Accumulus SYNERGY

Welcome to Accumulus Synergy

We are developing a global information exchange platform to transform how drug innovators and health regulators interact to bring safe and effective medicines to patients faster and more efficiently.

It’s time for a moon shot.

Multiple worlds have moved online in the past three decades, from entertainment to commerce and the arts. The world of information and data exchange between biopharmaceuticals and regulators has lagged behind in some respects. Filing a New Drug Application may have shifted from driving a truckload of paper to the relevant regulatory authority, to FedEx-ing a CD-ROM, to uploading a set of PDFs through the Electronic Submissions Gateway, but the documents themselves, and the underlying processes, remain little changed. It’s long past time to play catchup — it’s time for a moon shot.

At Accumulus Synergy, our vision is to accelerate the delivery of critical therapies to the citizens of the world. We should all want to accelerate these critical therapies to citizens globally in a safe and effective way. We use the word “citizens” intentionally, to include patients, caregivers, providers, and family members. At some point in our lives, we all benefit from medicines and vaccines.

We envision information exchange between a biopharma company and its regulators changing from the traditional dispatch of static information and documents, to an invitation to access a cloud environment to view up-to-date data as it emerges. Of course, the environment has to be access based, ensure data privacy and meet or exceed current cyber security parameters.

Maintaining Urgency

One of the learnings from the Covid-19 pandemic is that the biopharma world, including industry, academia and government, can move rapidly in the face of an unprecedented public health crisis. To go from first sequencing of a new virus to multiple neutralizing antibodies and vaccines in under a year is truly remarkable.

But that achievement stands in stark contrast to the normal timeline for new therapies, where not only does it cost $2.6 billion to develop a new drug, but the time from when that asset is identified in research to its first approval, is on average 10 years. The time from when the first approval is made, typically in the United States, until countries in the developing world have their approval, is not days, weeks or months, it's often years. That means a timeline of 12 to 15 years from research molecule identification to reaching patients all around the world.

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For cancer patients, for the parents of young children with rare diseases, every day is an unprecedented crisis. That is why the information and data exchange side of drug development must begin to match the unprecedented innovation that we have seen in the research and development side.

For new drug applications, "where the input is incredibly time intensive and tedious, the turnaround time can make an incredible difference, not just for the company, but for patients who will benefit from the eventual approval," says Brendan Parent, an assistant professor at the NYU Grossman School of Medicine. As it is now, "the process, because of all the time spent in back and forth, can feel almost adversarial. The cloud has fostered real time interchanges that are more efficient, but also more constructive."

Drug development and review needs two fundamental shifts: from organizational and regional silos to enhanced global collaboration, and from rigid and sequential event-driven interactions to real time communication, data exchange and synchronized engagement. We have to go from zero automation today, to a genuinely actionable, and much more efficient processes in the future, including by leveraging machine learning and artificial intelligence. We are confident we can do that — all while maintaining the high safety and effectiveness standards that patients, providers caregivers, and family members trust.

