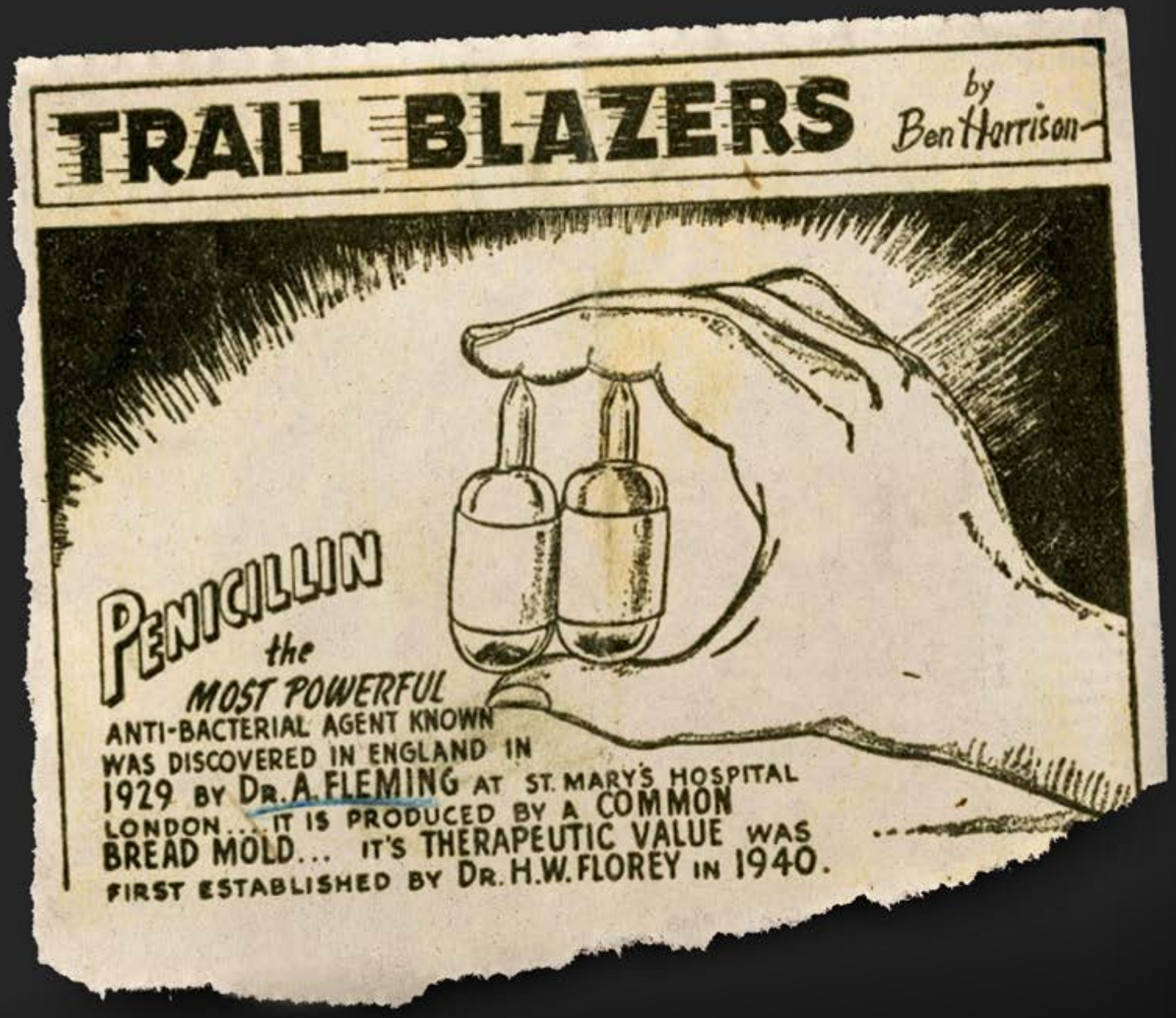

CLINICAL TRIALS

THE WORLD NEEDS CLINICAL TRIALS. HOW CAN REGULATIONS AND CUSTOMS MAKE LOGISTICS PROGRESS SMOOTHER?

Clinical trials have always been the lifeblood of medical progress, from James Lind's 1747 scurvy trial to Florey's first trials of penicillin nearly 200 years later to the Covid-19 vaccine trials of today.

DHL Customer Solutions & Innovation
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Panel cartoon graphic showing trailblazing medical discoveries: penicillin, by Alexander Fleming and Howard Florey. Newspaper cutting from the Milwaukee Deutsche Zeitung November 7, 1944

But the lack of standardization of procedures makes reaching new countries and territories fraught with administrative hurdles. So, if, as David Babaian suggests, 'inadequacy of logistics is the major thing preventing the development of medical treatments stepping up a gear' what can be done about it?

