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DXC TECHNOLOGY

Digitizing regulatory affairs:

The future of automation

Contents

Executive summary

The way life sciences businesses and regulators collaborate to bring safe new therapies to market is ripe for transformation. Digitalization and automation offer speedier creation, submission and querying of the volumes of documentation inherent in research and commercialization.

Yet the promise of automated end-to-end workflow leading to more efficient and error-free processes, as well as faster time to insight and approval, remains as yet largely unrealized. The advent of electronic standards (eCTD) for filing documents long ago, while proving its worth, has not yet been truly transformational.

Manual and paper-based processes die hard. Friction abounds internally and externally. Internally, pharma companies are still digitizing and harmonizing data. Externally, regulators are only slowly adopting digital and at different rates around the world.

But the lockdown-induced challenges during the pandemic to the way the entire healthcare system operates have changed everyone's sense of what's possible and their sense of haste. Digital-first approaches are now widely accepted as the way forward, automation is seen as key and new AI and other software tools to enable the next stages of transformation are almost ready for primetime.

Pharma's regulatory functions are already streamlining their internal processes to prepare for broader automation, pilots are underway, AI is being tested.

But significant challenges remain. The execution of master data management plans must go right. The talent needed to create, test, validate and deploy the end-to-end document automation processes is going to have to be cultivated. So does a 'machine-first' mindset that accepts the primacy of automated over human processes.

The ultimate destination of a dynamic regulatory system in which stakeholders evaluate data in real or near-real time and bring better outcomes to patients and payers faster, is still far from being realized but the path to getting there is at least in place.

Introduction

This paper explores the scope for life sciences companies to realize efficiencies and strategic innovation within regulatory affairs by driving digitalization further and faster to transform key business processes.

Engaging with regulators is extremely documentation heavy and today remains a patchwork of the paper based and the digital. This is despite the advent long ago of eCTD (electronic Common Technical Document), designed to simplify the process of submission.

The life sciences industry has yet to fully realize the potential to drive automation further in this area, through greater standardization and the scope to automate the summarizing of thousands of pages of documentation.

Not only can this create efficiencies, saving time and money; by speeding the process it can achieve a broader aim – ultimately providing faster time to market for new products, by providing data back to trial sponsors faster.

It also has the potential to make relationships between Regulatory Affairs and the internal and external stakeholders it deals with smoother and more productive – consultative and proactive, rather than proscriptive and reactive and thus increasing the scope for wider collaboration.

The paper will examine the current state of technological adoption in the industry, the solutions that are emerging, the opportunities they present, and the challenges faced in adopting them.

It will also explore the new challenges (and opportunities) presented by disrupted operational models, such as the transition to remote trials, and how these trends can be a catalyst in regulatory submission by increasing efficiency and value.

The paper will examine the wider environment of how disjointed the regulatory space is currently, both internally within life science organizations and when working with external stakeholders.

It will consider how an openness to collaboration, in part driven by new technologies, can improve processes for all.

Welcome to the digitalized, post-pandemic future

It's hard to overstate the importance of the change in attitudes to digitization and automation that has taken place in the last two years. These changes look set to create a drive towards deeper, broader and faster automation in the regulatory process.

The pandemic has underlined the need for a regulatory overhaul to help drive an acceleration in the innovation process, says Lada Leyens, Global Regulatory lead, Clinical Trial Innovation and Digital Health, PHC, Roche.

"Regulators have seen the need and companies have seen the benefit of using a digital system that can do everything and with which you can solve digital queries from wherever. We're seeing that change in mindset."

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The change is striking. Even the willingness to engage remotely rather than go through the inconvenience of diarizing and organizing meetings is a dramatic transformation in itself from the way pharma and regulators engaged prior to the pandemic, says Leyens. "We are having quicker conversations, not sitting in a room. Regulators that weren't open to electric signature for example or receiving data electronically are more open to it."