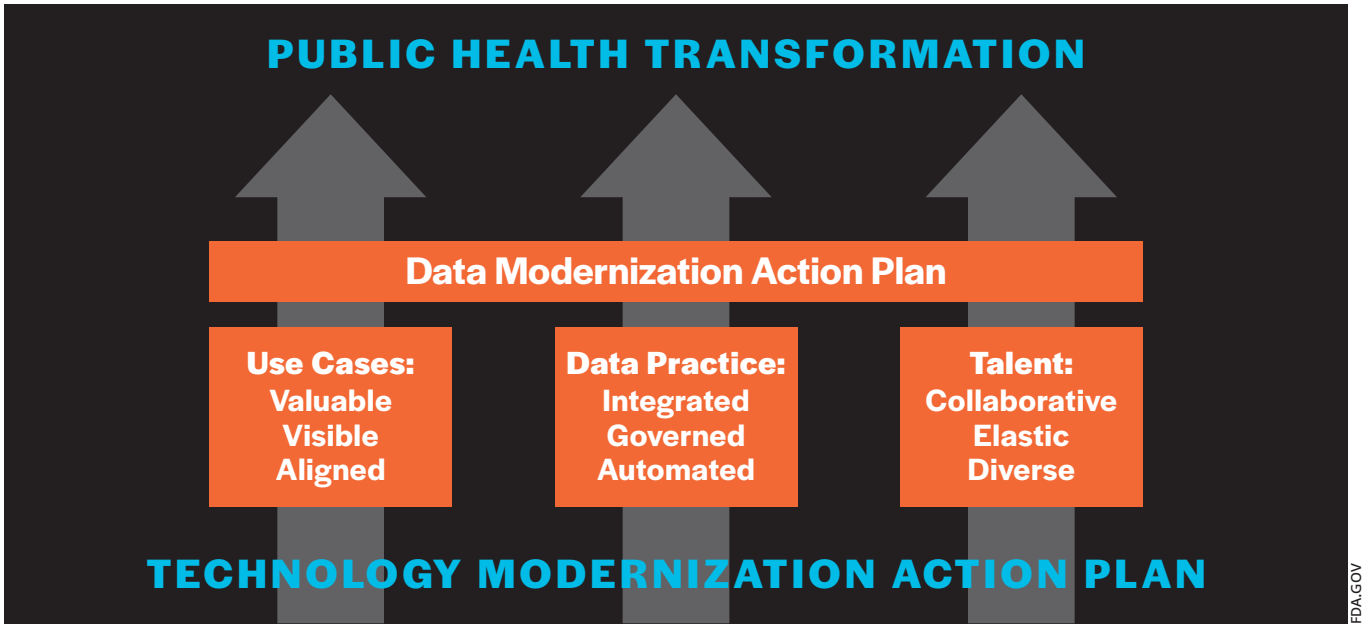
A Burning Platform

At a gathering of the heads of research and development at the world's largest pharmaceutical companies, Dr. Janet Woodcock, then Director of the Center for Drug Evaluation and Research (CDER), the FDA division responsible for the oversight of most drug products, challenged the group to join the 21st century when it comes to data exchange. The time to begin, she told them, is now.

"If you don't start technology products projects like this early, they're not going to happen for a long time," Woodcock says. "The FDA and the other regulatory agencies around the world are basically information managers; we take in information, we process it, and we make decisions based on it. We get huge volumes of information from all sorts of sources, and currently, a lot of that information is in PDFs and other semi-antique formats that are not really searchable and not very good."

In parallel with the industry response from Accumulus Synergy, FDA is moving forward on its own Data Modernization Action Plan (DMAP). DMAP has three components:

1. to identify and execute high value driver projects for individual centers and for the Agency;
2. to develop consistent and repeatable data practices across the Agency; and
3. to create and sustain a strong talent network combining internal strengths with key external partnerships. Woodcock says she sees DMAP and Accumulus Synergy as complimentary.



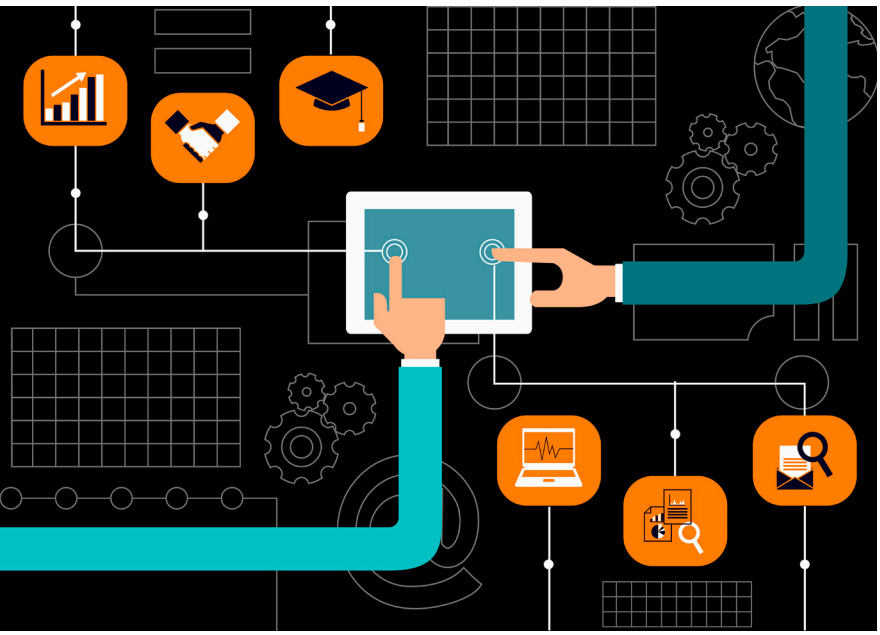
"I think they will dovetail nicely," Woodcock says. DMAP "is an overt statement of moving toward a modern platform that really uses data, rather than narrative."