Firstly, the overall context is worth laying out. In the present scenario, pharmaceuticals in general represents the world's most highly regulated industry, with each country mandating the detail of product registration, manufacturing, price control, marketing and distribution, IP protection and, of course, indispensable and hugely expensive clinical trials research and development (R&D).

All this local activity occurs in a global context. The World Health Organization (WHO), Pan American Health Organization (PAHO), World Trade Organization (WTO), International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the World Intellectual Property Organization (WIPO) have all got stuff to say that trial sponsors need to know about. In particular the ICH, founded in the 1980s, seeks to standardize many aspects of trials in an increasingly broad geographical area.

The overall effect is often seen as a drag on progress. For example, in 2019 co-authors including Maria Apostolaros reported in 'Therapeutic Innovation & Regulatory Science' that "Despite the potential benefits of decentralized clinical trials (DCTs), adoption has been slow and variable. Some barriers may include the perception of regulatory barriers with implementing and using data from DCTs."

So, it's fair to ask: whether regulation is indeed enabling better, more effective trials and tackling the problems we really need it to?

MENDING WHAT DOESN'T WORK

To see how regulators are at least attempting to help not hinder, we could consider the topical example of newly implemented European Union (EU) clinical trials regulation 536/2014.

Earlier directives in 2001 and 2005 were criticized as serving neither participants nor the industry and even, in one commentator's words, offering "false promises of safety through bureaucracy." Perhaps reflecting such views, EU clinical trials applications dropped by as much as 25% between 2007 and 2011.

So, things were improved. The new framework, agreed in 2014, lets sponsors apply for a clinical trials agreement (CTA) in up to 30 countries with a single application. This makes cross-border collaboration and expansion among European Union/ European Economic Area (EU/EEA) countries easier. Full implementation within three years means all trials, regardless of their start date, will fall within the new regime.

Certainly, one of the benefits of this for the EU/EEA is that it will remain an attractive clinical research hub globally. Not just design but also the actual reporting of trials, inconsistently administered for years across different countries, has been tidied up. Even a steep increase in the amount of overall documentation required for a trial is arguably outweighed by the benefits – for sponsors operating in different countries, at least.

STANDARDIZING THE PLAN, NOT THE EXECUTION?

However, we should note that what's being discussed here is the standardization of the design, conduct, and reporting protocols for a proposed clinical trial. The ICH has indeed encouraged much progress in this over the years. Trials which follow its recommendations are often able to obtain speedy approval of the resulting medicines, even in quite unrelated countries.

All good, then.

But of course, only if the relevant trials themselves are actually both completed and compliant.

Sadly, until recently there hasn't seemingly been the same focus on regulatory issues that affect the actual operation of trials in the field. Certainly, logistics services are greatly impacted by regulation as no trial can progress without materials moving from A to B and normally back again. And when A and B are in different countries or, as we will shortly see, perhaps even just in different states across the United States (US), problems can occur which trial design itself can't influence.

TRIALS HAPPEN 'OUT IN THE REAL WORLD'

Truth is, outside of trial design itself there are a lot of variations from place to place in practical aspects of trial logistics.

One might imagine a package of investigative medicine making its way from a test center in one country to the private home of a participant in another or vice versa. But first consider how it is being transported. Does the country concerned allow whatever it is (potentially an unlicensed medicine or a unique bio sample) to pass within its transport network and in what ways?

Next, what happens when it arrives at a customs post? How long does it stay there? For example, Pakistan's own border authority asks importers to expect 7 to 10 days in customs for normal goods. Clearly our trials cannot sustain that so shortcuts of some sort will need to be in operation.

Lastly, is it even legally viable to send or pick up the material concerned from a patients' private address?

With all these potential issues, the implication is that manual or verbal patient reporting is what's at fault. Moving forward, isn't the obvious solution to match more remote trials with automated reporting?

Absolutely, is the answer! And this is where new practices may come to outperform the old ones. Between 2017 and 2019, 58 separate wearable and sensor technologies were approved by the FDA for monitoring stress levels, blood pressure, emotions, eye movements, and VO2 max, and for carrying out electromyography (EMG) and electroencephalography (EEG). Readings in real time, derived from patients' saliva, sweat and so on, can now be uploaded.

This is potentially great news in terms of accuracy, but the benefits don't stop there. Removing human data entry can increase the volume of data collected many times over, thus harnessing the ability of AI to sequence and analyze DNA and other information. Such heightened understanding will provide the foundation for advanced new medicines of the near future.

So wearable or implantable devices are certainly starting to play a role. The rate of adoption within trials is less clear.

Caution will always be a strong balancing factor, as one industry expert confirms:

"We've several pilots currently in which there are wearables in use, but simultaneously we've been requested to also record in the more traditional 'clipboard' fashion. Basically, we're testing the correlation in endpoint data as a precondition before our sponsors will consider putting a lot of data responsibility onto the AI/wearable model."