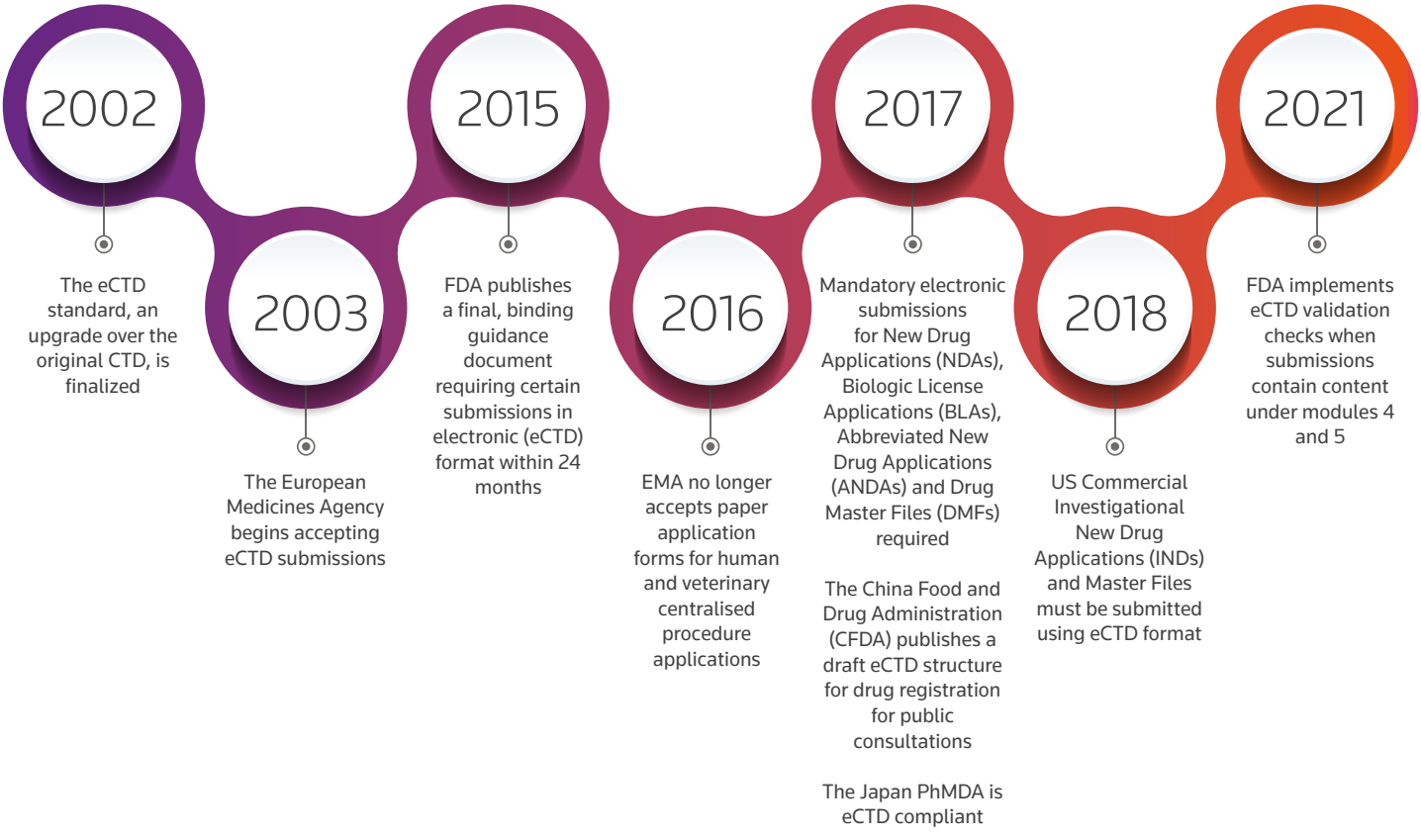
New approaches are being taken in trials and in manufacturing too, she adds. There is more video conferencing with sponsors and inspections that were wholly conducted in person have moved to being partly virtual. Marketing authorizations are happening virtually too, speeding the approval process.

The rapid updating of [vaccine] emergency approvals during the pandemic has illustrated the value of automation and its ability to compress timelines, says Manjunath Shanabag, Senior Executive, Global Consulting, Driving Global Sales, Enterprise Digital Strategy, DXC. "That could not happen without automation and AI."

The halting and then resumption of clinical trials during the pandemic also highlighted the need to accelerate the development of virtual or decentralized trials, says Shanabag.

This has accelerated pharma's engagement with the details of executing on trials with more virtual elements, he adds. "What do you do to validate this data and make sure it is secure and do you need to include all that information in the submission document and in what format? Automation becomes key."