"Moving from narrative-driven submissions to a data-centric model will eliminate costly, idiosyncratic and inefficient practices", Woodcock says. "Companies complain bitterly, and rightly, that each individual reviewer has their own set of internal standards. As we move toward data, and we can monitor that data, this process can become much more uniform and standard," she says.

From Documents to Data

Accumulus intends to disrupt document-based review. Capturing everything we do to generate a PDF is not the way of the future. We need to enable continuous data-driven review, which will lead to real-time data submissions. We know this will not happen overnight, nor will all regions of the world move at the same pace; however, directionally I believe this is where the future will take us.

"Imagine a new world, where from the point the molecule enters development, the data is sitting in the cloud and at any point in time we can invite regulators in to see it," says Michelle Rohrer, Global Head of Product Development Regulatory and Policy, at Roche. "We would live in a real-time world. You want to shorten the time from when you know you have a medicine to when you get it to patients. This is something that is completely doable, and this is something right to do for patients. It's more humane, and better for everybody."



The data-driven review will also promote simultaneous global activity. "Imagine a world where 180 countries around the world, and FDA, EMA, and Japan's Pharmaceuticals and Medical Devices Agency are all looking at the data at the same time," says Rohrer.

The outcome will look like a new normal, applied around the globe. Pharmaceuticals companies will not be redoing the same work separately for each regulator. A big part of the cost of drug development is because of these built-in redundancies, over and over again, and they will simply go away. The Accumulus Synergy vision is to leverage technology to make processes and communication more efficient — globally.

"There are two opportunities," says Andrew Plump, President, Research and Development at Takeda. "One is just efficiency; it's creating data standards that allow us to move information around in shared formats, so that everyone is speaking the same language. That's immensely helpful. The second is the opportunity to learn. Because each of our datasets are independent from company to company, or from one program to another within one company, they're not done at scale. There's a huge opportunity to bring data together to generate insights."

In the Cloud

Cloud computing is not new; the first providers launched over 20 years ago. But what exactly is it? The best definition is from the National Institute of Standards and Technology (NIST), a part of the U.S. Department of Commerce:

> Cloud computing is a model for enabling ubiquitous, convenient, on-demand network access to a shared pool of configurable computing resources (e.g. networks, servers, storage, applications and services) that can be rapidly provisioned and released with minimal management effort or service provider interaction.

Over time, cloud offerings have grown so robust that entire enterprises run on them, from Salesforce to Netflix. Countless people interact with multiple cloud platforms every day, typically unaware that they are doing so. The cloud computing model features ubiquitous access, on-demand availability, pooling of resources and elasticity. The Accumulus Synergy applications will leverage these factors.

The Accumulus mission is about real-time iterative drug development, simultaneous submissions, and efficient ways of working.

"Twenty years of invention in this space has highly commoditized it and also leveled the playing field," says Hal Stern, Chief Information Officer at Janssen. "The powerful thing about Internet scale technologies is if you have a cool idea for an app, you don't have to invent the whole Internet again. We now have the ability to have a very different kind of conversation: about how you structure a submission, how you sequence and capture its review dialogues, and how you assemble all the data that goes into it."

The Accumulus mission is about real-time, iterative drug development, simultaneous submissions, and efficient ways of working. That means reimagining the communication platform between health authorities and a biopharma sponsor.

