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Why 2020 Saw The Steady Rise Of In Silico Trials

by Vibha Sharma

Disruptions to clinical research during the COVID-19 pandemic has kindled a new level interest in using computer simulations to predict clinical trial outcomes. Regulatory guidance on "good simulation practices" can move things up a notch in this emerging field.

As COVID-19-related restrictions continue to pose challenges for the clinical research environment, big pharma is increasingly warming up to the possibilities offered by *in silico* or virtual clinical trials to continue their product development programs.

In silico trials allow companies to test their drug candidates in "virtual patients" using sophisticated computational modeling and simulation techniques before testing them in humans.

They can help companies detect a "failure in the making" early on in the drug development cycle, said François-Henri Boissel, CEO of Novadiscovery, a Lyon, France-based company that uses mathematical modeling-based simulation technology to predict clinical trial outcomes and cut their running costs.

Moreover, because *in silico trials* are based on computer simulations, they have not been affected by the ongoing COVID-19-related travel and social distancing restrictions, which have impacted many conventional trials.

In silico trials have been around for a while and have also piqued the interest of regulators. However, over the past three years their uptake has mostly been by smaller biotech companies, Boissel told the *Pink Sheet* in an interview.

"This year, we've started to see" mainstream big pharma companies "look into the [*in silico* trial] approach," driven by COVID-19-related restrictions that have prevented them from "running

trials as they would have hoped to," he said. There was a boost to the extent that "running those trials in real human subjects were not feasible."

Boissel noted that the "early adopters" of *in silico* trials "really helped us build our portfolio of tangible use cases and in demonstrating the value proposition" of the technology. In December, Novadiscovery collaborated with Janssen France to provide *in silico*-based decision support for its clinical development pipeline.

In the future, Boissel said that he would like to see *in silico* trials being established as the "third pillar" of drug R&D, supporting *in vitro* and *in vivo* explorations.

While COVID-19 has drummed up interest around *in silico* trials, there is still some way to go before this approach becomes a routine component of the drug development process.

"In terms of take up, realistically speaking, I would say that we are right in the process of, or [are] starting to, cross the chasm," the Novadiscovery executive said. "I'd say we're not yet into the mainstream adoption… but it should be a matter of a year or two."

There are a number of companies conducting *in silico* trials. Many of them started with simple pharmacokinetics/pharmacodynamics modeling approaches, and they have gradually become more sophisticated to the point that they are active in the quantitative systems pharmacology space. Examples of companies in this space are Certara, Applied BioMath and Rosa & Co.

Regulatory Activity

To accelerate the uptake of *in silico* trials, guidance is needed from the regulators that clarifies their expectations on modeling and simulation techniques, Boissel said.

Before guidance can be developed, the regulators are still trying to better understand all the underlying issues involved, and they have been teaming up with industry experts to help them.

In the US, for example, the Food and Drug Administration has been running a pilot program on Model-Informed Drug Development (MIDD) since 2018. MIDD approaches, when applied successfully, can potentially improve clinical trial efficiency, increase the probability of regulatory success and optimize drug dosing/therapeutic individualization in the absence of dedicated trials, the FDA said.

The US regulator said that it expects to learn "both from the number and types of submissions" it receives from companies under the pilot. Under this, companies can make submissions related to "any relevant MIDD topic," although initially priority was given to specific topics like dose selection, trial simulation and predictive safety evaluation.

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The pilot has seen some success already. Earlier this year, the FDA approved a new indication for AltaThera Pharmaceuticals' Sotalol IV (which was one of the first drugs to be reviewed under the MIDD pilot) for atrial fibrillation patients based on data from *in silico* trials.

One of Novadiscovery's clients that will be seeking approval of an investigational product is also participating in the MIDD pilot. While the Phase III trial for the product is yet to be launched, Boissel explained that in this case, data from *in silico* approaches "had a significant impact on some of the choices made by the sponsor in terms of trial design."

Trial Simulation, Drug Selection To Be Focus Of US FDA's Drug Development Modeling Pilot

By Michael Cipriano

16 Apr 2018 Meeting requests from sponsors that focus on safety prediction will also be prioritized. *Read the full article here*

In the EU, work on MIDD-related guidance is following an informal route. The European Medicines Agency told the *Pink Sheet* that guideline-related activities of its Modelling and Simulation Working Party "are currently scaled down due to business continuity" issues. It said the agency "may consider issuing guidance on this topic in the future."