This changed industry and regulatory mindset bodes well for helping drive adoption further and faster, says Stan Kachnowski, Director, Digital Health Program, Columbia Business School, Executive Education, Chair, HITLAB. "We are seeing one of the most rapid adoption rates of digital health in history whether in genomics, telemedicine or remote monitoring devices. As we move from pandemic to endemic we are seeing that there is a new order of things where the system is virtualized permanently."



The state of digital adoption now in regulatory affairs

There's no doubt that the automation on offer now is a clear benefit. The advent of electronic document filing, widely adopted in the US and Europe, has offered significant benefits in terms of smoothing submission, says Stéphane André, Senior VP, Head Global Regulatory Affairs, R&D Quality, Ipsen. "Preparing dossiers is very easy for us [given the] commonalities between US and EU dossiers. It's a major improvement in terms of organization: It is easy to copy/paste different parts of the dossiers.

"eCTD has been a big improvement for the industry and it was relatively easy for companies to adopt the same systems. We are relatively standardized today in our systems and tools as regards to submission of dossiers.

"I started my career with paper dossiers, which were a nightmare. Imagine photocopying papers - no one knew which version was which with which changes or reductions. Now it's much easier and saves time. We are now in a stable state of interaction. We have really managed very quick dialogue with the authorities. On this aspect of the dossier format and filing process, it is working fine."

Nonetheless given the fact that the electronic common technical document (eCTD) standard was created twenty years ago, progress clearly has not been fast as hoped. The regulatory documentation process today remains patchy. Large volumes of data are held across paper, disparate databases and spreadsheets.

Outside the US, some regulators are ready to accept content digitally but not all of it, certain processes remain paper-based.

As a result much friction, potential for error and requirements for extensive human inputs remains as information is moved around disparate systems and formats. The potential to automate this remains largely untapped.

The pandemic has accelerated regulators' adoption of digital and remote approaches. It has also accelerated the progress towards decentralized and virtual trials.

There is now a growing recognition of the value of and need for greater automation to every stakeholder - pharma, regulators and ultimately patients.

Now the challenge is harnessing deeper benefits to streamline internal and external processes. "The question now is how can we transform the information we have into [more useful] data," says Ipsen's André.

"The future of eCTD is to have direct access and communications with regulators. We want to harmonize our processes to be quick in filing, to have quick review and turnaround. Data management is important in the future. Regulators want data they can manipulate quickly and easily at any stage of the drug development process."

The uneven EU v US playing field

Further improvements to the processes in the EU, which in certain important respects lag those in the US owing to a lack of harmonization between EU member states, are in train. While only one R&D filing is needed per study in the US, the multiple ones needed in the EU for local national regulatory bodies should be replaced with a single dossier submission after a further round of EU harmonization following the implementation of its Clinical Trials Information System (CTIS) expected in 2023 and designed to harmonize the submission and assessment processes of clinical trials conducted in the EU.

Further EU harmonization ultimately comes down to greater resourcing for the EMA and the political horse trading among member states needed to effect this, but there are clear efforts to drive further faster regulatory harmonization in trials .

Patchy global adoption

Broader adoption of electronic filing beyond the US and Europe is patchy and so holds back the regulatory process in other jurisdictions, says André. But this is changing, new countries are joining and worldwide harmonization for most countries is now in prospect.

The opportunities of automation

While the process of moving from paper to digital made a practical difference to certain aspects of the filing process - such as version control and the ability to copy chunks of data with greater ease - pharma has only begun to exploit the full potential of eCTD, says Vijay Reddi, Regulatory Approvals & Information Lifecycle (RAIL) Lead, Roche Products Limited. "We're right at the beginning. eCTD was supposed to be this silver bullet to supercharge the process but that never came about."

Near term

While almost every large pharma business is well advanced with the basic applications of automated filing and eCTD, every organization is at different phases of adoption. For some there are relatively low hanging fruit still to pick.

BPO and automation of offshored work

There are several immediate or near-term gains to be gleaned from automation. The former includes already well-established business process outsourcing activities, which are still not yet fully exploited by all regulatory functions inside pharma, says Shanabag.

Applying automation tools to formatting work and other routine processes that are typically offshored to service companies is an immediate prospect. For some, that could cut the costs of that work now by 20% or more.

Pilots as proofs of concept

Roche's approach to near-term improvements is to conduct case studies with individual health authorities to drive more automation in specific interactions such as between sponsors and agencies, to demonstrate what's possible.

