ENDPOINTS NEWS

NEW APPROACHES TO DE-RISKING EARLY DRUG DEVELOPMENT

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Endpoints News talked with biopharma leaders at Merck, Sanofi, Catalent, Takeda, and J&J about their efforts to improve R&D efficiency

INTRODUCTION

The biopharma industry as a whole is spending more money than ever on drug R&D, but the payback on productivity keeps shrinking. On a long-term basis, that's unsustainable for the industry and has to change. We spoke with several of the leading experts in clinical trial design and drug development to see what they're doing to pick the right candidates for clinical development and how they're revamping projects to achieve approvals as efficiently as possible.

After all, most of a drug's development costs come late in the process. Running the kind of clinical trials needed to support an approval are expensive, and if they fail, all capital invested is lost. Is it time for animal studies to be discarded? What better technologies are available to improve early-stage development? Can optimal formulation improve a molecule?

We looked at all those questions and more.

Much of the problem is based on an incomplete understanding of biology and animal studies often seem to confuse the issues more than they provide fresh insights to researchers.

We know that sticking with animal studies for basic preclinical guidance will limit overall success rates in the clinic to only 5% to 10%. But the emphasis right now is more on evolution than revolution. Organ-on-a-chip technology can enhance preclinical work, just as collaborations among CROs and developers have been relied on to identify preferred dosages and delivery methods.

But you also have to keep things simple, to make sure that you don't overcomplicate your molecule, making it impossible to produce at a reasonable cost.

And throughout all the changes chronicled in this article, you will hear of case after case where large companies have been stripping down interior walls to allow for more partnering with investigators of all stripes, whether in the industry, government or academia.
In this field, borders are increasingly meaningless obstacles to change. Scientists and developers in North America, Europe and Asia are looking globally for the best solutions to this immense problem. Failure is not an option, as NASA might phrase it. These days, when you're doing a moon shot of your own, you need to use every important resource available, wherever it is, to avoid a failure to launch.

AN INCOMPLETE PICTURE

The vast majority of Phase I candidates never make it to market, putting the true cost of successful drug making straight into the stratosphere.

One recent estimate of the clinical-approval success rate was an abysmal 11.8%. Robert Plenge, Merck vice president and head of its Translational Medicine department, told Endpoints that one root cause of why biopharma R&D is so expensive and prone to failure is because of our incomplete understanding of human biology. He said companies need to dig further to find evidence to support a target before beginning a drug development program.

Developing a drug based on animal models just isn't efficient enough anymore, he stressed. That method involves making decisions about a molecule where very little was known in humans, but an interesting effect was seen in animals. Whether that model translates or not is often unknown, and it's not until the drug gets into a Phase I or Phase II trial that anything is learned about how that drug behaves in humans.

"We've done that experiment for 10 or 20 years, and that model tells us that if we prescribe to that model, 5% to 10% of things (depending on the disease indication) will ultimately lead to a successful drug. That rate of productivity is just not sufficient to sustain the industry."

Plenge breaks down his formula for increasing the effectiveness of R&D into four key strategies that, when implemented together, could be powerful change agents for improving R&D productivity. Those four components are: causal human biology, therapeutic modality, biomarkers of target modulation and clinical proof-of-concept studies.

IMPROVING TARGET VALIDATION

Improving target validation processes earlier in the R&D process could help drug developers make critical decisions sooner — including what compounds to kill.

Plenge says that safety and efficacy profiles are meaningless to guide target identification because drug developers should know at the beginning of the drug development program whether the target, when triggered, will achieve the desired effect. When asked to clarify whether that means some diseases just shouldn't be studied, he said there is always a balance.

"Even for those things that 'succeed' in development, too few of those differentiate from standard of care and just don't deliver value." For example, even for drugs that work in Phase II or Phase III, they often don't differentiate much from the standard of care, so the drug dies a slow death.

This "non-differentiation" is going to become a "bigger and bigger deal going forward as we think of the things that really add value in the real world," Plenge said.

Understanding how drugs are working in patients or how they are not working, why some people respond and why others don't, and then thinking about pharmacologic purposing — all of these types of experiments in nature can begin to provide insight.

"Then you need some mechanism to dive into the biology more deeply in a system that is human-like and imperturbable that often is very difficult to do," he added.