On the acceptance of MIDD data in regulatory submissions, the EMA clarified that "high quality modelling and simulation exercises can be accepted, on a case-by-case basis, as sole evidence to support regulatory claims in special populations (eg paediatrics), drug-drug interaction studies and dose recommendations/adaptations."

Separately, the EMA highlighted that experts from the EU medicines regulatory network have held discussions with the Avicenna Alliance, a global non-profit organization co-founded by Novadiscovery and other industry and academia/health care organizations that have a commercial or research interest in the development of *in silico* medicine.

The EU regulators and members of the Avicenna Alliance co-authored a commentary, published earlier this year, on how to verify and validate *in silico* models in drug development. "They are also preparing a white paper on the assessment of complex mechanistic models and related simulations, with a planned submission date in December 2020," the EMA said.

The white paper is expected to be a prelude to establishing "good simulation practices," which would provide a framework for the credibility assessment of computational models.

Boissel is hopeful that the efforts of the EU and US regulators will converge at some stage. "There are these sort of theoretical discussions" in the EU on good simulation practices "and then there are practical examples" under the US MIDD pilot, which can together provide useful insight, he

explained.

Complex Models

To run *in silico* trials, three essential components are required – a model of the "disease of interest," a sub-model (ie, much smaller model) of the drug candidate, and virtual patients.

Most of the work goes into building or updating the model of the "disease of interest," Boissel said.

When Novadiscovery made a disease model for non-alcoholic steatohepatitis (NASH), for example, it broke the pathophysiology into "fundamental bricks or sub-models," such as cholesterol and bile acids, apoptosis and endoplasmic reticulum stress, fibrosis, fatty acids and lipotoxicity, the immune system, etc. For each of these sub-models, "we extract from scientific articles, pieces of knowledge that are relevant to describe the underpinning mechanisms."

This results in so-called "mechanistic models," which are fairly complex with usually more than 1,000 to 2,000 biological entities represented in the overall disease model. These are then converted into mathematical equations in computer code, using available raw data from previous experiments – whether preclinical or early clinical trials – to calibrate and validate the disease model.

"Once everything is in place – which means we have generated our virtual patients, we have our drug candidate's mechanism-of-action sub-model and we have our disease model – then it actually is fairly straightforward to run a simulated trial," Boissel said.

Compared to conventional trials, the possibilities and advantages of *in silico* trials are huge, according to Boissel. Companies can test different doses, different timings of administration, compare a drug candidate to a standard of care, etc. A key benefit is that "you can run, for instance, an *in silico* Phase II trial on 10,000 virtual subjects, rather than being limited to let's say 10 or 20 or 50 real human subjects."

Another central benefit is that every virtual patient is his or her own control. "Every time you test an alternative assumption, you have the guarantee that the rest of the system is exactly identical from one test to another," Boissel explained. This can help decipher the impact of testing such assumptions on the predicted clinical outcome.

This feature comes in handy when running "optimization scenarios" and identifying, among other things, "optimal responders, the best drug regimen and all those applications that you can actually derive from this," he said.

Trial Optimization Vs Exploring Assumptions

As a robust disease model is a central component of *in silico* trials, it is important to ensure that the "disease of interest" is well-characterized.

Boissel acknowledged that in cases where new information about a disease is still emerging – for example, in the case of COVID-19 – *in silico* trials may have limited use in optimizing trial outcomes. Nevertheless, he said, in silico trials can still be used to speed up the exploration of assumptions for such cases.

Assembling a new disease model using emerging knowledge and a formalized mathematical model can make clinical explorations more reliable, Boissel said. In such cases, *in silico* approaches can be used to answer questions about "structuring, and rendering more efficient, the exploration of early assumptions."

While Novadiscovery has not yet been involved in any of the trials of coronavirus treatments or vaccines, Boissel said "our assumption is that a COVID-19 disease model will still be useful to the industry next year" for *in silico* trials.

In Silico Trials Are Not Just About AI

Commenting on the competitive landscape for Novadiscovery, Boissel noted that in the pharmaceutical sector there are a lot of companies that provide services related to big data and artificial intelligence. He explained, however, that most of them are focused on computational chemistry (ie, drug discovery) and not so much on clinical development.

"When the end game is to predict a clinical outcome before the human trial has taken place," Boissel said that "AI approaches do not work that well." This is because AI players "need large data sets to train their algorithms" whereas clinical development is a fairly "data-poor" environment.

Moreover, as AI algorithms tend to operate as "black boxes," there are concerns regarding their auditability. It may be difficult for companies to base the rationale of the design of an upcoming trial on a black box, he said. For these reasons, companies that deal purely with AI do not offer *in silico* trial services, Boissel said.