressed.

Developing such draft guidance is an important step, says Mark Summers, president of MedAvante-ProPhase, had the opportunity to bring ordinary people closer to the clinical trial experience data that can help sponsor with their ideas.

He FDA is challenging drug sponsors to come up with their own ideas for identifying and gathering the kind of patient experience data that can bring ordinary people closer to the clinical trial process without sacrificing safety or efficacy.

Unfortunately, we’ve seen challenges and opportunities in psychiatric trials.

In a recent conversation on the current psychiatric clinical trials environment, Mark Opler, MD, chief research officer at WCG-MedAvante-ProPhase, had the opportunity to gather insights from noted clinical psychiatrist and researcher Christoph Correll, MD. Dr. Correll’s work focuses on the identification, characterization and treatment of adults and youths with severe psychiatric disorders. His particular area of expertise is psychopharmacology.

Dr. Opler: Could you tell us what you see as the top three challenges in our current clinical trials environment?

Dr. Correll: Unfortunately, we’ve seen many programs look promising but ultimately fail. The transition from Phase II to Phase III has been particularly difficult, and we need to understand that better. We get signals in smaller trials that are suggestive, but once they go into large explanatory Phase III trials, the results are disappointing.

One of the related big problems is the rising and enormous placebo effect that has really inflated and undermined the signal-to-noise detection. In schizophrenia, over 45 years the placebo effect has increased by 12.2 points and the drug effect by 1.2 points. When you have more and more sites and more study arms, the placebo response increases; we really need to get that under control. Perhaps there is more expectation bias — and maybe some baseline inflation. We need to have methodology that can deal with that. I think that’s a major challenge.

Dr. Opler: For patients? Yes, for patients. We need to develop processes to make sure that these trials are patient-centered, not just drug-centered.

Dr. Correll: Absolutely. We need to ensure that the patient experience is central to the design and conduct of clinical trials.

Interview: Challenges and Opportunities in Psychiatric Trials
FDA To Consider Event-Free Survival, Complete Response in Cancer Trials

Drug regulators will consider event-free survival and complete response as surrogate endpoints and symptom improvement or relief as a clinical benefit in cancer trials, the FDA says in a new final guidance issued in mid-December.

The agency is also willing to talk about emerging endpoints such as minimal residual disease or metastasis-free survival, the 19-page document states.

The new, final guidance replaces a final guidance issued in May 2007. It reflects, FDA officials say, updated thinking in an industry that has evolved rapidly in the last decade or more.

The revised guidance makes clear that regulators see tumor measurements as the better endpoints than other biomarkers. Its biggest change appears to be the event-free survival discussion, which has been tacked on to the guidance on disease-free survival. Either can be “a surrogate endpoint to support accelerated approval, a surrogate endpoint to support traditional approval, or it can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, the disease setting, available therapy, and the risk-benefit relationship,” the FDA says.

The same is true for complete response, the document states.

Decreasing the severity of cancer’s symptoms has already been used to support traditional drug approvals as long as the candidate drug has also been shown to attack tumors. But sponsors should take caution that using symptom relief as a clinical benefit “requires that the population” of the trial “be symptomatic at baseline, which can be problematic in many cancer trials where patients can often be asymptomatic at baseline,” the guidance states.

Symptom relief can also fall victim to open label response bias, “the magnitude of which is not well described,” the FDA says.

Emerging endpoints, such as minimal residual disease have already been used as surrogate endpoints for accelerated approval — in minimal residual disease’s case, in approval for treating acute lymphoblastic leukemia. But the FDA urges sponsors to talk with regulators before designing a trial with emerging endpoints.

If trials are going to measure tumors for their endpoints, the protocol should carefully define an adequate measure for each patient visit. “The analysis plan should outline a comparison of the adequacy of follow-up in each treatment arm,” the guidance states. “Methodology for analyzing incomplete and/or missing follow-up visits and censoring methods should be specified in the protocol. The analysis should specify the primary analysis and one or more sensitivity analyses to evaluate the robustness of the results.”

When possible, an analysis should include the number of deaths of “patients who have been lost to follow-up,” the guidance states.

Read the FDA’s guidance here: https://bit.ly/2UXSG9K

R&D Returns Shrink to Lowest Level in Decade, Analysis Finds

Drug companies’ returns on R&D investments have sunk to their lowest level since 2010 and analysts at Deloitte attribute the decline mostly to the soaring costs of clinical trials.