Animal models are useful to tease out the underlying biology of a known pathway and to understand general pharmacology and how a drug behaves in an intact organism. But they're not useful for picking targets or understanding causality in humans, Plenge stressed.

When asked whether adaptive trials could be a solution whereby smaller more targeted studies focused on early terminations, Plenge said that would only partially solve the problem.

"If you're still picking the wrong targets, if you haven't done the appropriate therapeutic reconfiguration, you don't really have a robust model you can test in humans. Either you don't have the right target dose, you don't have the right understanding of target engagement or target modulation — this gets to the biomarker piece — then you end up making decisions with incomplete information." "That's why you have to have that causal human evidence," Plenge says. "You have to be confident that your molecule is recapitulating that biology. You have to have some way to measure a read out in humans that allows you to make that decision. The faster we can do that and the faster we can actually incorporate and adapt a design, the better off we will be in the industry."

The organ-on-a-chip model might help cut through some of that animal data that doesn't translate to human biology. The technology encompasses miniature models of human organs whose channels are lined with human-derived cells. In this way, more can be learned about human systems to make better decisions earlier rather than relying on inaccurate animal models.

Could organ-on-a-chip models replace animal models? Merck's Plenge says that animal models are still a valuable tool, but they shouldn't be used to pick targets.

But organ-on-a-chip models can provide insight into functions within the human body that could better inform researchers about target modulation. In some cases the organ-on-a-chip model could also be used for assays that can be more complex, he suggested.

SANOFI'S ORGAN-ON-A-CHIP PLATFORM

Sanofi has been testing a range of technologies that replicate the cell dynamics of major organs in the lab for the last three years, Philippe Detilleux, global head for Preclinical Safety at Sanofi, told Endpoints. "These technologies show great promise, not least because they allow researchers to test chemical compounds and their expected toxicity," he said, but they're still at a very early stage of development and are not used outside of pilot programs.

Over the last few years, Sanofi has entered into numerous collaborations to explore the organ-on-a-chip technology. The company has collaborated with the Wyss Institute, Hurel, Mimetas,

and CNBio as well as the Innovative Medicines Initiative Project MIP-DILI (Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury).

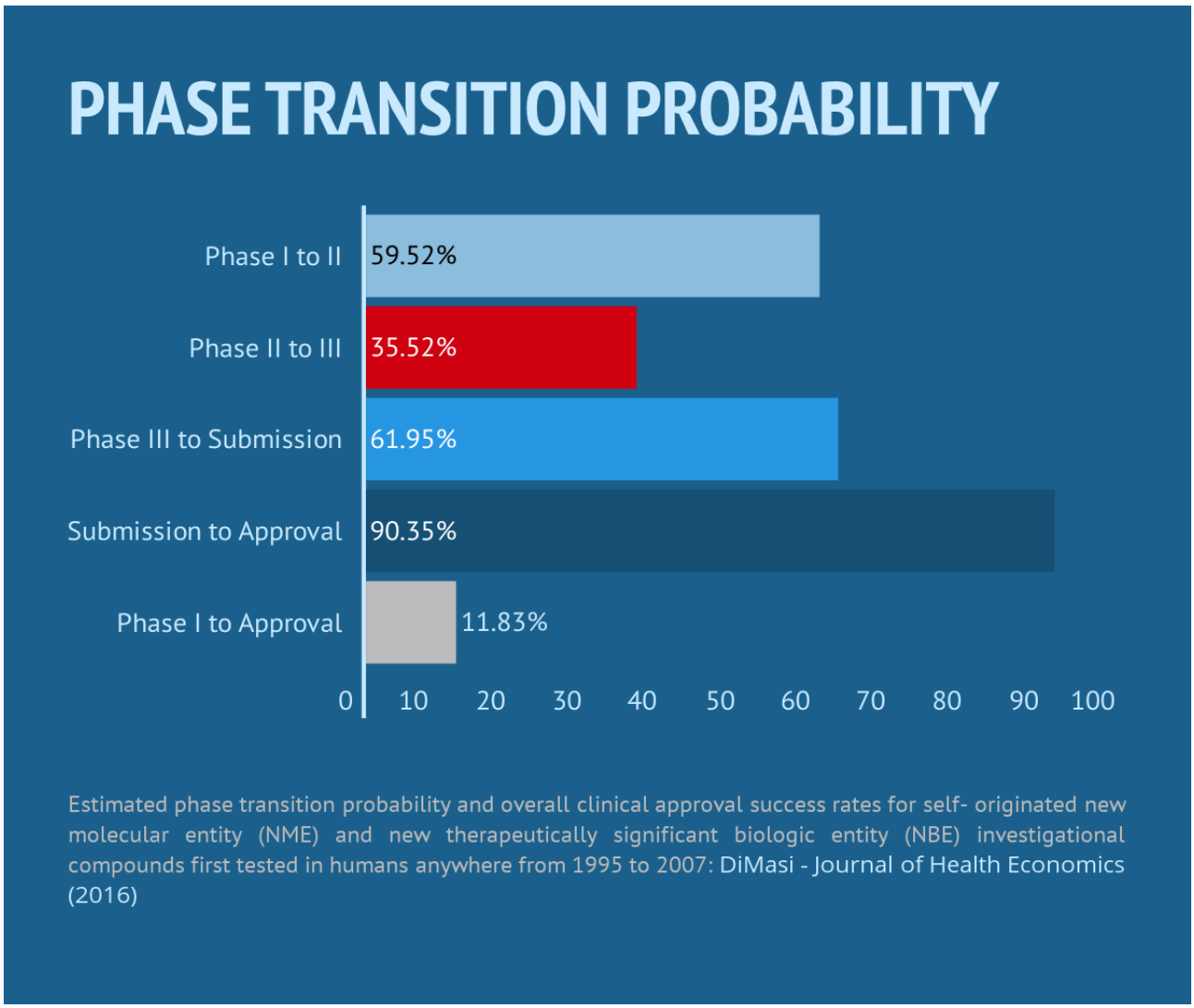
"One area where we have been quite active is in developing in silico approaches to anticipate potential toxicity liabilities of small molecules. At a very early stage, we are able to screen molecules virtually on a computer."

