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COVER IMAGE: iStockphoto ©

PUBLISHED BY:

Pharma Publications 50 D, City Business Centre London, SE16 2XB United Kingdom

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The next issue of IPI will be published in Autumn 2020. ISSN No.International Pharmaceutical Industry ISSN 1755-4578.

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REGULATORY & MARKETPLACE

08 Successful Post COVID-19 Disinfection Was Conducted in a Major Pharmaceutical Manufacturing Facility, China

Following the COVID-19 lockdown, environmental monitoring at a major international provider of biologics contract development and manufacturing organisation (CDMO) services in China indicated spore contamination in a production room. This case study, conducted by **Bioquell**, shows how successful post-COVID-19 disinfection was conducted in a major pharmaceutical manufacturing facility.

10 Controlled Drug Regulation in Russia: A Regulatory Factsheet

This article reviews the regulatory requirements of controlled drugs in Russia with the help of a factsheet, and also provides an insight into the changes in Russian federal law pertaining to narcotics and their implications for society. Balamuralidhara V. and Mahalakshmy R. at JSS College of Pharmacy outline their findings as being key for researchers and institutions, focusing on the Russian Narcotic Regulation as a basic reference model.

14 Reaping the Rewards of Structured Content Management in R&D Regulatory Operations: Preparation is Everything

Investing in structured content management and authoring capabilities without making sure there is a supporting backbone first is a bit like owning a Porsche when there are no suitable roads to drive on, yet life sciences firms are embracing the potential with great expectation and more than a little impatience. AMPLEXOR's Agnes Cwienczek issues a reminder that the journey towards structured content authoring could involve a 15-year roadmap, and substantial progress cannot be made until companies have the right foundations in place.

16 Pharma Firms will Need Academic Expertise Like Never Before in the Post-COVID World

In recent weeks, much has been made of the challenges arriving at a global consensus around the response to the coronavirus pandemic. However, one area for encouragement is the way in which the academic research community has aligned around the issue. Academic institutions are examining coronavirus epidemiology and pathobiology from all angles in the hope of accelerating our recovery from the crisis. **Graham Mills at techspert.io** shows why funding is being made available from both public and private sources to support innovation projects – estimated to be at least \$985 million since the crisis began.

20 The Vital Role of Translation within Pharmaceuticals during COVID-19

The world has become accustomed to accessible vaccines that enable us to enjoy longer, healthier lives. The majority of people have grown up being able to get the vaccines they need to protect them from diseases that impact the young, and those you're likely to contract when travelling around the world, so it's understandable they may not appreciate just how much research and time were invested in developing them in the first place. These medicines are so established and have been so successful in their duty, that the public can be forgiven for their lack of understanding as to just how difficult they were to develop the first time around. Alan White at The Translation People reveals more on how Coronavirus has presented a whole new challenge.

24 Successful Marketing of Medicinal Cannabis and Cannabis-derived Products

The European Union (EU) is missing a harmonised law on medical and, if appropriate, recreational use of cannabis. **Barbara Siebertz and Ute Hegener at PharmaLex** look at the national legal requirements of some European countries on medicinal cannabis, while highlighting the differences within the EU.

DRUG DISCOVERY, DEVELOPMENT & DELIVERY

28 Guiding Drug Optimisation Using Deep Learning Imputation and Compound Generation

The use of machine learning (ML) methods is now commonplace in many disciplines and Artificial Intelligence (AI) is on the rise, promising better and smarter solutions to 'all your problems'. However, despite the hype, there is increasing evidence we have entered the next 'AI winter' or the so-called 'trough of disillusionment' in the ongoing hype cycle. Benedict Irwin and Matthew Segall at Optibrium Ltd and Alexander Wade of University of Cambridge explain why there is still a gap in understanding on the route from traditional and well-understood statistical modelling methods to the poorly-defined promises of AI and how the majority of researchers can cross that gap, which is not yet clear.

32 Could Greater Diversity and Inclusion Improve Innovation in Pharma?

The past few weeks and the response to the COVID-19 crisis have shown how vital the pharma industry is to the global economy and society. The big question is whether the industry can really meet diverse, new patient and customer needs if it hasn't yet fully embraced inclusion amongst its own staff base. **Stephen Frost at Frost** Included looks at how greater diversity and inclusion improve innovation in pharma, and why it is important.

36 Dissolution Specifications for Oral Drug Products (IR, DR, ER) in the USA – A Regulatory Perspective

The development of a dissolution method with suitable specifications is a key part of any oral drug product control strategy. Dissolution testing is a highly important in vitro technique for pharmaceutical dosage form in development and formulation and, under certain specified conditions, the in vivo dissolution test can be replaced by an in vitro dissolution test. **Balamuralidhara V** *et al.* **at JSS** provide an overview of dissolution specifications and acceptance criteria that should be considered for IR, DR, ER dosage forms.

44 Barriers in Medical Device Innovation

The healthcare industry is extremely complex and, due to rising costs and patient demands, the medical care delivery environment is under growing pressure. Such stresses and the industry's inherent existence itself make healthcare development more complex than it is in the consumer products market. **Tarun Nag S S and Balamuralidhara V at JSS** show that in order to break through the complexities of medicine and drive science forward, inventors and medical testing and production firms must first resolve the many obstacles to the creation of healthcare products.

CLINICAL & MEDICAL RESEARCH

48 Expiry Dating: A Complex Mathematical Puzzle

Many times, during the course of a pharmaceutical clinical study, expiration dating and the extension of clinical product beyond the original date becomes a critical need for sponsors. **Dan Zuccarello at Sharp Clinical Services** shows how through statistical analysis based upon both first-order kinetics and the use of the Arrhenius Equation, we can offer this rationale to clients in an effort to provide scientific reasoning that can reasonably extend the expiry of the product.

TECHNOLOGY

52 The Rise of Al in Pharma

Over the last few years, the use of Artificial Intelligence (AI) in the pharmaceutical industry has gone from a promising prospect to an indispensable and proven tool. Largely driving the use of AI is the digital transformation that is occurring in the industry. Laura Marozsan and Ajay Shrestha at Thermo Fisher Scientific demonstrate how digital transformation is enabling pharmaceutical companies to innovate in new ways to drive scientific discoveries and get life-transforming treatments into the hands of patients more quickly.

56 Establishing a Sound Data Footing for AI

Emerging smart technologies offer a means of delivering more value and better business outcomes in many industries, not least life sciences. But the transformation potential relies on the quality, credibility and completeness of the data these intelligent systems are working from. Here, **Steve Gens of Gens & Associates and Remco Munnik at Iperion Life Sciences Consultancy** offer the five best-practice tips for achieving a definitive, trusted regulatory and product information asset base capable of supporting intelligent process automation.

58 Adopting More Agile Process Management and IT Advancement: The Need for Speed

External demands from regulators and the wider market are evolving at an accelerating pace, which is challenging life sciences firms' ability to respond. Project cycles of 12–24 months are no longer practical, especially given that new or updated requirements may have entered the frame along the way. In this article, **Romuald Braun at Amplexor** discusses the need for greater responsiveness from IT teams and suppliers to the changing needs of the business and how they might achieve that.

MANUFACTURING

60 How Aseptic Nanomilling can Provide a Solution for Today's Insoluble Compounds, Including HPCs

High-energy media milling (nanomilling) has become an increasingly popular drug delivery technique and for good

DISPENSING ISSUES?



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62 Greening Up our Act to Secure Supply: The Push for Pharma to Move towards more Environmentallyfriendly Propellants

Global warming accelerated by increased consumption of potent greenhouse gases has become a serious public concern and has triggered initiatives to further reduce the carbon footprint of all industries. Over recent decades, there has been a transition to more environmentally responsible industry practices. Lei Mao, Mark Knowles and Ron Roscher at Recipharm also stipulate that these gases have been shown to have an impact on global warming due to their high global warming potential (GWP) and long atmospheric life (AL).

PACKAGING

66 Printer Validation Packs: Don't Leave Compliance to Chance

Validation impacts every process and component of pharmaceutical production, including machines, systems, equipment and computer systems. Part of the validation process is in the documentation – there needs to be integrated support for documentation with 100% clarity and traceability. **Bart Vansteenkiste at Domino** looks at today's supply chain and how the printer is arguably the final key element in the validation process.

68 Polymer Syringes plus Functional Labels – A Combination with Added Value

Prefilled syringes (PFS) are continuously gaining market share as a convenient form of administering drugs. In particular, PFS made of high-quality polymer such as cyclic olefin co-polymer (COC) has become a well-established alternative because they offer greater design flexibility while reducing the breakage rate throughout the value chain. Andreas Hofenauer and Stefan Krauss at Schreiner MediPharm and Tom Van Ginneken at Schott AG have a discussion on polymer syringes along with functional labels.