Such a process feels like due diligence, pure and simple. Hopefully there is just a small further step to take before industry really starts exploiting the possibilities of automated, bias-free data to increase trial compliance and ultimately improve success rates.

IS THE STATUS QUO A REAL OPTION?

Even before we discuss the pandemic, there is an urgency to accelerate progress of human medicine. This suggests that inconsistent or conflicting regulations are just not sustainable.

Deloitte predicts a record number of regulatory decisions will occur in the US alone this year for cell and gene therapies. Consider that any cell and gene therapy trial will very probably need to utilize decentralized clinical trials (DCTs) and the potential is obvious for hold-ups of physical material and for issues around trials data which might endanger or invalidate individual results.

That's the threat to advanced and highly expensive new medicines of a continued lack of standardization. So let's consider the other end of the scale.

It is now widely accepted that something must be done about the discrepancy in clinical trials between developed and least-developed countries. The International Journal for Equity in Health stated in 2018 "Diseases of relevance to high-income countries are investigated in clinical trials seven to eight times more often than diseases whose burden lies mainly in low-income and middle-income countries."

In plain language, not enough trials are being directed at conditions that kill or adversely affect populations in places like sub Saharan Africa. Of course if the Western world ever thought it could deprioritize health crises originating outside its borders, the pandemic has changed that. DPDHL's Chief Operating Officer and Head of DHL Customer Solutions & Innovation Katja Busch states "Collaboration has proven key to a succesful pandemic response, and the same applies to reach the next level of clinical trials."

In accordance with this, ways are needed to facilitate compliant, successful trials in wider locations.

Unfortunately a recent survey which examined 92 instances of clinical failure worldwide cited issues with regulatory complexity or approval in locations across Latin America and in Ethiopia, Saudi Arabia, and India. This is certainly not a comprehensive global list of countries where rules are preventing medical progress.

As already stated, many of these obstacles will be peripheral to the core design of a trial, being more in the area of practicality or logistics. Medical legal expert Dr Maeve Malone is well placed to comment on this issue in one developed market. She and colleagues at the University of Dundee, UK, completed comprehensive research on a single logistics-related issue involving legal and national Medical Product Licensing Authorities (MPLAs)/European Commission/European Medicines Agency (EMA) guidance.

Now every article in this series so far has touched on the importance of good patient experience to encourage better trial participation and completion. To contribute to that positive experience, logistics providers are already meeting the challenges of IMP direct-to-patient delivery and collection. Forcing people to travel to a pharmacy is a poor alternative.

> "Collaboration has proven key to a successful pandemic response, and the same applies to reach the next level of clinical trials."

Katja Busch
DPDHL Group COO
and Head of DHL CSI

"We examined the viability of direct supply of IMP direct to patients' homes within the EU," Dr Malone says. "The timing of the study was interrupted by Covid, so we were able to monitor the situation starting in 2019 and then later after the EU had responded both to the pandemic and the completion of Brexit [the UK's withdrawal from the EU]."

Clearly the ability to send trial medication via ambient or temperature-controlled delivery to a participant would be core to any decentralized clinical trial involving a new drug or therapy. But submitting questionnaires to EU/EEA MPLAs), Dr Malone's team found great variants in the local restrictions (or lack of those) which sponsors, CROs, and logistics partners would need to work around. By no means all EU countries allowed direct-to-patient distribution, perhaps partly because not all MPLAs were seemingly referring to relevant ICH Good Clinical Practice guidance specifically designed to achieve standardization.

The report was eventually titled 'When Innovation Outpaces Regulation' which feels significant, given our discussion here. Team member Thomas McDonald explains what prompted the university research:

"MEMO, a UK academic clinical center, encountered significant issues when trying to meet the request of EMA regulators to expand an ongoing study. IMP was already being posted direct to UK and Denmark addresses but other MPLAs advised this was illegal in their own EU states. In the end we had to compromise, for example, dispensing medication to Swedish pharmacies who handed them to patients for a fee. Other EU member states also had significant barriers to direct-to-patient supply of IMP."

University of Dundee *– Picture courtesy of Delong Chen* ▶

HAS THE PANDEMIC REALLY CREATED CHANGE?

The potential of Covid-19 to kill tens of millions or more appears to have been a textbook case of clear and present danger overriding the normal, cautious mindset prevalent within the healthcare industry and its overseers.

Steven Pope, Group Head of Trade Facilitation at DPDHL Group and an ex-UK Customs official, was in a good position to witness the global clash between urgency to meet the pandemic challenge, with movement of healthcare materials in general, and the fixed procedures of border checks between countries.