The company sees potential in terms of its preclinical work, where organs on a chip can help accelerate tests with chemical compounds for elimination and for toxicology work, where the resistance of hepatocytes in the liver model tend to last longer and thus show stronger toxicity results, Detilleux said.

While the technology will complement preclinical programs in the short term and eventually reduce some animal work, it's unlikely to be able to replace it all together given the regulatory framework, he added.

The most immediate impact though may be in predicting human metabolism and pharmacokinetics, rather than toxicity. "Progress on the DMPK aspects of liver and GI models is being made and these may be implemented soon. If some of these models are successful in predicting human metabolism and PK, reduction or refinement of human studies could reduce costs significantly."

WHAT ABOUT NEW GENOMIC-BASED TARGETS? "These new modalities create new ways to recapitulate the human biology," Merck's Plenge said. "It might be with small molecules and biologics we can do these types of therapeutic recapitulations. We can inhibit enzymes, we can remove circulating proteins from the system and that's if small molecules and biologics do respectively pretty well. There are more complex ways in which the human system causes disease and by having things like CRISPR and mRNA delivery increase the way in which we can perturb the targets of interest. Suddenly things that were intractable before maybe become tractable today." For example, there are disease indications where you can overlap human genetics with approved therapies to understand how genetic targets have led to approved therapies either directly or indirectly. "You can see that in lipid-lowering therapies, you can see that in osteoporosis, you can see that in rheumatoid arthritis and in rare diseases like cystic fibrosis where genetics have led to approved therapies or genetics have retrospectively identified the targets."



CAN OPTIMAL FORMULATION IMPROVE A MOLECULE?

"We kept seeing products in Phase II that we knew we could fix to optimize the dose or formulation," said Cornell Stamoran, vice president of Strategy & Government Affairs for CMO Catalent.

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"We tell clients not to kill a molecule until they're sure they have done everything they could to improve it."

Once a company identifies a lead molecule, it makes decisions about which variant of the molecule to use, and those choices can have a direct effect on patient adherence or side effects.

"If you make decisions right in the design of the molecule – the route of administration, design of the dose form, the dosing regimen as well as packaging– those choices can produce a clinically different product."

Making intentional design choices that are informed by patient focus at very early stages — between late discovery and early clinical development — is one of the places that Catalent believes drug development can be accelerated and the clinical trials outcomes can be improved.

He explained that the choices companies make about formulation and even capsule size and shape matter. For example, if you're trying to reach certain first generation immigrants as part of your target patient population, in some cultures there are strong associations between color and health or sickness, so choosing the color of the pill matters when it comes to drug adherence in your target population.
He said roughly 60% to 90% of drugs in development face PK/PD and other delivery challenges, and Catalent has built a predictive platform

can identify optimal formulation approaches to address solubility and other issues.