LOGISTICS & SUPPLY CHAIN MANAGEMENT

72 Fake Coronavirus Medicines, Tests and Protective Equipment – Proof of Originality More Important than Ever

Where there is an acute lack of protective equipment, testing and medication in the fight against the coronavirus, product fraud grows rapidly. Even in exceptional times like these, criminals do not shy away from putting counterfeit and inferior goods into circulation, directly putting the public, healthcare workers and patients in harm's way. Mike Isles, the Executive Director for the Alliance for Safe Online Pharmacy in the EU and Dr Marietta Ulrich-Horn at SECURIKETT explain how in the race against time, less attention is paid to where the goods have come from.

76 The Evolution of Clinical Trial Supply Chain Flexibility

When it comes to clinical supply chain management, the need for greater flexibility feeds innovation and can be seen in the emergence of intelligent IRT systems, personalised packaging and labelling and direct-to-patient distribution. But why is flexibility so coveted within clinical supply chain management? Where did the concept come from? What benefit does it deliver? And what role does it play in shaping the drug development landscape of tomorrow? **Natalie Balanovsky at Almac Clinical Service** discuss these questions further.



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We are now in the middle of 2020. This first half of the year has certainly made us realise that the world changes and we have to be adaptable; as everyone everywhere has

been affected by COVID, I want to look at the reality of what the virus has brought to our sector.

Certainly within our lifetime, our world has become accustomed to accessible vaccines that enable us to live longer and more healthily than we would have 100 years ago. However, over the past 10 years, antimicrobial resistance has been widely talked about, with few antibiotics and new vaccines being found, so I do wonder how the world thinks it is going to locate a silver bullet for the COVID virus.

Alan White at The Translation People reveals more about how Cononavirus has presented a whole new challenge in regard to translation within pharmaceuticals. This is also very important when there are ethnic minorities living in communities where they do not understand the local language, thus presenting a challenge in ensuring they adhere to the local COVID rules to stop the spread of the virus.

Graham Mills at Techspert.io talks about why pharma firms will need academic expertise like never before in the post-COVID world, as \$985 million has been put towards funding from both public and private sources to support innovation projects.

In the first half of the 20th century, science fiction familiarised the world with the concept of artificially intelligent robots. The life science sector has talked about this and how it is going to revolutionise the way we can work. Benedict Irwin, Matthew Segall at Optibrium Ltd. and Alexander Wade of University of Cambridge explain that there is increasing evidence we have entered the hype cycle "trough of disillusionment" due to the gap in understanding the route from traditional and well-understood statistical modelling methods to the poorly-defined promises of Artificial Intelligence.

Natalie Balanovsky and Gillian Wilson at Almac Clinical Service discuss why flexibility actually feeds innovation and the evolution of clinical trial supply chain flexibility. This will also be interesting the further we move towards individual healthcare and personalised medicine, along with directto-patient distribution.

I hope you enjoy reading this edition of the magazine and I am looking forward to seeing how the second half of 2020 continues; will we be any nearer to finding a vaccine and will we be able to find a new normality in our everyday lives?

Have a lovely summer.

Lucy Robertshaw Director, Lucy J.Robertshow Consulting



The outbreak of Coronavirus Disease 2019 (COVID-19) has caused enormous challenges to worldwide's economy and people's lives. With the epidemic on the rise,

society has paid more attention to the healthcare and pharmaceutical industries, which will impose both positive and negative consequences across different sub-sectors.

Pharmaceutical companies have deep scientific knowledge gained from decades of experience with similar viruses. Companies are researching vaccine candidates and undertaking inventories of research portfolio libraries to identify additional potential treatments for R&D.

Some have donated compounds with the potential to treat coronavirus for emergency use and clinical trials, including compounds formerly tested on other viral pathogens such as Ebola and HIV. Others are exploring ways to use existing technologies that provide the ability to rapidly upscale production once a potential vaccine candidate is identified.

In the coming weeks and months, life sciences companies will take the lessons learned from this crisis, as the industry has with other events in the past, and work to improve their agility and resiliency. The impact on clinical trials and the drug approval pipeline will also come into focus and underscores the need for the same energy, collaboration, and commitment by industry and governments to minimize disruption and provide patients with new medicines and treatments.

I wish you all a safe and health summer, and I look forward to bringing you more informative articles in the autumn issue.

> Virginia Toteva Editorial Manager – IPI

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Successful Post COVID-19 Disinfection Was Conducted in a Major Pharmaceutical Manufacturing Facility, China

Background information

Issue: Following the COVID-19 lockdown, Environmental Monitoring (EM) at a major international provider of biologics Contract Development and Manufacturing Organizations (CDMO) services in China indicated spore contamination in a production room.

Despite exhausting all disinfection methods in their records, including the manual application of a sporicide, there was a repeated failure of the EM test standards. Consequently, the production of a valuable batch of product worth \$5M USD was being delayed.

Our Solution: The fungal species identified, (*Cheatomium globosum* and *Chaetomium unguicola*) are notoriously challenging to remove using conventional methods, as the key is to locate and eliminate the reservoir from where the contamination starts.

Bioquell, an Ecolab Solution, was able to provide its Rapid Bio Decontamination Service (RBDS), utilizing 35% hydrogen peroxide vapour technology to cover every exposed surface as well as the air within the deployment area. This provides a 6-log sporicidal kill, including in the contamination reservoir.

"Bioquell RBDS allowed us to quickly resolve our challenge and begin operations with confidence." QA SENIOR DIRECTOR



Challenges

Timescale

Requirement: To rapidly resume production immediately following the COVID-19 outbreak and lockdown.

Our Solution: Almost immediately after the lockdown was lifted, Bioquell was able to quickly complete the decontamination of almost 4000m³ of production space including the HVAC.

Efficacy Needs

Requirement: 6-log bio-decontamination throughout the entire enclosed space to ensure no spores remain.

Our Solution: Bioquell hydrogen peroxide delivers a 6-log sporicidal kill on all surfaces in an enclosed area.

Documentation Needs

Requirement: To demonstrate efficacy against the spores causing the continuous EM failures.



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Additional Challenges

Requirement: Integrity of wall panels must be maintained to avoid blistering. No compatibility testing possible in advance.

Our Solution: To provide evidence of previous results on panel integrity after Bioquell Bio Decontamination in other comparable facilities.

Requirement: Validation of eradication of identified fungal species (*Cheatomium globosum* and *Chaetomium unguicola*) in the HVAC with use of Biological and Chemical Indicators (Bls & Cls).

Our Solution: Use of an alternative decontamination protocol involving pulsing through hydrogen peroxide vapour during a decontamination cycle.



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Controlled Drug Regulation in Russia: A Regulatory Factsheet

Abstract

The Russian pharmaceutical market ranks 14th globally, as per the report by Deloitte in 2018. The global market comprises 64% generic drugs and 36% original drugs in terms of value. Prescription drugs represent 64% in value. Russia is suffering from a growing community wellbeing catastrophe and awkward medication ingestion concern. Drug addiction is an autonomist, securitised and ethical problem in Russia as it is a transit and destination country for Afghan heroin. Controlled substances are regulated, controlled and monitored by the "Federal Drug Control Service (FDSK) of Russian Federation" and several modifications were made in the FDSK to powerfully implement the law. This article reviews the regulatory requirements of controlled drugs in Russia with the help of a factsheet, and also provides an insight to the changes in Russian federal law pertaining to narcotics and their implication for society. This will provide a key for researchers and institutions focusing on the Russian Narcotic Regulation as a basic reference model.

Key words: Controlled Substance, FDSK, Drug Addiction

Introduction

Russia is one of the major countries facing illicit drug trafficking, even after imposing harsh penalties.1 Most of the imprisonments occur due to the application of Article 228² related to drug crimes, as it is a hub for Afghan heroin. Similarly, possession of 6gm of cannabis is an administrative offence, having a penalty of a fine or detention for 15 days.³ Any usage above 6gm is a criminal quantity and is liable to be penalised. The new Russian law on the pharmaceutical industry was implemented with effect from 1st September 2010. The federal laws and guidelines were modified in 2013-14 to institute obligatory drug usage.

Even now, the police actions are to be regulated as innocent people are getting arrested without humanity. Hence this review study was conducted to have knowledge of controlled drug regulation in Russia focussing on regulatory framework, offences and penalties, current scenario etc., which will be enlightening to scholars in this area.

