Supporting Value Across the Regulatory Submission Continuum

In a recent webinar, Luca Pani, MD, Vice President for Regulatory Strategy and Market Access Innovation at WCG VeraSci, and Janet Wittes, PhD, President Emerita and Founder of WCG Statistics Collaborative, discussed the importance of continuity in the submission process, from regulatory strategy and statistical methodology to market access. In an era of gene therapy and digital therapeutics, continuity has never been more important.

New types of therapeutics require a new value framework, one that include payers as well as regulators and scientists.

We already know that continuity between the scientific and regulatory parts of a dossier is essential to the registration of a medication. However, considerations of reimbursement need to be an early part of that continuum, although they typically come up much later. That's a strategical and positioning mistake, argue Pani and Wittes.

Nearly 1,000 cell and gene therapies are in development. If current estimates hold, 39 will be evaluated for approval in 2022, many with multiple indications. Existing value frameworks are simply inadequate. Specialized therapeutics require a different approach to assessment of health technologies.

What works for small molecules does not necessarily work adequately for specialized therapeutics. An important problem is sufficient evidence to capture the full, long-term benefits of these therapeutics adequately. Pani recently coauthored a paper that argues for the ongoing generation and incorporation of evidence to support reimbursement.[1]

WHAT MATTERS TO REGULATORS MATTERS TO PAYERS

Evidence should be frequently generated and presented to payers, not just to regulators. This allows development of innovative pricing models that will enable payers to have an affordable, risk-mitigated means of funding new therapies in a timely manner. As a result, this ensures patient access to new, potentially life-saving therapies, while providing manufacturers with a return on their investment.

The strength of the evidence provided to support biomarkers, which direct precision drug development, should also direct reimbursement criteria. Of four classic pillars—population, endpoints, comparators, and duration of response—

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the last one is particularly important for advanced therapeutics. In gene therapy, the duration of the response is based on the disease-modification brought by eradication of the disease.

Consider the populations for whom a gene therapy is "only one-shot treatment and eradicating the disease for good." It does not change the disease progression that has already occurred. "It's a disease-modifying therapeutic that changes the complete trajectory of the disease," Pani explains. "These sorts of miracles carry a very big price, and the payers are not ready," he adds. The ability to price a product with such potential cannot be simply compared to anything else we have ever approved and reimbursed thus far.

Sponsors need to make the case early, considering both regulators and payers.

"If you don't plan in advance and if you don't think about how to sustain your very innovative drug, the drug you have seen literally making very efficacious responses in your patients, and you are not making them available, accessible, and affordable, then your drug is not an innovation at all," he warned.

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ENTER THE STATISTICIAN

In this time of revolutionary change, sponsors must initiate a dialogue among investigators, payers, and regulators," Pani argued. Wittes agreed, adding that statisticians must be part of that conversation. "Think of us as your

friends who are trying our best to help develop the drug from the beginning until the end, even at the payer stage."

She stressed that the protocol team should have at least one statistician discussing not only the protocol, but also the whole development plan, including how the product will go to market.

The development team should not treat statisticians as outsiders. "Make sure we understand the study. Make us an integral part of your team. And don't let us talk over your head. If we talk in a way that isn't clear to you, ask us what we mean. Think of the system of everybody involved in development as a set of gears working together, meshed really well so that the whole process works smoothly." Drug development is not an assembly line or a relay race.

COMMON PROBLEMS

The statistician can identify problems early and often. Among the most common:

1. **Inadequate controls.** Too many people in the industry think, "Oh, with real-world evidence, you don't need a control." Not so, she says. "If you use real-world evidence, the question is how." Other times, the comparison is to a standard of care, but the standard is not typical in the US. Or there's too much crossover from the control to active or vice versa.

2. **Varying results.** For example, sometimes, the data show very different results in different regions of the world.
3. **Missing data.** "It's very important, at the site level, for everyone to understand the seriousness of missing data." This is yet another reason statisticians need to be involved in the conversations - even before the protocol is finalized.
4. **Misunderstanding of what the FDA says.** Statisticians tend to speak their own language. "So very often at an FDA meeting, if the statistician from the Sponsor isn't there, then the words that the FDA statisticians say don't get translated in a meaningful way." Again, that's why the "gear" metaphor is so important: Everyone needs to be involved across the drug development process.

NOT NEGATIVE, JUST CAREFUL

"One of the things that people want us to do is to find the gold in the pile of data, the diamond hidden away. And that's really hard. If you've

been involved in a study, that shows clear harm, inference is easy. But when the data shows some benefit but not enough, it's really hard to weigh risk and benefit. What I'll say to myself sometime is, let me do an analysis and let me look at it and see, if somebody else did it would I believe it? Or would I think, oh, this person's just trying to squeeze the data in a way to tease out benefit. And the errors come in both directions. If you don't squeeze enough, you might miss a signal that was there. But if you squeeze too much, you may be finding false gems."

Statisticians trying to strike this balance may come across as negative. They aren't, she said. "We don't relish finding fault. We're trying to kick the tires and see what the data are really saying. Please think of us as your friends—people who understand how a statistician at the FDA and the EMA think. And if you do that, and if we listen to you and you listen to us, I think the process of development will improve."

REFERENCE

1. Pani L, Becker K. New Models for the Evaluation of Specialized Medicinal Products: Beyond Conventional Health Technology Assessment and Pricing. Clin Drug Investig. 2021 Jun;41(6):529-537. doi: 10.1007/s40261-021-01041-6.

ABOUT THE SPEAKERS

Luca Pani, MD, Vice President for Regulatory Strategy and Market Access Innovation of WCG VeraSci

Dr. Pani is former Director General of the Italian Medicines Agency (AIFA), CHMP and SAWP Member of the European Medicine Agency (EMA) and a globally recognized expert in psychiatry, pharmacology, regulatory science, and market access negotiation model contracts. During his tenure as Director General of AIFA, he pioneered several new approaches to drug approval, pricing, and reimbursement strategies by using advanced informatics to follow and certify real-world data. As a European regulator, Dr. Pani has been a leading figure for approval and scientific advice for CNS products and served as Chair of both the European Union Board Telematics Committee and of the European Risk Management Strategy Facilitation Group.

Janet Wittes, PhD, President Emerita and Founder of WCG Statistics Collaborative

Dr. Wittes is a member of many advisory committees, including a number of Data Monitoring Committees (DMCs) for randomized clinical trials sponsored by industry or government. She is a former member of the Food and Drug Administration (FDA) Cellular, Tissue, and Gene Therapies Advisory Committee (2014–2018) and a current member of the Circulatory System Devices Panel. She has held leadership positions in may large randomized trials in a number of therapeutic areas and has been actively involved in drug for orphan diseases. Her publications include many contributions to statistical methods for clinical trials.

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