The company acquired a molecule optimization platform from GSK, and combined it with Catalent's formulation know-how and intellectual property to predict which formulation approach is likely to give a molecule the best clinical results based on available evidence. One of the barriers that companies have had historically is that because there weren't platforms that provided predictability, they focused on formulation techniques they knew in-house, to see if it got them to a "good enough" formulation point. Redoing to improve the formulation further takes time and money at a stage of the process where time is constrained.

The problem is, settling for something that is "good enough," can have side effect implications or monetary implications down the road. "We focused on trying to build predictive tools into algorithms and workflows, so we could do this on an outsourced basis in a short amount of time – 12 weeks – to make a recommendation on what platform addresses solubility and availability best and to bring a GMP-based product for animal studies.

Founder and co-chair of Catalent's Applied Drug Delivery Institute, Stamoran says Catalent evolved as a drug delivery company, and it has added many additional offerings, from clinical trial supply

management to biomanufacturing and antibody drug conjugate technology.

Through it's Applied Drug Delivery Institute, Catalent is engaged in precompetitive collaborations with companies like Allergan and Takeda to work on non-invasive delivery of large molecules. Today Catalent already producing dose forms for biologics that are delivered orally, nebulized or delivered via the eye.

An optimal Phase I product, he said, needs to be a formulation that is scalable – ideally something that can go to a rational process that is not overly complex.

"You don't want to have to do 17 different things to a molecule," he said.

PRECOMPETITIVE PARTNERSHIPS

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Takeda has been active in the Structural Genomics Consortium – an open source consortium that aims to better understand major diseases. The group has characterized 15% of all human protein structures, and the data is open to the public. According to Tufts, the group is generating characterizations of three novel molecules each quarter, with the goal of validating target molecules sooner and to engage scientists to develop new therapies sooner.

Industry partners in the consortium include Abbvie, Bayer, Boehringer Ingelheim, Janssen, Merck, Novartis and Pfizer.

"We recognize that some of the best science comes from outside a company's walls, and Takeda's partnership with the Structural Genomics Consortium has been a valuable conduit for Takeda to accomplish this," Daniel Curran, head of Takeda's Center for External Innovation, told Endpoints.

Beyond just being a member of the SGC, Takeda has invested time and energy to understand what assets and technologies already exist within the SGC. By connecting these resources to Takeda's own

internal research, Takeda and SCG have identified multiple synergistic opportunities to exchange materials and collaborate. On the receiving end, Takeda has worked with SGC to gain access to patient samples for use in identifying and validating novel drug discovery targets. Takeda has also identified proteins and assays that were already developed by SGC member institutions that Takeda can readily use in its existing drug discovery programs.

Takeda also has provided SGC with compounds from its compound library to use as tools for discovering new targets.

Takeda recently revamped its R&D program to narrow in on three key areas: oncology, gastroenterology and the central nervous system as well as vaccines.

The focus on those key therapy areas was a strategic move to de-risk its R&D pipeline by focusing on areas of unmet medical need where Takeda had relevant expertise and know-how. If the needed capabilities to develop a potential medicine are found lacking, the company will seek the right partner, Curran said.

"To be truly innovative, Takeda believes you need to be part of a community of experts who leverage their unique strengths and share a common goal," he said. To that end, Takeda has been hosting 'innovator network' events that bring together members of that

community to connect and share ideas, best practices and learn more about game-changing breakthroughs.

"Our approach is more holistic," he said, "meaning we start with understanding of biology and disease states, and then we consider the target, diverse modalities, targeted delivery, translational sciences and genomics. With all of these considerations, we believe this should equate to a more risk-balanced approach."

In the last year, Takeda entered into a number of strategic partnerships that build upon expertise in diverse modalities. A few examples include:

- Prosetta Biosciences – discovering and developing therapies to treat neurodegenerative diseases;
- Enterome Bioscience – targeting GI disorders using microbiome therapeutics;
- Ultragenyx Pharmaceutical – developing therapies to treat rare genetic diseases;
- Frazier Healthcare – created Outpost Medicine, a new biotech company with a focus on women's health;
- Mersana Therapeutics – developing next-generation antibody drug conjugates;
- Thervance Biopharma – looking at a novel agent for gastrointestinal motility disorders;
- ImmunoGen – developing anti-cancer therapies using novel ADC technology; and
- Cour Pharmaceuticals – developing GI therapies including Celiac disease.