Organisation of FDSK

The following figure shows the organisation pattern of the Federal Drug Control Service of Russia.

Current Scenario

Data from multiple sources shows that there are 7.3 to 8.5 million drug users in Russia. In the Saint Petersburg conference conducted in October 2017, specialists stated that 6, 37,482 people were incarcerated in Russia in 2016, 63% of which were for drug crimes.⁸

The table below shows that the prescription drug market of Russia rose abruptly from 2016 to 2019. The prescription drug sales contributed around 62.3% in 2018.

Agency	Role
"Anti-Drugs	State Committee against the illegal trading in
Independent Russian	NDPS
Agency"	
"State Committee of	Monitor the illegal trading of Narcotic Drugs and
Russian Federation"	Psychotropic Substances (GOSNARCOCONTROL)
"Federal Drug Control	Extension of the Committee after renaming
Service of Russia"	
"Main Directorate for	Replaced FSKN ⁴
Drugs Control"	
	Agency "Anti-Drugs Independent Russian Agency" "State Committee of Russian Federation" "Federal Drug Control Service of Russia" "Main Directorate for Drugs Control"

Table 1: History of Narcotic Drug Control in Russia

- Federal Drug Control Service
 - Directorate for Analytical Coordination
 - Operative Directorate
 - Operation and Search Directorate
 Directorate for coordination of Operative Activities
 - Directorate for combating against
 - Drug Crimes in TransportationDorectorate for combating against il-
 - Dorectorate for combatting against ne legal activities in narcotics sphere
 Directorate for combatting against
 - Directorate for combating ag Money laundering
 - Department for International Cooperation
 - Investigative Department
 - Dept. for Special Technic Activities
 - Department for Internal Security
 - Directorate for Special Communications
- Source:Federal Drug Control Service of Russia⁴

Figure 1: Organisational pattern of FDSK

As per 'Pharma 2020 Strategy' the Russian government is engrossed in crafting its own pharmaceutical industry to lessen dependence on imported pharmaceuticals. Moreover, it is anticipated that the native manufacture may be amplified from 28.5% to 75% of all medications in Russia by 2020.

Conclusion

Russia needs to adopt a more broad and comprehensive plan that balances banning and law enforcement with management, anticipation and harm reduction methods. Moreover, collaboration must be established between

	2016	2017	2018	2019 estimated
Pharmaceutical sales	16,415	20,095	20,095	21,03
Prescription drugs sales	9,839	12,285	12,524	13,309
Generic drugs sales	6,529	8,239	8,466	9,096

Units: \$ millions

Source: Fitch Solutions (formerly known as Business Monitor International)⁹ Table 2: Overview of Prescription Drug Sales during 2016-2019

Country	Russia	Drug Type	Narcotic Drugs and Psychotropic Substances			
Regulating Ministry	Ministry of Healthcare (the "MOH"), the Ministry of Industry and Trade (the "MIT")	Regulatory Authority	Local Russian Federation authorities			
Act/Law	Federal Law No 3-FZ Russian Federation Federal Act on Narcotic Drugs and Psychotropic Substances					
About Country	Area Population Language Capital Currency		17.1 million km² 143,456,918 Russian Moscow Russian ruble			
Geographical Distribution	Russia, the world's large as well as the Pacific and	Russia, the world's largest nation, borders European and Asian countries as well as the Pacific and Arctic oceans. Economic Status				
	St	atistics				
GDP growth	-1.2% (Q1 2016	5 Est.)				
GDP per capita	\$8,058 (2016)	(nominal) \$23.8	75 (2016) (PPP)			
GDP by sector	agriculture: 40%	inductry: 36 30	6 services: 59 7%			
GDT Dy Sector	agriculture. 470	, maasay. 50.57	0, Sel VICES. 59.770			
Pharmaceutical Market	A new draft law was implemented late 2016-2017 for the tracking and tracing of medicines, ensuring that legal drugs reach the shelves. An additional 10 factories for the manufacturing of biosimilars are set to be completed by 2020. According to leading business reports, the Russian pharma market will reach \$36.61 billion by 2021.					
Classification	Narcotic drugs, psychotropic substances and their precursors controlled in the Russian Federation shall be included in the schedule of narcotic drugs, psychotropic substances and their precursors controlled in the Russian Federation (hereinafter referred to as the "Schedule") subject to control procedures of the State. They are listed below:					
	List I – Trade of drugs in the List II – Trade is restricted on Russian Federation and List III – Psychotropic s exemptions List IV – Precursors list, the and international agreer	nis category is pro ed and control r nd international substances list; he trade of whic nents	phibited in the Russian Federation neasures are established based agreements to which it is party trade is restricted, with some h is based on Russian Federation			
Drug Laws	Federal Law No. 61-FZ on the Circulation of Medicines, dated 12 April 2010, as amended (the "Law on Circulation of Medicines"). Federal Law No. 184-FZ on Technical Regulation, dated 27 December 2002, as amended, governing technical regulation.					
Regulation	The official foundation of Federal Law No. 323-FZ or the Russian Federation. Th Federal Law No. 61-FZ or as amended (the "Law on from 1st September 2010 Additional regulations that healthcare division embra dated 27 December 200 the pronouncement of or preparations; Federal Law as amended (the "Law on Federal Law No. 99-FZ or 2011, governing licensing Russian Federation Federa	Russian pharma n the Fundament he chief statute on the Circulation of Circulation of Me at are also imper ce "Federal Law N 02", governing p conformity and a w No. 38-FZ On A Advertising"), lea n Accrediting Def g in the Russian F al Act on Narcotic I	ceutical regulation is positioned in als of Citizens' Health Protection in n the medicinal market in Russia is of Medicines, dated 12 April 2010, edicines") implemented with effect ative for the pharmaceuticals and lo. 184-FZ On Technical Regulation, rocedural directives, specifically authorisation of pharmaceutical advertising, dated 13 March 2006, ding advertising of medicines; and finite Sorts of Deeds, dated 4 May federation. Drugs and Psychotropic Substances			
	As per the approval of Fec Act launches the legal four drugs and psychotropic su the purposes of shielding public welfare.	deration Council d Idations of State p Ibstances and pr g communal wel	on 24 December 1997, the Federal policy regarding the trade in narcotic eclusion of unlawful trafficking for Ibeing, national safekeeping and			

Figure 2: Factsheet for Controlled Drug Regulation in Russia - Part a^{5,6,7}

government and non-government organisations and communities to counter the drug problems and implement the federal laws in a manner useful to society. The Russian medication strategy is a significant situation to study to perceive the consideration of the corrective and slurring principles of international drug control. In Russia there is unrestricted drug law enforcement which has resulted in extensive, uncivilised and methodical violations of human rights and fundamental liberties.

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Regulatory & Marketplace



Figure 2: Factsheet for Controlled Drug Regulation in Russia - Part b^{5,6,7}





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Reaping the Rewards of Structured Content Management in R&D Regulatory Operations: Preparation is Everything

Investing in structured content management and authoring capabilities without making sure there is a supporting backbone first is a bit like owning a Porsche when there are no suitable roads to drive on, yet life sciences firms are embracing the potential with great expectation and more than a little impatience. AMPLEXOR's Agnes Cwienczek issues a reminder that the journey towards structured content authoring could involve a 15-year roadmap, and substantial progress cannot be made until companies have the right foundations in place.

In 2020, there are numerous external and internal drivers for life sciences organisations to be collecting, preparing, publishing/submitting and managing more and more data, and to be doing this more and more using a structured format. Regulatory agencies are demanding increased safety and traceability detail in order for products to be licensed and stay registered; requirements about what goes on packaging and labelling are becoming ever more particular; and the public at large is calling for greater transparency about the drugs they take and the medical devices they use. Inside the organisation, meanwhile, companies need to be smarter, faster, more accurate and cost-efficient in the way they capture information and create critical content - from clinical trial studies data collection and reporting, to managing product labelling and patient instructions for use over time. Success in these areas should mean they are able to manage resources more effectively, reduce lead times, and more readily maintain compliance/minimise risk.

As a result of these growing databased demands, we've seen a surge in life sciences companies asking for help – especially large organisations, and generics manufacturers with high volumes of content throughput and a significant need to reduce costs/ boost efficiency. They see the sizeable challenges they are facing, and the spiralling problems these are creating internally, but in the main these organisations have little idea where to begin. Clearly they need to bring their data under control and find better ways of managing it, but how they might go about this remains an unknown to them.

Start Small, With Focus

When approaching transformation, we advocate that companies start with a clearly-defined business case in one small, targeted area which will help them to secure internal funding for improvements. Once specific benefits have been demonstrated, this will help to make the case for wider change and to justify additional budget.