The 12 largest drug companies were expected to see an average of 1.9 percent return on every dollar invested in R&D in 2018 — the lowest percentage since Deloitte began analyzing the data in 2010. Returns fell for smaller drug companies, too — from 12.5 percent last year to 9.3 percent this year.

R&D returns have fallen steadily over the past decade — the average rate was about 8.2 percent in 2010. Clinical trial costs have nearly doubled since 2010, Deloitte says.

Adding all the failed trials, each new drug costs more than $2.1 billion to bring to market, according to researchers at Tufts University. Trial costs have grown in six of the past eight years.

EMA Seeks Comments on Rare Allergy Trials

The European Medicines Agency is seeking public comments as it prepares new guidelines for rare allergy clinical trials.

Clinical trials work best when disease strains can be isolated, but that’s a tall order for allergies. Individuals who have a rare allergy usually have several other kinds of allergies, making it hard to test the efficacy and safety of a proposed allergy treatment on a big enough patient population, the agency says.

The EMA hopes to clarify clinical endpoints, provocation tests and surrogate markers for allergy trials.

The agency has committed to releasing draft guidance by July 2020. The comment deadline is June 30, 2019.

Read the EMA paper here: www.fdanews.com/ema-concept-paper-allergan.pdf

Drug Sponsors Urge FDA to Think Bigger about Master Protocols

Leading drugmakers are urging the FDA to think bigger about its master protocol

continues on next page »
guidelines for clinical trials and expand beyond cancer trials.

In September, the agency issued a draft guidance on master protocol design, hoping to encourage sponsors to use more adaptive trials and speed life-saving anticancer drugs to market.

In comments on the draft, Pfizer, Novartis and Regeneron urged the agency to look beyond cancer for master protocol designs.

Regeneron said the use of master protocols in rare diseases presents a good opportunity to expedite orphan drug development. Novartis suggested that the FDA work with the Oncology Center of Excellence, CDER and CBER to identify areas where more flexible trial designs might be effective.

Most comments on the draft guidance were positive about the FDA’s moves toward more flexible trial design. But some groups urged the agency to flesh out some areas more carefully. The Association of Clinical Research Organizations, for instance, noted that the draft document doesn’t have a robust discussion of clinical endpoints. ACRO urged the agency to make “a clear statement” about whether regulators would accept the use of different endpoints in different sub-studies.

Read the draft guidance here: https://bit.ly/2GLFa6l
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Patient Experience continued from page 1

of patient engagement at WCG Clinical.

“Nobody in the clinical research world is looking for extra things to do,” he says. “But I think the idea behind [the draft guidance] is tremendous.”

Sponsors should probably focus their efforts on coming up with common measures of patient experience, Summers says.

“You want to be sure that the information is standardized as much as possible,” he says. A seven on one person’s pain scale could be another person’s four, and that kind of variability must be eliminated.

Equally excited about the new draft guidance is Dana Dornsife, founder and chairperson of the Lazarex Foundation, a California-based nonprofit group that helps patients absorb the costs of participating in clinical trials.

“It really reflects a new attitude at the FDA,” she tells CenterWatch. “I think this is a great development for patients. I think that what they’re doing is really trying to create organization around a very chaotic phenomenon right now, which is all these big data projects. Everybody’s collecting data right now, but they’re asking ‘What do we do with it?’”

It’s early in the process, but Dornsife says she hopes the ongoing understanding of how real patients react to treatments will get sponsors to rethink some of their enrollment criteria for trials.

“We don’t want to walk away from a promising treatment. But that clinical trial nirvana doesn’t reflect our larger society,” she says. “People are being left out of the equation on the statistical and scientific impact on their communities.”

Once new draft guidelines have been proposed, the FDA will open a new docket for public comment, but the agency won’t commit to issuing guidance of its own.

Read the FDA’s draft guidance here: https://bit.ly/2Q5mC04

“Everybody’s collecting data right now, but they’re asking ‘What do we do with it?’”

—Dana Dornsife, founder and chairperson, Lazarex Foundation
Another important development — one that’s underappreciated — is that we can use more technology to both assess and treat patients."

—Christoph U. Correll, MD, Professor of Psychiatry, Zucker School of Medicine, Hofstra/Northwell

adrenalin or dopamine. Now, we can harness receptors related to abuse with ketamine or cannabinoids — and benefit the patient. That’s what I’m excited about.