Greater automation of content, such as protocol summaries

The automation of content creation is a tougher nut to crack but a desirable one. "Can you create a bare bones document to be reviewed by a writer? Automating this would be one big step," says DXC's Shanabag.

But the potential efficiencies are significant. It might currently take five days to create a summary report, but automation can cut this in half. "That saves significant time and effort for each document. Given that it may take you three weeks to respond that can significantly speed up the process," he adds.

"Applying automation tools to formatting work and other routine processes that are typically offshored to service companies is an immediate prospect. For some, that could cut the costs of that work now by 20% or more."

Manjunath Shanabag, Global Head, Life Sciences Solutions, DXC Technology

Medium term

There is enormous scope to reduce handoffs in the documentation creation process, the number of people involved, and the time taken as internal processes are aligned and automated.

Less friction on the exchange of documentation will create more time for pharma's regulatory function to spend less time on operational legwork and more time engaging with scientists and health authorities on meaningful knowledge exchange.

"Right now, scientists are heavily tied up operationally," says Reddi. "To move between those systems, they need to go in and check that information is being transcribed and translated correctly. This needs to be physically rechecked as there may be slight differences regionally. By removing and automating that process you free up all their time to look at more strategic and scientific areas."

A series of pilots being developed or run today promise to drive end-to-end process improvements in specific therapeutic areas that should serve as proving grounds for wider adoption.

Roche's aim is to deliver two to three times more medical insights at half the cost to society by 2030. A continuous increase in the pipeline with transformational efforts are required to achieve this moonshot.

Externally there need to be changes such as greater collaboration between regulators in different countries. Digital solutions, such as piloting real-time reviews of regulatory processes on certain types of drugs or indications, can speed up this process dramatically.

Much of the most promising medium to long-term potential to automate regulatory interactions depends on the emerging generation of AI tools. "We will see more adoption of this over the coming year and it will become the norm ultimately over the next five years or so," says Shanabag.

Automating correspondence

AI tools, many still at the proof-of-concept stage, will find increasing use cases in the medium term. A good example is a high degree of automation in conducting correspondence. "When responding to correspondence from the FDA, for example relating to questions on specific aspects of a document, can pharma then open up the document and review that section automatically? Automating program review requests from regulatory authorities can be a huge time saver," says Shanabag.

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> Vijay Reddi, Regulatory Transformation Leader Regulatory Approvals & Information Lifecycle (RAIL) Lead, Roche

Long term

Mature documentation automation processes would handle highly interoperable data, pulled from various sources in and around highly integrated data ecosystems, compiled and reviewed rapidly for anomalies or errors. These processes would spot problems sooner, cut out most manual legwork and free regulatory teams to do more strategic work. It would all ultimately yield faster, cheaper insights and approvals.

The use of AI and analytics to identify potential issues with a trial earlier and thus to secure better quality data earlier is being proven. An example of a use case example of automation here might be the collection and analysis of EHR data as part of a trial. This would be used to verify patient identity, spot a safety event or identify data points that are anomalous and be able to tell the difference between them, for example out-of-range values for a set of blood pressure readings.

Rather than such factors being assessed every few weeks this could be done in real time, says Roche's Leyens, and this has obvious applications for regulatory filing. A system that analyses trial data automatically online, combining it with day-to-day health data and making sense of it all, could help support filings.

In a slightly more distant future, everything is connected, patient sensors communicate via the cloud as part of heavily digitalized trials that sponsors and regulators review in real time. Such automation efforts would be part of wider opportunities to automate the identification of future indications or routinely run synthetic trial control arms.

This ultimate goal of free flowing data around such an integrated ecosystem is probably 15-20 years away. Large-scale, industry-wide collaborative efforts such as the proposed cloud-based Accumulus project, the global information exchange platform designed to transform how drug innovators and health regulators interact, are needed to get there and remain long-term efforts.

Accumulus: Towards a collaborative future

Accumulus, a collaboration across the biopharma sector, aims to develop a cloud-based ecosystem that facilitates seamless interaction between pharma and health systems, reducing regulatory review times and transforming global data exchange.

This fully digitalized system should enable clinical trials to go to regulatory bodies for ongoing review in a dynamic, responsive and agile regulatory review process.

Its ultimate iteration would be highly automated, exploiting the latest AI and other analytics tools, constantly updating data in the cloud, enabling regulators to review live data, work through questions in almost real time and ultimately drive faster approval.