It is important to note here that changing the way organisations manage content – for regulatory purposes and to support more efficient global practices around reporting and labelling – requires disruption to the way people behave and work. Getting their buy-in to the transformation is critical, then. Identifying corporate-level champions, and creating a team that can showcase successful initial use cases, will be important in creating momentum.

The other critical factor to be aware of is the criticality of a strong technical 'backbone' to support current and future use cases for regulated product data from one end of the global organisation to the other, across and between different departments and content use cases. Too often, project teams try to apply a new data management approach to address an isolated problem, expecting that focus alone - and perhaps the simple application of XML to publish the same information to different channels - will bring the results they need. But unless they approach their goals in the context of a wider journey, towards creating a credible master data source that can be relied upon time and again for accuracy, currency and compliance in every corner of the organisation, such investment will see a poor and limited return.

Scoping the Challenge

It is easy to underestimate the scope of what may be needed by an organisation to 'put its house in order', after decades of working in fragmented ways with too much freedom and variation around how product-based data is captured and published. Across international operations, life sciences companies are likely to be sitting on huge and highlydispersed volumes of data – comprised of multiple different formats, of variable completeness and quality, and including considerable duplication and redundancy. All of this limits the value and reusability of that information.

For any data transformation initiative to provide maximum longterm benefits, companies need to think in terms of building a road to their desired destination: one that will help their operations run more smoothly once the way is clear. And this will take time, not least because there will be existing minor roads in a poor state of repair and disused dead-end routes to be attended to as part of the new construction effort.

Just as Rome wasn't built in a day, so a definitive data backbone will take time to create – one that companies can run their business on without fear of incident. By that, I mean years (as many as 10–15) rather than months to deliver complete transformation.

Ideally, it would be possible to analyse and transform content by tackling small sections at a time, comparing different sources to look for discrepancies or overlap. However, if respective systems and teams have captured data in different formats and with differing degrees of granularity, comparisons will require too much time. Other potential issues in clearing a path through the complexity include data ownership. If content ownership has tended to exist at a document level rather than a sourcedata level, then it may not be immediately obvious who should be driving any data transformation initiative and own the content in future.

Define the Future, Then Tackle the Legacy

In the meantime, setting up common structures and templates for data will help to put a hard stop to continuing data complexity, by imposing firmer parameters over what and how data is captured from document/report authors. By restricting data input to what is needed by regulators, companies can start to curb the spiralling of free-form content. This will help to keep everyone focused on building consistent, high-quality data with the potential for extensive re-use as long as the accuracy and currency of the data is maintained across its lifecycle, so that it remains trusted as a definitive information source. (If, by contrast, content continues to be cut and pasted between documents, version control and confidence in data sources will remain compromised, and information complexity will continue to blight productivity, efficiency and compliance.)

Establishing a common 'dictionary' for use across the organisation's content backbone will be instrumental in the huge task of transforming existing content so that it can be retro-fitted into the new structured templates, and invested with new business value. There is no getting away from the fact that this will be a vast undertaking – assessing content, de-duplicating repeat records, addressing subtle linguistic differences between versions of content, and so on. Yet there are some excellent tools that can help with this: for example, analysing and comparing documents between countries and languages.

A common dictionary will set down agreed rules for referring to products and data around them. It will also define any metadata linked to that content which makes assets searchable and connectable to context. Once historic product data has been drawn down, 'cleaned', transformed and assigned proper schema (mapping relationships between data, differentlanguage versions of the same content, etc), and processes are put in place to ensure that information maintenance (edits, additions) adheres to the new structure, the positive impact of the transformation will begin to be felt in everyday activity.

So, where to start?

Look for 'Easy' Wins First

We recommend that companies initiate their data transformation endeavours/ proof-of-concept projects in an area where documents are fairly simple in make-up. That is, they are factual rather than descriptive, and default to a single language in many cases. Some CMC/manufacturing documents fall into this category, detailing the composition of a drug and usually in a common language. Descriptions of formulae can be readily transferred to a table format, following standard fields describing the composition of a drug or its manufacturers.

Labelling might appear to invite structured formatting too (in fact structured authoring is ideal for labelling management), but it will take a lot of work to get to this point from current approaches. Analysing and retrofitting content from existing labelling files will not be straightforward, given that each market or country has its own precise regulatory requirements, as well as local language and phrasing needs. Once the correct core content has been identified and stored as modular content assets, labelling data is extremely reusable, because a number of elements will remain the same between different product information documents, so labelling should definitely be a target for transformation in due course. That's as long as the system managing everything has access to metadata that maps the relationships and interdependencies between the data appearing in different places and/or in different languages. Once this has been set down, and trusted content exists in modular form so that it can be called up and repurposed readily, managing future edits and additions as well assessing changes to labelling content becomes much more efficient and reliable

CMC Documents – Then Clinical, *Then* Labelling?

Given all of these factors, we would propose making headway with CMC documentation to start with, especially given the likely backlog of existing content that needs to be processed. Clinical documentation will make for a good second area of focus, especially given the expected efficiencies where certain elements of reporting will apply across more than one market. Also, clinical study narratives – although free-form historically – will contain common elements, and tend to be generated in English as the default language.

Once companies have amassed decent experience, learnt what works best and proved the potential of a common, structured way to capturing and managed content, they can broach international labelling management from a structured basis, harnessing reusable master content. While a more complex prospect to transfer to the new discipline, the potential efficiencies of transforming this vital branch of regulated content are substantial. A more structured approach to labelling creation and change management will also make the delivery and updating of electronic product information a viable prospect, with significant safety and convenience benefits for patients looking for more accessible information about the products they are consuming.

The main takeaway from all of this should be that there are no shortcuts to structured product information management. Data-driven operational transformation has a great deal to offer life sciences organisations, certainly, but only if they are prepared for the substantial groundwork they will need to put in, which simply cannot happen overnight.



Agnes Cwienczek

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Pharma Firms Will Need Academic Expertise Like Never Before in the Post-COVID World

In recent weeks much has been made of the challenges arriving at a global consensus around the response to the coronavirus pandemic. However, one area for encouragement is the way in which the academic research community has aligned around the issue. Academic institutions are examining coronavirus epidemiology and pathobiology from all angles in the hope of accelerating our recovery from the crisis. All over the world, funding is being made available from both public and private sources to support innovation projects estimated to be at least \$985 million since the crisis began.

While it's unusual for so many academic institutions to be so heavily focused on a singular challenge, the emphasis on 'translational' research – i.e. research intended to deliver tangible benefit in the here-and-now – is nothing out of the ordinary within healthcare and life sciences.

In the UK, for example, there's been £530 million of new translational research funding from the Medical Research Council alone in the past decade, which has in turn generated a further £1.1 billion in private sector investment.

Translational research is heavily relied upon by the world's leading pharma and life sciences organisations, largely because it is the academic domain that fosters and nurtures the sort of highly specialised expertise that allows these firms to address genuinely new problems as they arise.

The Limitations of Existing Knowledge Networks

COVID-19 is a perfect example of a new, complex problem that requires us to first understand the mechanics of the virus and how it operates, and then to translate that knowledge into a practical solution for curbing its impact, i.e. a vaccine. The challenge within the pharmaceuticals and life sciences industries – where the delivery of a coronavirus vaccine is of paramount importance – is that identifying appropriate sources of academic advice and expertise is already fraught with difficulty.

This is not so much a question of finding talented research scientists. After all, most businesses within these industries already maintain healthy and productive relationships with relevant university faculties, enabling them to collaborate on lab-based research around how certain diseases work, or to test a company's own drugs.

The problem is that even the biggest companies can't afford to engage with every single university or potentially relevant academic, hence they prioritise partnerships with the institutions with the best overall reputations, or those best-aligned from a commercial perspective. Hence, what each pharma and life sciences business will end up with is its own necessarily narrow, closedloop network of academic expertise.

While this may be perfectly sufficient for meeting ongoing business priorities, it poses an acute challenge on the occasion that a firm requires expertise beyond its existing network – for example, when seeking additional opinions on a potentially interesting new technology, with a view to a potential acquisition or licensing arrangement.

No pharma business can afford to rest on its laurels for too long; irrespective of whether there's a pandemic ongoing, each firm has a vested interest in discovery and innovation. Getting this right, however, is easier said than done. If they're given bad advice that causes them to back the wrong technology, it can mean billions of dollars down the drain, not to mention years of misdirected resource and productivity. These situations occur all too frequently, despite organisations' best efforts. The more complex the problem, the higher the stakes.