Another important development — one that’s underappreciated — is that we can use more technology to both assess and treat patients. Patients — and people in general — use technology all day, for many, many hours. Getting information for clinical trials from either the e-mental health tools that can be used as medical devices or maybe devices that measure and improve adherence. This is something I’m most excited about, that this could yield additional benefits for patients.

Dr. Opler: What do you see as the top three opportunities in clinical development for psychiatry? Where can we make a dent?

Dr. Correll: I just mentioned the use of technology. Wearables provide the opportunity to gather more objective data and to perform interactive assessments and momentary assessments. This will help us determine whether patients actually hear voices all of the time vs. only saying it when we have them at baseline. During screening, this could actually refine the patient population we want to enroll based on frequency and severity of certain symptoms. I think that’s exciting.

Another challenge is this: The field must move away from these broad-stroke diagnostic approaches for molecules. We must re-stratify medicine and stratify clinical trials. When a medication has a target engagement, let’s say an alpha-7 agonist in the nicotinic system, you want to see whether you can actually measure that system and only enroll patients who have the deficit.

For people who use an anti-inflammatory drug, just measure people with inflammation and enroll those patients. But what the companies are still doing is, they have a hypothesis, they take all patients and then run their biomarker afterwards — when it’s totally underpowered — to see if it could have yielded a result. I think that’s something where we really need to get into subgroups of patients. We might also need to reanalyze some data to see who are the super-responders; we can learn from even failed trials by identifying the potential subgroups.

These are two areas where progress can be made quickly. Other than that, obviously, I would say we need mobile mechanisms. We need also treatments for dimensions that are not captured in the current treatment algorithm, such as negative and cognitive symptoms for people with schizophrenia, treatments for the elderly who are agitated and aggressive, and treatments that have lower risks for increased mortality. These are lower-hanging fruit than, for example, understanding and treating dementia.

Dr. Correll: I think the most exciting area at the moment — because approval appears to be right around the corner — is harnessing a glutamate system for depression. We’re seeing rapid-acting antidepressants. Esketamine is on the forefront, including as an IV and now as an intranasal treatment. We’ve learned that our hypothesis — that it takes several weeks until depression improves — is not necessarily right. If you have another receptor system and another approach, people feel better 40 minutes after a single IV dose and achieve the maximum effect after a day or two. That’s really exciting. Also, it is anti-suicidal; that opens different treatment paradigms. People who are currently helped in emergency rooms and are sent for admission could maybe be spared the admission. We actually get “speed jumps” into improvement and faster recovery.

Related to that is, we have basically now, for the first time in 40 or 50 years, an opening into different receptor systems. In psychiatry, it’s always been around serotonin or...
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<td>Daiichi Sankyo Company, Ltd.</td>
<td>quizartinib, a FLT3 inhibitor and an MDM2 inhibitor, milademetan (DS-3032)</td>
<td>relapsed/refractory FLT3-ITD acute myeloid leukemia (AML) or newly-diagnosed FLT3-ITD AML unfit for intensive chemotherapy</td>
<td>Phase I trial initiated enrolling up to 110 subjects in the U.S., EU and Japan</td>
<td>dsi.com</td>
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<td>Carmot Therapeutics</td>
<td>CT-868</td>
<td>type 2 diabetes</td>
<td>Phase I trial initiated enrolling overweight or obese but otherwise healthy volunteers and subjects</td>
<td>carmot-therapeutics.us</td>
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<td>Viriom, Inc.</td>
<td>VM1500A once monthly injectable</td>
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<td>CSTone Pharmaceuticals</td>
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<td>MiNATHerapeutics</td>
<td>MTL-CEBPA in combination with Sorafenib</td>
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<td>Phase Ib trial initiated enrolling 38 subjects in the U.K., Singapore and Taiwan</td>
<td>minatx.com</td>
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<td>Vedanta Biosciences</td>
<td>VE303</td>
<td>recurrent Clostridium difficile infection (rCDI)</td>
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<td>HB-101</td>
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<td>AL101</td>
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<td>Phase II trial initiated enrolling subjects at eight sites in the U.S.</td>
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<td>Isofol Medical AB</td>
<td>arfolitixorin</td>
<td>metastatic colorectal cancer (mCRC)</td>
<td>Phase III trial initiated enrolling 440 subjects aged 18 years or older</td>
<td>isofolmedical.com</td>
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<td>Rakuten Aspyrian</td>
<td>ASP-1929</td>
<td>recurrent local regional head and neck squamous cell carcinomas (HNSCC)</td>
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<td>rakutenaspyrian.com</td>
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<td>CathWorks</td>
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