Within our platform there will be areas where companies can work in their own virtual rooms with robust privacy and data security protections. There will be a shared space where a sponsor and health regulators can communicate, and there will be a regulatory-only space where regulators can review the data, can interpret the data, can speak and exchange information amongst themselves. All of these features will be governed by appropriate permissioning structures to ensure the integrity of the platform and regulators' important work.

Privacy and data security are at the core of what we are developing. Working with the best technology companies in the world, the Accumulus platform will provide each client company and health authority their own secure space, as well as a shared space. We will meet countries' privacy laws and will implement appropriate safeguards to ensure that data is appropriately protected in the Accumulus ecosystem.

"We can have a faster, more collaborative review process that ideally brings medicines to market faster for patients," says Stern. "It's always been important; now it's possible."

Use Case 1: Parallel Review Shared-Space

The main goal of our first planned Accumulus platform is to enable concurrent, collaborative review of submissions among global health authorities or within agency committees and divisions. By creating a shared space for parallel review of submissions, we can accelerate approvals and reduce lag time across geographies. The new platform will simplify the processes for robust scientific review and improve efficiency by facilitating global health authority collaboration, and it will enable more consistent and consolidated feedback by improving communication between a sponsor and health authorities.

"There is a large gap between where clinical trials are conducted around the world and when and where patients can access successful medicines and vaccines they helped develop," says Jennifer Miller, Assistant Professor, Internal Medicine at the Yale University School of Medicine.

"Good initiatives that can help reduce complexity, fragmentation, and unnecessary duplicative work in the drug market application submission and review process are valuable to help speed access to medicines for patients globally," she says. "There is a mosaic of regulatory processes governing market access to medicines around the world: improving harmonization appropriately is a needed effort."

There is a proven model for parallel review. In 2019, FDA's Oncology Center of Excellence launched Project Orbis, a global collaborative review program to facilitate faster patient access to innovative cancer therapies across multiple countries. Current Orbis partners include the health authorities of Australia, Brazil, Canada, Singapore and Switzerland. While FDA serves as the primary coordinator for application selection and review, each country remains fully independent for their final regulatory decision. Like Project Orbis, the parallel review use case would not change the high standards for safety and effectiveness.

"Orbis was the FDA doing its part on joint review," says Jerry Stewart, Vice President, Head of Global Regulatory Policy and Intelligence at Pfizer. "The FDA reviews oncology products pretty quickly compared to the rest of the globe; through Orbis it's accelerating reviews outside of the U.S. in a joint fashion. Orbis could be amplified by Accumulus Synergy to allow more seamless reviews, looking to expand it beyond oncology," he says. "Accumulus can fill an immediate need. This is not something pie in the sky or 'nice to have.' It can be an enabler from day one."

The world got a preview of parallel review on September 17, 2019, when FDA announced the conclusion of a review conducted simultaneously with Australia and Canada for lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda) for the treatment of patients with advanced endometrial carcinoma. The three regulatory health authorities reviewed the application in collaboration, which allowed them to identify any regulatory divergence among the review teams, resulting in simultaneous approval in all three countries.

For the first full year of Project Orbis, from June 2019 to June 2020, a total of 60 oncology marketing applications (for either new molecular entities or supplements adding new indications) were received through the project, resulting in 38 approvals.

Another collaborative effort is the Access Consortium, comprised of the national regulatory authorities of Australia, Canada, Singapore, Switzerland and the United Kingdom. Access explores opportunities for information and work-sharing initiatives in areas including: assessing therapeutic product manufacturing sites; post-market surveillance of therapeutic product safety; assessment reports for medicinal products; development of technical guidelines and regulatory standards; and collaboration on information technology.

"The other part needed, and this is what Covid really uncovered, is the rapid exchange of data on a platform, that has interoperability across multiple frameworks," Stewart says. "That's what we also envision for Accumulus, playing a role in the short term, and being able to connect with different systems, different regulators and different platforms. This can serve the role of facilitating greater data exchange, not only in a pandemic, but when we're really trying an all-hands approach for a life-threatening illness or an unmet medical need.