Such a system requires an almost complete reinvention by every stakeholder but would free internal regulatory teams to spend their time on useful engagement with regulators. "The regulatory function would be much more involved with strategic issues. We already do a lot of relationship management with agencies and we would be able to do even more," says Leyens.

A move towards regulatory reliance

Such an ecosystem would also promote much closer collaboration between health agencies internationally, she adds. "It would hopefully lead to more reliance on approvals between health authorities. If they are connected on one system you would not have to submit to 50-plus countries."

Currently smaller health authorities that lack eCTD adoption or indeed many of the resources needed to drive automation do not harmonize approval with better resourced health authorities but such as system would enable them to do so more easily.

Accumulus is not the only possible way to collaborate. An alternative to a cloud-based collaborative approach is a federated system, whereby information is not held in the cloud but rather held in a distributed set of databases to which specific and discrete types of access are granted to eligible parties to conduct specific kinds of work. The EU's DARWIN project is an example of a federated system.

To an extent, however, these definitions are semantic niceties with their distinct characteristics, pros and cons but ultimately both approaches would offer a means by which pharma, regulators and other stakeholders could collaborate effectively. The direction of travel is clear, says Leyens. "All stakeholders realize they can't operate in siloed systems anymore."

Barriers to automation

Before the promise of automation can be fully realized, a number of internal organizational and IT issues as well as technological shortcomings need to be resolved.

Inconsistent global adoption

The lack of broad or consistent eCTD adoption globally is a big impediment to its fuller applications, says Reddi. "We deliver medicines in 120 countries so we need eCTD in 120 countries but we only have it in about 10. Even in those countries that have adopted it there are different flavors, language issues and states of maturity."

Bespoking regulators' documents from country to country presents technical challenges which can be a key input adding to the cost of delivering medicines and can lead to longer lead times for patients, says Reddi.

"The mechanism of medicines being approved in countries such as the US and EU is becoming more efficient as standardization of the process grows, such as the use of eCTD. It is standardization which is foundational to allow automation tools to thrive. In all countries we need acceleration of standardization which will help to deliver medicines faster to patients. The more we move towards standardization of our regulations, the quicker we can provide medicines to patients."

A part of the reality here is that many regulatory bodies outside the richest economies are not well funded to realize the digital opportunities available.

Multiple internal systems

A significant source of internal friction is the use of multiple information systems across the organization. This will only be resolved with internal streamlining and harmonization.

Immature authoring and translation processes

Authoring software suited to the requirements of digitization and automation remains outdated. Specialist seamless solutions designed on web-based formats that can enable multiple sources to work on a document at the same time don't yet exist. Functionality such as transposing written text created with an Apple pen, for example, into digital format for translation 'as-you-write' to enable multi-country and multi-language collaboration in real time is another feature that does not yet exist. However the technology exists and can be developed to meet this aim.

A more basic barrier is translation tools that don't work well for medical documents which are replete with scientific language.

The resulting lack of functionality and interconnection comprises a significant barrier to a fully automated submission process, says Reddi. "You want to cut the number of handoffs and reduce the time in each handoff and how many people are involved. We are tying to connect our IT backbone with translation so information can flow seamlessly between the components, similar to the Apple device ecosystem, but that for us this is probably 15-20 years away, however we are taking the right steps and delivering impact with each step."

> "The more we move towards standardization of our regulations, the quicker we can provide medicines to patients."
>
> Vijay Reddi, Regulatory Transformation Leader Regulatory Approvals & Information Lifecycle (RAIL) Lead, Roche

Manual validation and compliance

Policies written by regulators for a paper-based world do not capture the potential of documentation in the digital era. In theory information only needs to be captured once if it is recorded in the correct format. A write-once, digital protocol is key to this digital transformation, says Reddi.

"eCTD is typically treated in the same way as paper-based policies that depend on humans rather than technology to validate data. Instead we should look at it from a computer's point of view in terms of validation, compliance and re-use. That is one part that's missing. We need to re-write our external policies to consume data and not paper, this would be a game changer from governments."

AI tools are still nascent and need to be proven in practice

Many of the automation tools with the greatest potential utility are not yet proven, says Shanabag. "The documents they create are well done in some cases, in others less so. These tools are not repeatable yet. It's all in proof-of-concept stages and the organization of the data and metadata is often not accurate enough."