J&J's INVESTMENTS IN EARLY-STAGE INNOVATION

J&J is having some success getting NMEs to market after it recreated itself about four years ago, launching the J&J Innovation Centers with a mission to invest in "highly differentiated" early-stage innovations. Located in Boston, California, London and Shanghai, the innovation centers are regional hubs created to access the best science and technology in their respective regions.

Robert Urban, head of J&J Innovation, Boston joined J&J about four years ago when Johnson & Johnson Innovation was launched.

At the time, there was some redundancy on the pharmaceutical side of J&J, so the company sought to transform itself by refocusing on five specific areas: neuroscience, oncology, immunology, cardiovascular and metabolism, and infectious diseases and vaccines.

Since that time, the company has had 14 new drugs approved in the last five years, and those were all in unmet need areas, Urban told Endpoints.

“Each of them are breathtaking innovations,” he said, and many of them moved swiftly through the approval process.

The company expects to have 10 more NMEs filed by 2019, all of which represent a substantial new type of product. It anticipates another 25 or so NMEs will be nominated between now and 2019.

“The focus has been on building an infrastructure of very deep science on the inside but an extraordinary network of relationships put in place through outreach efforts all over the world.”

Some of the things that have come from this are first-in-class NMEs, such as J&J’s TB drug Sirturo, the very first TB drug that’s been launched in 40 years for multi-drug resistant TB.

There’s also been some innovative kinds of partnerships that show how boldly the organization has embraced some of these challenges. The YODA Initiative — the Yale Online Data Access platform — is an example where J&J was one of the first companies to push out open access to clinical data.

“You need to get the data in the hands of many, and that allows us to do that. We’ve seen in this last decade a really interesting transformation in both the way we see ourselves, but also doubling down on how we see ourselves fitting together in a much more networked context, with investigators all over the world.”

The global organization works 24/7, so as the sun moves across the planet, data shifts into the hands of other team members.

J&J spends nearly $9 billion on R&D per year, and in the last 20 years, the company has invested $200 billion in R&D. About $85 billion of that has been invested in ideas that came outside of the organization.

“Being an expert in the areas that you invest in is critical,” he said. “As we’ve started to focus on fewer things, we’ve gotten much, much deeper in our competency, which means we’ve been able to understand and appreciate the biology and understand and appreciate the potential of interesting products that are emerging in those areas.”

That also gives you a much keener intuition about how likely something might work when looking at innovation around the world. Also part of J&J Innovation is the company’s corporate venture arm, Johnson & Johnson Development Corp., which provides early-stage research funding, seed funding, equity investments as well as licensing opportunities and other collaborations.

So far, the company has made about 200 investments across the world, and the innovation centers themselves make up an ecosystem of incredibly talented people across these five business areas.

"We participate in helping to select the companies that are allowed to go in and utilize these incubators. It's quite a rigorous process to get into one of those facilities, and there are no strings attached. You don't have to have a partnership with us in order to get in. You have to simply be working on something quite remarkable that's more likely than most to generate a growth-oriented life science company."

Roughly 140 companies now live somewhere within one of the JLABs, and the group expects to have as many as 200 companies by the end of the year, Urban said.

The centers themselves are designed to be inspiring spaces to foster creativity where new start-ups get access to state-of-the-art facilities and equipment very quickly so they can focus on generating the data they need.

They all pay what is appropriate rent for the size of space they need without having to sign a multi-year lease, buy new equipment or get all the permits.

"It's a transformative way to start a biotechnology company."

"The companies leave different than when they came – not just because the science is always this twisty-turny thing we have to follow – but the impact that they have on each other by being right there sharing ventures and sharing coffee is extraordinary. We are thrilled

by the work."

Many of J&J's investments have focused on technology that enables R&D, such as biomarker analysis platforms. The company is actively exploring the microbiome and trying to understand how the microbiome itself can be manipulated.

The other investment that's quite substantial is the human investment. Although there's financial participation, some of the things that turn out to be the most transformative are access to individuals in the organization.

"At the same time, we do the best we can to anticipate what's going to be around the corner to prepare ourselves," Urban said.