Use Case 2: Chemistry, Manufacturing, Control (CMC) Data and Analytics

The second use case to be released on the Accumulus platform will will be for Chemistry, Manufacturing and Controls (CMC), which is an integral part of any pharmaceutical product application. CMC is critical to attaining a successful registration filing. CMC is applicable to the entire product lifecycle — it starts during the drug candidate selection phase and continues through post-approval and beyond.

"Realistically, what can be done in this first year is to look for quick wins," says Hilmar Hamann, Head of the Information Management Division at the European Medicines Agency (EMA), in Amsterdam.

"The area we are looking at primarily at the moment is CMC," says Hamann. "There is a high volume of submissions in that space. Even though it's all data, it's not really submitted to us in that form. For instance, stability data — the idea is to move away from the paradigm of submitting information, to sharing information on a permission basis, allowing the regulator to see the data in a form that permits analysis, that can be sliced and diced."

CMC ensures that pharmaceutical and biopharmaceutical drug products are consistently effective, safe and of high quality. It sustains a connection between the drug that is used

in clinical studies and the commercial drug that is marketed and available to consumers. It isn't a one-size-fits-all checklist or list of tests to be performed on every product but is instead tailored to the platform and delivery system, whether oral, injectable, inhalant or topical. CMC applies to both the product and its manufacturing facility.

Because CMC is such a core part of the regulatory process, the application we create for it will be extendable to other uses, just as a spreadsheet application like Excel can be used to develop a budget or to track inventories. If an organization manages CMC data with our application, it will know how to manage clinical data, how to manage preclinical data, how to manage summary data.

"That's why we gravitated toward the stability data, because the data is itself highly standardized," says Hamann. "The technology is an enabler, but there's a lot more that has to happen to make this successful. A lot more has to happen in terms of policies, standards, development of organizations, and those operate on very different timelines. I would be careful of expecting a miracle in a year, but [CMC] should demonstrate the concept, get the platform established, and deliver value that we can then expand on."

The Future, Near and Far

Accumulus Synergy is a joint effort initiated by 10 of the world's leading biopharmaceuticals companies, fueled by a global vision and a critical mission. Accumulus Synergy is also a startup organization, driven by ambitious goals, an optimistic outlook and a keen sense of urgency. The impact on global public health can be profound.

Like many startups, we aim to disrupt the status quo. But unlike most startups, Accumulus Synergy already has potential partners in the initial launch, in the 10 sponsors, who will help beta site and stress test our first applications in the coming year. In the longer term, we want to be the platform provider for all biopharma, not just the big companies.

"This is aggressive, but over the next one to three years, we want to have components across the development lifecycle, and ultimately, in 10 years, to have a cloud NDA, and not just through the FDA," says Stewart. "We'll be collaborating with the other regulators along the way."

There will also be secondary value opportunities around how biopharma runs the supply chain, how they run clinical trials, the data granularity they're able to achieve, and some of the analytics they'll be able to run against the data. There will be opportunities to digitalize much of the clinical trials process. Health authorities also will have an opportunity to improve productivity, efficiency and speed.

Accumulus Synergy will be inclusive, embracing solutions from multiple sources. Just as Orbis shows how parallel review accelerates development, we will also build upon the work of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH developed MedDRA, a standardized medical terminology for sharing regulatory information internationally. And Accumulus will partner with technology vendors large and small that seek opportunities in this field.

The Accumulus Synergy platform will make data and information sharing between a sponsor and health authorities more rapid, more transparent and more collaborative. But the goal of these efficiencies will always be improving outcomes for patients and unlocking the maximum potential of the therapeutic intervention. At the end of the day, our vision is the one we began with: to accelerate the delivery of critical therapies to the citizens of the world.

Accumulus Synergy is a consortium formed in July 2020 by 10 leading biopharmaceuticals companies: Amgen, Astellas, Bristol Myers Squibb, GSK, the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen), Lilly, Pfizer, Roche, Sanofi, and Takeda. This paper was written by Francisco Nogueira, CEO, Accumulus Synergy