Considering the Ramifications of COVID-19

COVID-19 has created perhaps the biggest market opportunity in the history of modern medicine, one that carries incredible risks for the organisations that choose to involve themselves in the race for a commercially viable vaccine.

Internal resources within many pharma firms are being reallocated towards COVID-19 treatments and vaccines, understandably so given that every government in the world has an urgent need for these solutions. But this race will inevitably deliver both winners and losers, and prioritising COVID-19 means deprioritising and diverting resources away from other treatment areas, at a time when the pharma and life sciences industries are already working at full capacity. Firms are facing massive challenges in carrying out clinical trials due to over-stretched hospitals and shortages in the patient recruitment pipeline. There are fears that the current problems could lead to a bottleneck in drug development years down the line, particularly given that big pharma only tends to acquire or license smaller providers' technologies once they've run successful trials.

Efficiency needs to be the watchword of the industry over the next few years. This means ensuring that organisations can swiftly tap into the academic and clinical worlds to access the accurate specialist knowledge and translational research they need to get big decisions right first time.

Unfortunately, here we can see the shortcoming of relying upon a limited, closed-loop network of expertise. Time pressures and resource constraints will likely mean firms are forced to revert to the experts they've worked with before or the sources readily available via their existing professional network, rather than who is genuinely the best qualified, the most up-to-date on research or academically at the forefront. The fallback position is 'who they know' rather than 'who they need'.

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Traditional Methods of Discovery No Longer Work

This is a problem that stretches well beyond COVID-19, although the pandemic is certainly casting it in a new light. A perfect illustration of this can be found within the global medical conference industry. Historically, events and conferences have formed the cornerstone of most pharma companies' business development and research and insight strategies. Firms send legions of staff out to the most highly-regarded events because they know that this is where they're most likely to encounter cuttingedge expertise and the potentially game-changing technologies and innovations they need to sustain their businesses for the next decade.

COVID-19 has now caused the global shutdown of the entire conference industry, at least as far as physical, in-person events are concerned. Many industry insiders are unconvinced about the potential for replicating these events in the digital domain, yet there are no guarantees either that large-scale conferences will be back on the agenda by 2021, or that they'll be commercially viable in a world in which people are far more reluctant to travel, particularly by air.

This over-reliance on medical conferences - itself a rather limited avenue of discovery - simply serves to reemphasise the underlying truth: that the pharma and life sciences industries are being held back by fundamental shortcomings in our knowledge-sharing processes between the domains of academia and business. The pandemic might have crystallised this issue, however, it is a problem that has long been endured by organisations that have embarked on troubled M&As, or that have encountered unanticipated challenges in a new market, or that have launched new drugs only to find that the science or evidence behind them is flawed

University Sector Challenges Could Create Further Problems for Commercial Pharma

At the same time, COVID-19 has also created a strange dichotomy within the world of academia, one that could have huge ramifications further down the line for the pharma and life sciences industries. On the one hand, the pandemic has reemphasised the vital importance of scientific research and expertise, not just in terms of treating the virus, but in shaping all aspects of policy-making. The general public has predominantly turned to health experts and leading medical practitioners for the answers on how to navigate through the crisis. Michael Gove's infamous remark during the Brexit campaign that "people ... have had enough of experts" now seems archaic and irrelevant.

However, on the other hand, universities across the western world have come under tremendous scrutiny as the shortcomings of their current operating models have been exposed by the various restrictions implemented by different nations.

The over-reliance on overseas students paying hefty tuition fees has left some institutions facing a sizeable funding gap and a deeply uncertain future. eLearning is being increasingly cited as a legitimate substitute for in-person lectures and seminars, and while we're yet to see evidence that it can adequately replace lab demonstrations and practical work, questions are being raised nevertheless about future students' willingness to pay for a conventional university education.

There are legitimate concerns that we see a significant contraction of the academic world over the coming years, that we will lose the next generation of academics and researchers to better paying careers, and that the domains of teaching and research could be pulled further apart, to the detriment of the future pipeline of academic expertise.

These fears – if realised – could hold profound consequences for myriad pharma and life sciences businesses that will be relying on the academic community more than ever as they bid to combat COVID-19 while also keeping up the pace of their other ongoing concerns. We simply cannot take the availability of academic expertise for granted.

Using Technology to Break Open Our Academic Networks

Given this multitude of internal and external pressures, how can pharma and life sciences companies start to address the problem of access to academic expertise?

Well, one answer to this longstanding challenge lies with artificial intelligence (AI) technology, not as a means of replacing human expertise, but as a means of transforming our ability to access it.

The progress of AI adoption has been somewhat hampered over the past five years by vendors' over-emphasis on 'intelligence' as the desired end-goal – technology that makes decisions for us rather than helping us to make better decisions. Many of these technologies have fallen short of user expectations, to the detriment of the field as a whole. In contrast, the truly inspiring applications of AI have typically involved less glamorous, but vastly more useful applications within the realm of data processing.

Al can sift through huge volumes of data processing to deliver time and efficiency improvements many magnitudes greater than similar manual, human-powered processes. This is AI doing our legwork for us, in a way that's speedy, precise, and intelligent. Apply this to the realm of life sciences and the potential benefits of AI for improving access to academic expertise becomes clear. AI can make world-leading experts easier to identify, by analysing and intelligently assimilating millions of data points in seconds to pinpoint and profile the people who are truly at the coal face of any given topic. Furthermore, it can then track these data points over time to accurately map the ever-changing nature of global expertise. Or to put it another way, the leading expert a few years even weeks - ago might not be at the top of the game today. While conventional knowledge-sharing systems won't necessarily recognise or reflect this, AI tools are far better equipped to spot real-time change in status or reputation.

With high-priority research areas such as COVID-19, new studies and data are being published on an hourly basis. In the race for a vaccine, it's vital that pharma businesses are on top of precisely who holds the most accurate and up-to-date knowledge from one week to the next.

In contrast, as long as our systems for connecting and sharing knowledge

remain manually operated and restrictive in nature, pharma and life sciences businesses will go on struggling to access the academic expertise they need at the right moments, to the detriment of their strategic decisionmaking capabilities.

Identifying Better Sources of Truth

With so much now riding on the development of a COVID-19 vaccine, resources constrained and a plethora of misinformation circulating through global health networks, pharma and life sciences firms need to make sure they're



able to access the best sources of proof from the most accurate and informed academic sources.

They also need to explore new ways of establishing academic collaborations at speed, given that the pandemic has caused many of their traditional networks to break down at a time when drug development needs to happen faster than ever.

Thankfully, AI technology can now grant these organisations faster access to academic expertise, as well as enabling the more efficient transfer knowledge from the classroom, lab, or library, to the practical world of day-to-day business.

Ultimately, we have not yet reached a 'new normal' for the pharma sector. Organisations need to keep across every corner of the market, and expert third-party academic insights will be essential for understanding how areas such as patient treatment and drug development are changing as the medical world responds to the long-term consequences of COVID-19.

How will we know when we have arrived at the new normal? My guess is that we'll hear it first from academia.



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The Vital Role of Translation within Pharmaceuticals During COVID-19

For the pharmaceutical industry, perhaps the least surprising outcome of the coronavirus pandemic so far has been the public's realisation that vaccines are not produced overnight.

The world has become accustomed to accessible vaccines that enable us to enjoy longer, healthier lives. The majority of people have grown up being able to get the vaccines they need to protect them from diseases that impact the young, to those you're likely to contract when travelling around the world, so it's understandable they may not appreciate just how much research and time were invested in developing them in the first place.

These medicines are so established, and have been so successful in their duty, that the public can be forgiven for their lack of understanding as to just how difficult they were to develop first time around.

This coronavirus has presented a whole new challenge. Almost as difficult as creating a vaccine itself is the pharmaceutical industry's ability to communicate with multiple stakeholders around the world the developments, issues and opportunities it presents; in particular, this includes the media and the public, who are keen to know if a vaccine is feasible and when it might be available, as well as with other pharmaceutical companies to ensure they can offer their support to the vaccine development programme taking place worldwide.

One of the most severe pandemics in recent history – that of Spanish Flu in 1918 – came at a time when there were an extremely limited number of channels to communicate the impact it was having around the world. Though it could be seen as a positive that we have a wealth of platforms and tools to enable global communication about COVID-19, in many instances, the urgent need for ongoing updates with rolling news and social media brings with it new challenges for governments, universities and organisations involved in tackling coronavirus.

Different messaging from each country, a lack of joined-up approach from world leaders and sensationalism in each territory's press means the public is lacking a single, consistent and clear set of guidance which informs everyone about the development of a vaccine.