> "At the start, the biggest logistics priority in the world was movement of PPE [personal protective equipment],"But because other goods were not moving normally, the warehouses and borders were full – PPE consignments became like emergency services trying to get through a traffic jam."

Happily, regulation itself soon got out the way. "Less technically capable countries found ways around the problem of customs clearance using things like email and PDF. Meanwhile the major economies found a digital approach to border management – something that in our view should be standardized now."

In a similar way, authorities suddenly needed to tackle the obstacles to traditional clinical trials methodologies that were caused by potential vaccine trialists right across the planet being forbidden to leave home.

In the US, after an initial hold on much recruitment, barriers were lowered to allow trials to be quickly licensed and enrolled. The US Food and Drug Administration (FDA) provided guidance, for example allowing sponsors and site providers to care for patients in more flexible ways and to waive a lot of arguably unnecessary data points during trials, focusing on primary endpoints and safety.

Such was the reported experience of Catherine Gregor, MBA, CCRP, CCRC, Chief Clinical Trial Officer at Florence Healthcare, Atlanta. However, she concluded "The question that remains to be answered now is how all of those minor deviations will add up to potentially impact regulatory approval decisions in the future."

Steven Pope
Trade Facilitation Group Head
DPDHL Group

Read the full University of Dundee report HERE

This subject has been raised separately by the University of Dundee team. Their research project's second stage occurred well into the pandemic, reviewing different EU Member States' innovations in response to the issue above. "Some states, like Romania, enacted legislation to temporarily permit direct posting of IMP," recounts Dr Malone. "Others took a softer approach by referring to guidance published by the EC and EMA and their subsequent recommendation paper, along with Heads of Medicines Agencies in December 2022."

Either way this provided "much-needed assurance and permission" to the clinical trial industry regarding what sponsors, investigators, and distributors of IMP should consider if adopting direct delivery. A clear case then of guidance at least evolving to fit new circumstances?

Not precisely. Firstly, the university team points out the EC Guidance is clear that what it describes as 'simplification measures' are temporary, non-legally binding, and will only last until "there is a consensus that the period of the COVID-19 outbreak in the EU/EEA has passed."

Secondly, although the guidance is clear and intended to help facilitate direct-to-patient trials, it's necessary to read it in conjunction with the latest overall EU Regulation 536/2014, any relevant national Member State legislative provisions, the trial protocol itself, and the question of whether 'substantial modification' is taking place and should therefore alter the protocol itself. Effectively the onus is put back onto the sponsors to decide the last part for themselves.

"This could be considered the nutshell of the issue," suggests Dr Malone. "There are many documents including national laws, the National MPLA and EU Guidance, and the remit of the protocol all to reconcile before a proposed cross-border clinical trial can progress with confidence."

If we want and need reform that will be permanent, this temporary workload-heavy fix doesn't seem to fit the bill. Where more mundane trial materials, such as those described by Steven Pope, are concerned, there is also apprehension that some countries are backsliding on the relaxations they introduced.

WHAT WOULD "GOOD" LOOK LIKE FOR THE FUTURE?

Less ambiguity and more standardization, is one simple answer.

To start to overcome regulatory burdens that are holding back future clinical trials, contributors to this article had some clear suggestions. Regarding border checks, Steven Pope feels progress must be maintained rather than abandoned, suggesting:

"Many authorities have shown us that they can cut red tape quickly and learn new processes. Such stakeholder management, digitalization, coordinated border management, and risk-based controls should be allowed to continue making consignments simpler and more effective."

Identifying goods which qualify for expedited clearance opens up the possibility of a digital solution, described by Pope as follows:

"Firstly, data about a given consignment needs sending in advance to the border, so it's expected. Then all the border administration authorities, notably customs and health, should work together to scrutinize the data at the same time instead of in sequence. Lastly, country of export/country of import data should be identical, the principle being that one person's export is another person's import."

This is one ideal situation which is already being worked towards, but the current regulatory environment does not fully support it. Interoperability of IT systems is one issue – basically the rules might be the same, but the mechanics are not. However, Pope points out DHL has already done work, presented to the United Nations recently, in developing apps which allow data originated in differing systems to be compared on a like-by-like basis. This feels like part of the future solution.

Where IMP delivery is concerned, the University of Dundee's firm recommendation (Journal of Clinical Pharmacology 2021) is that:

"Specific regulation permitting defined categories of clinical trials to be conducted remotely should be enacted in the EU. Delivery of IMPs to a patient needs to be regulated and accommodated urgently to facilitate lawful conduct of such remote-centered clinical trials."

Precisely how this will be done is for regulators to determine, hopefully in conjunction with the clinical trials industry.

Positive change is needed if we are to continue to follow in the footsteps of Lind, Florey, and all the others whose successful experiments have made humanity safer. It feels as if this change should happen as a matter of urgency, because. it isn't a matter of if, but when the next great health crisis will come around.

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