Differing stages of regulator adoption of eCTD and differing adoption maturity among regulators remain barriers to greater automation. "We need to consider not all health authorities have adopted electronic submissions. We are still working with paper with some health authorities - we can use technology from our end but submit [in paper]," says Leyens.

For example the Swiss regulator operates on a paper-based system for marketing submissions but an electronic for medical devices and electronic trials.

Resourcing

The need for pharmacists, PHDs and medical doctors to be able to engage in the data management processes involved in more automated and dynamic regulatory filing and engagement will put a new strain on most industry players. The need for expertise will especially challenge small and mid-size companies who will struggle to hire the right specialists.

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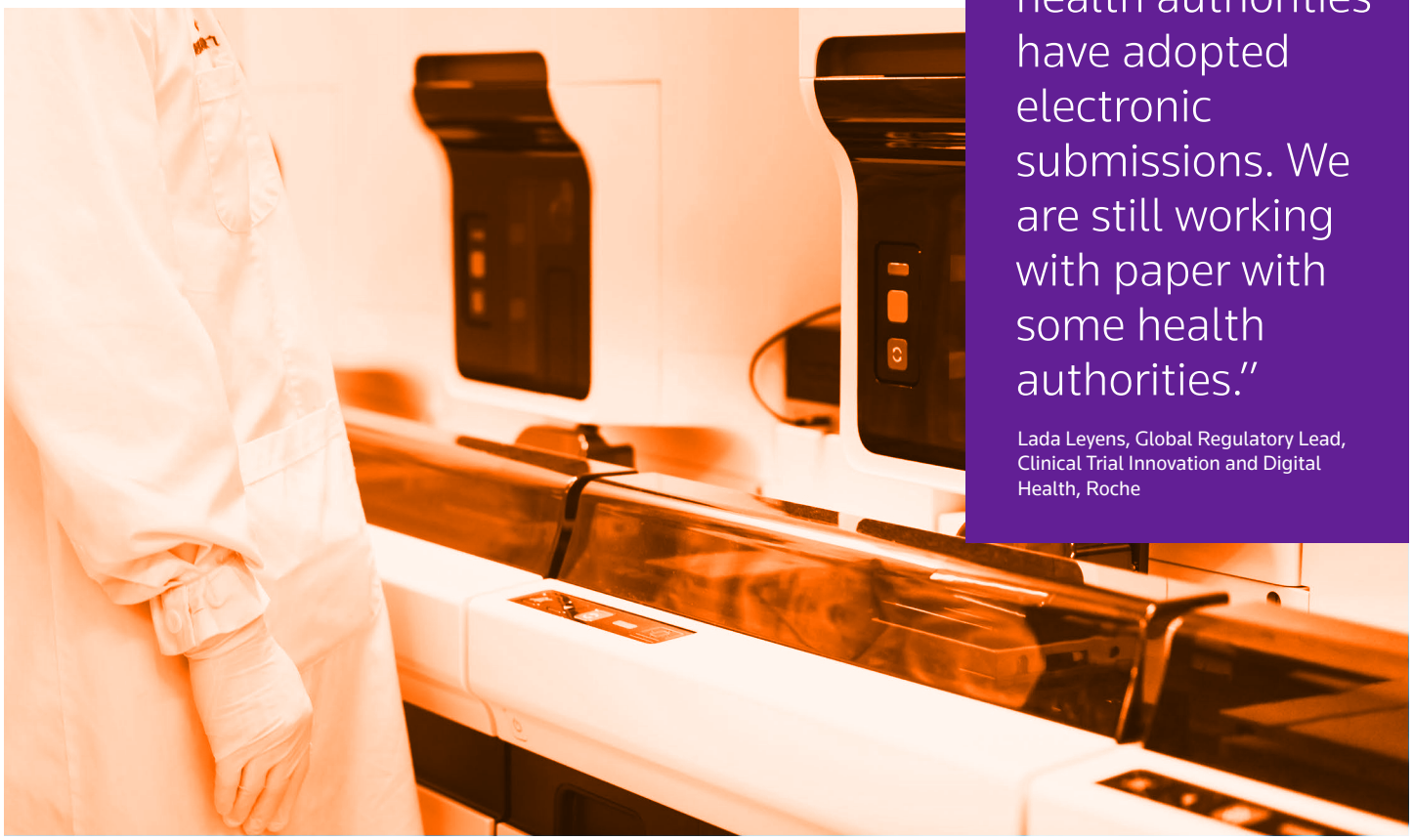

The way forward

The right talent, tools and collaborations are key to driving automation further and faster now.