Creating this structured approach, of course, is not black and white. But when there is such an immediate need for a globally-available and distributed medical response, there is now a need for a collaborative movement more than ever. And this should be underpinned by reliable, culturally-sensitive translations.

One Globe, Many Languages

At the time of writing, 213 countries are currently infected with COVID-19. A couple of weeks ago, world leaders from these nations contributed a collective \$7.4bn, or £6.5bn, to research COVID-19 vaccines via a virtual event hosted by the EU¹. It is the sort of global gathering that would have normally required weeks – if not years – of upfront planning, as well as the hiring of dozens of interpreters to ensure attendees were provided with real-time translations of the information being presented.

It was a demonstration of the ways the whole world has reacted to coronavirus, and has adapted to be more agile in its pursuit of a collective solution. Though this was a political event, it provided an insight into how industries may have to utilise high-performance, multilingual conferencing tools to facilitate their agenda; in the case of pharmaceuticals, expertise from around the world coming together to develop a vaccine.

For example, there is technology available which facilitates virtual interpreting booths that are accessed remotely by organisers of and participants in events around the world; each user is allocated a qualified linguist who translates live, delivering a seamless, translated conference. These platforms allow linguists who specialise in specific sectors – from pharmaceuticals, medical and healthcare, to manufacturing, agriculture and logistics – to expertly translate even the most complex of sector terminology in real time, to aid international organisations looking to work together.

Sanofi and GSK recently signed a letter of intent to collaborate, using innovative technology from both companies to develop an adjuvanted vaccine for COVID-19², which can be rolled out not just nationally, in their home countries, but globally.

Never before has a vaccine needed to scale as rapidly as is required to tackle COVID-19, and doing so effectively, on a worldwide scale, will require the immediate turnaround of internal and external communications into multiple languages. Translators who not only know the industry but understand the technical terminology of scientists working in both France and the UK - as well as the governments and partners they're working with - will help to ensure findings and messaging which transpire from their joint working are made easily accessible, relatable and understandable to everyone, all around the world.

Translation in Clinical Trials

The USA claims its record for developing an entirely new vaccine is at least four years³. But with countries around the world recording coronavirus infection and mortality rates daily, and extreme lockdown measures in place, time isn't a luxury available to the industry.

Though it is widely reported that a vaccine could be produced as early as September⁴, to do so will require willing participants around the world to offer their health in exchange for the trial of drugs, which may or may not have an adverse effect on their life. Trying to communicate the critical role of trials in the development of modern medicine, how the process works and what the potential outcomes might be to people







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of one nation would be hard enough; conveying it to hundreds of different countries around the world, who are each following a different strategy in order to combat the virus, is an even greater challenge.

There are currently 650 groups around the world carrying out 460 different coronavirus vaccine trials⁵ on hundreds of thousands of individuals from different nationalities. Each must be informed – via a consistent, transparent message - as to the role they play in developing this vaccine, including any risks to their health and safety. Doing so will require the use of multiple platforms across online, print and video, and the production of swathes of collateral including patient information leaflets, patient questionnaires, patient-reported outcomes, informed consent forms and much more.

Multilingual countries must ensure any content they produce in relation to clinical trials is accessible to those who speak the native tongue and to those who have a different first language. For this purpose, and for global pharmaceutical firms who perform their trials around the world – with different languages spoken – translation becomes an essential service.

For example, foreign language voiceovers and subtitles are highly effective on pre-recorded videos which explain how a vaccination trial works. Meanwhile, transcreation - a highly creative translation service, which falls somewhere between translation and foreign language copywriting - can transform marketing campaigns from informative to impactful, by creating unique messaging in a tone of voice that is known to engage people of different cultures and nationalities, their different nuances and colloquialisms, encouraging them to engage and take a specific action. In this case, sign up for clinical trials.

Translation service providers with a specialism in pharmaceuticals support in the development of all the collateral relevant to vaccination trials. Project managers, who co-ordinate the delivery of this material, use teams of translators who work across multiple languages to ensure consistency and efficiency across all content, regardless of the number of languages it is translated into. Turning the pharmaceutical expertise and technical knowledge behind the development of a vaccine into engaging, accessible content that can be utilised by individuals of any language will play a huge part in accelerating the medical science developments in response to COVID-19⁶. And, better yet, might lead to even greater engagement with medical and clinical trials well into the future.

Introducing a New Vaccine

The continued success of vaccines depends on high rates of acceptance⁷, and any example of misinformation or a lack of clarity during their introduction to mainstream society can severely hinder their long-term effectiveness.

Add to this a wide range of theories that alternative science can cure coronavirus, the 8 per cent of people globally who think vaccines aren't important for children⁸, and the conspiracy theories circulating that coronavirus doesn't exist at all, and there will be a challenge in communicating to the masses that having the vaccine is essential.

If society is to return to any level of normality any time soon, this will require not just the rapid scale-up of vaccine production but widespread outreach of the benefits of simultaneously vaccinating every person on the planet. This is not something that has yet been achieved or needed to be delivered with such speed. When this process eventually transpires, communications will play just as important a role in moving ahead from this disease as the vaccine itself.

In the past, 'traditional' communication and outreach methods have been used to drive immunisation rates up to 85-90 per cent⁹. Healthcare professionals are still the most trusted source of vaccine information and advice¹⁰ and will be the first port of call for those who seek a finalised vaccine. But while, with previous vaccines, it would have been sufficient to develop registration dossiers and a brief collection of marketing material, in today's world there are a variety of less traditional routes that could be taken to ensure a to-be-developed coronavirus vaccine reaches even more of the global population.

The World Health Organization (WHO) has a long-established, sevenstep process for introducing a new vaccine and its foundations include the crafting of messages and materials which inform and involve the public of its benefits via mass media. This has to extend beyond the realms of newspapers; healthcare websites must have dedicated areas which inform the public about how to source a vaccine; social media channels must be flooded with the benefits for families; advertising slots on television should include jargon-free explanations about the future of society once the vaccine reaches the majority of a country's population. And all of this needs to be translated into the languages which make it accessible and clear to every person on this planet.

In doing so, the WHO says, a trust in the new vaccine will be built, while awareness of its availability and the immunisation programme in general will see additional demand as a consensus will grow in how it prevents widespread disease¹¹.

Looking Ahead

If the coronavirus has revealed one thing about the world, it is that there is a huge disparity in healthcare and medical messaging, even if the virus or disease in question knows no bounds in terms of its geographical impact. There have been ongoing comparisons between how COVID-19 is affecting different countries at different rates and different times. This is leading communities to make their own predictions about the impact that following or ignoring another country's actions could have on their own society. As such, it is crucial for leaders to develop a single, consistent, easily translatable and widely relatable set of communications about any vaccine that emerges to beat coronavirus, and any vaccines in the future, to create a single resource of trusted information about globally-available vaccines.

With regard to the pharmaceutical industry specifically, the need for the quick production of a vaccine to cure the pandemic is shining a spotlight on the hidden – but constant – role the sector plays in keeping the world safe; for them, this revelation is nothing new. However, looking beyond the pandemic there will be a need for the ways in which the industry works to change, to ensure we can continue to develop new medicines using expertise from around the world when there is a high possibility we won't be together, in a physical capacity.

By communicating effectively all the steps and processes required to develop a vaccine for a virus that is so high on the agenda, in the future, we will see an even greater understanding of the need for clinical trials, and a dependence on human testing. Ensuring the science behind this is translated into relatable messaging, available in languages spoken all around the world, will develop greater public confidence in this practice and will mean more people are on board with coming forward to volunteer. Failing to do so will simply position the vaccine as inaccessible, and only available to those who speak the more popular languages around the world. When we are literally



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talking about life and death, there is no rationale for ignoring the huge difference it makes to be spoken to in your own language.

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Successful Marketing of Medicinal Cannabis and Cannabis-derived Products

The Current Legal and Marketing Situation in Europe

The European Union (EU) is missing a harmonised law on medical and, if appropriate, recreational use of cannabis. A high-leve I overview of the national legal requirements of some European countries on medicinal cannabis is provided below, thereby highlighting the differences within the EU.

Denmark:

In December 2017, Denmark adopted its legislation for a four-year medical cannabis pilot project, allowing physicians to prescribe cannabis products which, until then, were not legal in Denmark (INCB-Report, 2018). With the implementation of the medicinal cannabis pilot programme, cannabis is legally available. Cultivation and production for medical use started with the introduction of a special development plan, giving companies the ability to apply for a cultivation and handling licence to produce cannabis for patients as well as for export. Up to now licences have been given to two companies.

Since July 1, 2018, the Executive Order on Euphorizing Substances has been amended. Hemp (content of tetrahydrocannabinol (THC) up to 0.2%) does not fall under the definition of an euphoriant substance. Depending on the products manufactured from hemp, rules on medicines, food and food supplements need to be followed. Denmark defines cannabidiol (CBD) as a pharmacological substance; only products with low concentration of CBD might be classified as food supplements.

France:

In France, cannabis is regulated by the Code of Public Health, including "narcotic substances". Article R. 5132-86 lists the kind of exclusions which are effective for:

 "cannabis, plant and resin, products containing it, or those obtained from cannabis, plant or resin"; and, "tetrahydrocannabinols, except for delta 9-tetrahydrocannabinol, and its esters and ethers, salts and the salts of the aforecited derivatives, and products containing them".

The Code of Public Health also lists exceptions (Article R. 5132-86-1) to the exclusions, e.g. for delta 9-tetrahydrocannabinol used for the production of Marinol, which is authorised as part of a Temporary Use Exemption by name (Roquette Pflister, M, 2019). After establishing a group of experts, Temporary Specialized Scientific Committee (CST), in September 2018, analysing the use of medical cannabis in other European countries and results of clinical trials and medical literature, the National Agency for Safety of Medicines and Health Products (ANSM) accepted the proposal of CST to experimentally allow medical use for certain defined indications, e.g. palliative situations or painful spasticity of multiple sclerosis. Follow-up shall be conducted via a patient register. ANSM started to prepare, with the various government departments concerned, technical arrangements necessary to establish the experimental phase. According to information from Franceinfo, ANSM announced on January 22nd, 2020, the experiment on medical cannabis will start in September 2020 and will include approximately 3000 patients; planned time schedule of the experimental phase is two years.

Another exception to the Code of Public Health is related to cannabis free of narcotic properties (Article R. 5132-86, Il subsection 2) and describes authorisation by ministerial order for culture, importation, exportation, industrial, and commercial use. A ministerial order dated August 22, 1990 defines the conditions for cannabisbased non-narcotic requirements and allowed the manufacturing of liquids for electronic cigarettes, cosmetic products, or capsules as legally acceptable (Roquette Pflister, M, 2019). Concerning CBD products, MILDECA (Mission interministérielle de lutte contre les drogues et les conduites addictives) published an update of the legislation (Cannabidiol (CBD) le point sur la législation) in June 2018.

Germany:

With the amendment of the German Narcotic Drug Law in March 2017, the doors were opened for marketing of medical cannabis products in Germany. The bases of the amendment were the definitions of cannabis in Annex I and III of the Narcotic Drug Law.

Annex I of the Narcotic Drug Law lists cannabis as a narcotic drug not being marketable, but defines exemptions: for seeds, for specific certified varieties originating from European countries, the content of THC may not be more than 0.2%, and only for use as defined in Annex III. Annex III defines exemptions for marketing and prescription of narcotic drugs to which cannabis was added as: "Cannabis (Marihuana, plants and parts of plants belonging to the species of Cannabis) - based on state-controlled cultivation according to article 23 and 28 paragraph 1 of the Single Convention on Narcotic Drugs from 1961, as well as preparations approved and authorised as finished medicinal products."

Germany's supervising authority on medical cannabis is the "Cannabis-Agentur". A tender on cultivation of medical cannabis in July 2018 led to signed contracts with three companies, for a total amount of 10,400 kg of cannabis, scheduled for a period of four years. The first harvest is expected in the last quarter of 2020.

Cannabinoids, not being psychoactive, e.g. the pure form of CBD, do not fall under the Narcotic Drug Law. Careful review on the production process is considered since CBD extracts from the plant / parts of the plant might still contain psychoactive substances (e.g. THC) and will then keep falling under the Narcotic Drug Law. In 2016, CBD was transferred to the list of prescription substances, without restriction to any strength, leading to necessary prescriptions for CBD products with a medical claim.

CBD and food: since CBD-containing products or CBD were not used as food or food ingredients before May 15th, 1997, these products are defined as novel food, according to the Novel Food Regulation ((EC) 2015/2283), implemented on January 1st, 2018. The Higher Regional Court of Hamm/Germany had already decided in 2016 (21.06.2016, Az.: 4 Res 51/16), that the precondition for marketing of cannabis-based products, like CBD-oil, is the cultivation of plants with a THC content below 0.2%, from certified seeds only, for the purpose of commercial and scientific use. With this decision cannabis-based products containing CBD, with a TCH content below 0.2%, like CBD-oil, were not marketable in Germany. Two other court decisions prohibited marketing of CBD products, as these products are either defined as novel food and as such need a marketing authorisation (administrative court of Düsseldorf 2019, 27.09.2019 -16 L 2333/19 and Hannover, 18.11.2019, 15 B 3035/19) or contained THC contents which were higher than the legal limit of 0.2% (administrative court of Gießen, 11. November 2019, 4 L 3254/19.GI).

The use of cannabis in cosmetics is regulated by entry 306 of Annex II to Regulation 1223/2008. Narcotic drug substances are excluded from use in cosmetics, thereby excluding cannabis. This restriction is not applicable to the use of hemp seed oil or synthetically produced cannabidiol; see Cosmetic Ingredients database (Cosing database), but still excludes plant-derived cannabidiol.

Italy:

Decree 309/90 is the Law on Narcotic Drugs (governing psychotropic drugs and substances, prevention, treatment, and rehabilitation of the related states of drug addiction). Psychotropic substances are defined and divided into four tables according to Article 14; cannabis is listed in Table II (Table II and Table IV provide for minor penalties).

From November 2015, the Italian Competent Authority took the responsibility of supervising all companies registered for cultivation, manufacture, use, marketing and sale of psychotropic substances. The Italian Competent Authority has the only licence to grow medical cannabis in Italy. To ensure patient demand on medical cannabis, Italy ran an additional tender in July 2019. Import licensees of medical cannabis are now issued to companies from the Netherlands and Canada.

The Italian Legislation differentiates between two different categories of products:

- products containing THC (controlled substance) are considered as medicinal products only.
- products containing CBD without THC, or THC at very low levels, are considered cosmetics, food supplements or medical devices. Only extracts derived from cannabis sativa seeds are allowed for this category.

Medical products are prescribed as magistral preparation (non-renewable medical prescription on a "named patient" basis) and are considered 'off-label', needing in addition an authorised consent by the patient. Marketing as food or food supplement is admitted only for products containing traces of THC below 0.2 mg/kg. Decree dated November 4th, 2019 established maximum levels of THC in food and food supplements. For food supplement the limit is of 0.2 mg/kg (as sum of (-) -trans-Δ9-THC and non-active precursor $(\Delta 9$ -THCA-A and $\Delta 9$ -THCA-B)). For food use, Law n. 242 dated December 2nd, 2016 set a maximum THC concentration in cultivated cannabis. which is 0.2% and, in any case must not exceed 0.6%, applicable to varieties listed in the Common Catalog of varieties of agricultural plants, following Article 17 of the Directive 2002/53/EC.

Ireland:

Cannabis is listed in Schedule 1 of the Misuse of Drugs Regulations 1988, as amended. In 2019, Ireland implemented the Misuse of Drugs (Prescription and control of supply of cannabis for medical use) Regulations 2019, to facilitate import, prescription and supply of cannabis-based products, that meet the requirements of the regulations under the Medical Cannabis Access Program (MACP). The first stage of the MACP is for companies to apply for assessment of their product by the Health Products Regulatory Authority (HPRA) for suitability and inclusion to Schedule 1 as a specific controlled drug. When accepted, prescription via a registered medical consultant is possible for patients who failed to respond to standard treatments for the following medical conditions: spasticity associated with multiple sclerosis, intractable nausea & vomiting associated with chemotherapy and severe, refractory (treatmentresistant) epilepsy. Currently only three cannabis-based products have been accepted. As part of the MACP, the Health Service Executive (HSE) will keep a central register to record data including enrolled prescribers, anonymised patient identifiers and the products prescribed / supplied. The MACP is running on a pilot base for five years; further information can be found at: Government of Ireland, Medical Cannabis Access Program.

CBD as a pure substance, e.g. manufactured synthetically, does not fall under the Misuse of Drug legislation. CBD products produced from hemp (cannabis sativa) via cold-pressing are legally accepted due to low quantities of THC; however, health claims are not accepted when selling as food supplements (further information: Food Safety Authority of Ireland). Products containing CBD extracted via CO₂-extraction fall under the Novel Food Regulation (EC) 2015/2283 and require a market authorisation.