Internal regulatory streamlining

Roche, like many other pharma companies, is removing internal barriers to fuller automation by harmonising its internal information systems, says Reddi. "We are aligning the process and the technology internally by moving ahead with regulatory information management."

For instance, it currently has one system for authoring internally, a second for publishing documents to health authorities and a third for archiving documents for auditing purposes. There is handoff between those three systems and they need high-skill, high-expertise people following it end to end to make sure those documents are aligned. Those three systems will be replaced. One version of a document will exist with complete version control and no hand offs. "It will be a lot quicker and will require fewer resources," says Reddi.

This process will bring different systems used across Roche's different regulatory functions and streamline them into one. "In the next couple of years we will work off the same system," says Reddi. "One of our key strategies is transforming information without changing the source data, which will come from a single source of truth that you then translate into multiple formats."

This process of defragmenting information systems will help significantly cut internal handoffs, enable greater automation and realize significant efficiency gains. Without this capability in place emerging AI tools cannot be used to help drive towards new or faster insights.

Talent needs to be nurtured internally

But even though larger players with deeper pockets might fare better, resourcing nonetheless remains an in industry-wide challenge, says Ipsen's André. "Dual education programmes don't exist anywhere in the world. It's a major challenge for the future of the pharma industry to drive the data revolution. You need an army of very good techies in computerized systems and data management. We have to select the right people and train them. This is the future for Ipsen, where we will have a [dedicated] training academy."

Mindsets need to change

There is a very human barrier to faster take up of automation and that is a reluctance to let machines do the legwork, particularly in the arena of regulation where the risks of error have potentially profound consequences. But the fact is that if properly executed, automation can de-risk whole swathes of activity, says Leyens. "People still don't trust machines but machines are better at some things and we need to let them do those."

Validation, and the infrastructure to do this end to end needs to be assured since validating automation processes is vital to guarantee error-free operation

When a system is moving data from A to B it needs to be without error. This means the infrastructure to enable validation as well as the processes and expertise (either in house or from consultants) is there to carry out effective validation.

This entails carefully mapping out the processes being automated from end to end, "not just looking at the regulatory process as many other processes link into that," says Leyens. "You need to make sure it always works. It's not easy to develop and validate these systems. You need a deep understanding of the needs for validation and that is not yet well known, I don't think."

Regulators will also need to adapt and update the technologies and processes they use to facilitate greater automation.

Master data management plans will be critical to automation initiatives

The need to integrate data and ensure its validity is well understood by the industry and the proper execution here is important. The ability of AI to work as advertised depends on the data being set up for it correctly for it with the right metadata, says DXC's Shanabag. "The rate and success of adoption will depend on how well organized the data is."

Collaborative engagement with regulators across pharma is vital

If a key role of the regulators is to improve the process of harmonizing best practices, their duty to further the potential of digital filing is clear.

Digital plays a clear role in making data more accessible, visible and transferable across platforms where you can glean insights and regulators can look at the signals in the data and have better assurance. That requires the right systems and access points.

To achieve this, close industry engagement is vital. The traditional regulatory framework is probably not adaptable enough for this, so the more industry engages, the more regulators can be informed about how the regulation needs to change and adapt.

The FDA's creation of the Digital Health Center of Excellence is a good example of how regulators can evolve to meet the greater pace of innovation and this is a source of hope, there's a traditional mindset on drug therapies but what about drugs connected with a digital tool? What about med tech - it's not one size fits all. It's important for legislators to understand how adapting a regulatory framework can improve access to innovations.

"The ability of AI to work as advertised depends on the data being set up for it correctly for it with the right metadata."

Manjunath Shanabag, Global Head, Life Sciences Solutions, DXC Technology

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DXC's RIM Platform is a cloud-based open digital platform designed to deliver an end-end enterprise solution by securely integrating and connecting the flow of data frictionlessly across regulatory affairs (RA) ecosystems. The platform simplifies the management of regulatory affairs content, data, and workflows by integrating electronic document management (EDM) systems, publishing solutions like electronic common technical documents (eCTD), and regulatory information management (RIM) systems.