Netherlands:

In 2001, the Office of Medical Cannabis was established as the concerned authority controlling cultivation and delivery of cannabis for medical and scientific purposes. Cannabis is defined as soft drug (list II) and underlies the Dutch Narcotic Act. Cultivation of cannabis started with a first licence in 2003 to Bedrocan. In 2019, the Netherlands developed plans for licensing a second company for cultivation of medical cannabis to overcome the shortage of medical cannabis, the product in Europe.

Cannabis-based products carrying a medical claim fall under the Medicinal Product Act. Products containing CBD in combination with THC fall under the Opium Act and require a prescription, while products containing pure CBD do not fall under the Opium Act but still need a prescription (CIBG, June 2019).

The Dutch law is working with exceptions to the drug law leading to CBD-based products legal for marketing, in case they fulfill the following prerequisites:

- a) the amount of THC does not exceed 0.05%
- b) the product should not bear a medical claim
- c) maximum daily use is not more than 160 mg CBD per day.

Authority advice from the Medicines Evaluation Board or Netherlands food and consumer product safety authority regarding product categorisation is recommended (van Weren M, 2019).

Portugal:

Medical cannabis has been legal in Portugal since 2018, with Law No. 33/2018 of 18 July, establishing the legal framework for use, preparations and substances for medical purposes, including prescription and dispensation in pharmacies connected to a licence from the National Authority for Medicines and Health Products, Infarmed. Cultivation of cannabis is under state control, and permission via a state licence is needed.

Amendment of Law 33/2018 in 2018 classified CBD for medical use only, leading to availability of CBD-based products only per prescription. Import of cannabis or CBD needs an import licence to be issued by Infarmed.

CBD as food and food supplement has been banned since 2018, due to the Novel Food regulation.

Cosmetic products are legally regulated by Regulation (EC) No 1223/2009, consultancy no. 15/CD/ 2013, Decree-Law no. 189/2008, September 24th prohibiting the use of narcotic substances. Consultation with Infarmed is recommended for classification before marketing of a product containing CBD as a nonpsychogenic substance.

Spain:

Spain is still missing a legal regulation on medical cannabis. The Spanish Agency for Medicines and Medical Products

(AEMPS) bans controlled dispensing of cannabis flos and cannabis extracts for medical use, although authorisation for the cultivation of cannabis plants for medical and scientific purposes are granted. The national legal background on narcotic drugs is laid down in Law 17/1967, of April 8, implementing the regulation on narcotic drugs according to the provisions of the 1961 United Nations Single Convention. AEMPS lists companies which received a license for controlled cultivation of medical cannabis being either exported to entities authorised in the country of destination or which have been previously authorised by the AEMPS (Autorizaciones vigentes emitidas por la AEMPS para el cultivo de plants de cannabis, 13. De agosto de 2019). The only authorised product which is on market in Spain is Sativex, approved in 2010. Expectation for the launch of Epidiolex is during 2020 (Kanaval S., 2019).

Since Spain has a strong tradition in establishing Cannabis Social Clubs (CSC), medicinal users may have access to cannabis by joining a CSC (Sanchez, 2018). Regarding quality and safety this is still an unsatisfactory situation: relevant analysis to ensure the absence of pesticides and other residues are not carried out and the concentration of active ingredients is unknown.

Marketing of products containing cannabidiol was stopped almost immediately, with CBD being defined as a novel food by the Novel Food Regulation ((EC) 2015/2283), implemented since January 1st, 2018. Supervising authorities of the food market stopped marketing of CBD products in Spain already in 2018. Spain is lacking a national regulation for cannabis to be used as food.

United Kingdom:

Cannabis is a Class B controlled drug in the UK, listed in Schedule 1 of the MDR 2001 and in the Misuse of Drugs Designation Order 2015. However, in 2018 so-called 'cannabis-based products for medicinal use in humans' (CBPM) were included in Schedule 2 of MDR 2001, allowing specialised physicians to legally prescribe them to patients with unmet clinical needs without the pre-requirement for a Home Office licence. Nevertheless, companies wishing to supply, manufacture, etc. these products still require a Home Office Controlled Drug licence.

A CBPM is defined as a medicinal product or substance used in the preparation of a medicinal product, which contains cannabis, cannabis resin, cannabinol or a cannabinol derivative and are unlicensed products prescribed on a "named patient" basis. Cannabidiol (CBD) in its pure form does not fall under the control of the MDR 2001. A CBD product with a medical claim needs a marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA).

Following the MDR 2001 update and the resultant mix of licensed and unlicensed status of such medicines in the UK, the National Institute of Health and Care Excellence (NICE) published a guideline on November 11th, 2019 which covers prescribing of cannabis-based medicinal products for specific conditions. The NICE committee determined that the initial prescription of such a product must be made by a specialist medical practitioner who should also have a special interest in the condition being treated. Products covered by the guideline include: CBMPs as set out by the UK Government in the 2018 regulations, licensed products THC with CBD (Sativex) and nabilone, plant-derived cannabinoids such as pure CBD and synthetic compounds identical in structure to naturally occurring cannabinoids (e.g. dronabinol).

Regulation 2 of the MDR 2001 allows that some products may be considered exempt from control, in limited circumstances. To market a CBD product containing cannabinoids (e.g. THC), it must meet all three limbs of the exemption definition. These specify that the controlled drug should not be designed for usage as a narcotic drug, the controlled drug cannot be recovered by readily applicable means, and limits the maximal amount of each component of controlled drug to one milligram per product or preparation.

Concerning food products, the Food Standards Agency (FSA) clearly stated: "Businesses need to submit, and have fully validated, novel food authorisation applications by 31 March 2021. After this date, only products for which the EFSA has a valid application will be allowed to remain on the market."

Manufacturers of cannabis-based products should take the chance for legal advice on product classification with the respective national authorities, on safe time to market, and to have their products compliant with the individual national legislations.

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Guiding Drug Optimisation Using Deep Learning Imputation and Compound Generation

The use of machine learning (ML) methods is now commonplace in many disciplines and artificial intelligence (AI) is on the rise, promising better and smarter solutions to 'all your problems'. However, despite the hype, there is increasing evidence we have entered the next 'AI winter' or the so-called 'trough of disillusionment' in the ongoing hype cycle¹. There is still a gap in understanding on the route from traditional and well-understood statistical modelling methods to the poorly-defined promises of AI, and exactly how the majority of researchers can cross that gap is not clear.

Researchers in drug discovery are familiar with quantitative structure activity relationship (QSAR) model building methods. Many of these methods now employ forms of ML, a sophisticated form of 'fitting functions to data'. The question is how to leap forward from this well-known and comfortable ML space toward sophisticated AI tools, by which we mean: A connected set of ML components in an automated system which together produce a rich behaviour capable of solving complex tasks. The lesser known 'Al' is *augmented* intelligence, and there is no reason why a human cannot be part of the connected components in this sophisticated AI system. The combination of a human expert and superior tools has been found to be optimal as well as convenient².

We will describe the outcomes and discoveries made by connecting: A state-of-the-artdataimputation method³, in this case using deep learning^{4,5}; generative methods based on machine learning⁶ and evolutionary⁷ algorithms; optimisation processes for goal-seeking; and probabilistic scoring⁸, a form of multi-parameter optimisation (MPO) ⁹ for guiding compound prioritisation decisions, without resorting to harsh filtering methods¹⁰. We illustrate this with an example application finding a confidently active compound against a novel malaria target¹¹, and outline our future vision for these methods.

Method

The schematic for the 'Al' process used in this work is shown in Figure 1. Each block represents a component or process, colour-coded as either an input (data, or parameters), ML method, automated step (such as a script or advanced software process), or outputs, which amount to confident predictions of active compounds with an appropriate property profile and confident identification of missed opportunities. In general, humans will only have to interact with the inputs and outputs of the system, but this feedback is essential to get the best results out of the system, through augmentation of the AI with human expertise and vice versa.

negative log of the IC_{50} in Molar units). Molecular descriptors are also generated for the compound structures as input; for this work, descriptors were generated, including whole-molecule properties such as logP, MW, TPSA and SMARTS based fragment matches, but in principle any descriptors can be used at this step.

Modelling

The next step is critical: the sparse and noisy data are *imputed* using a state-of-the-art deep learning method called Alchemite⁴, which has seen great success in heterogeneous datasets from real drug discovery projects⁵. Modern imputation methods offer clear benefits over a standard predictive approach³, they make better use of existing data, can handle sparse and noisy experimental results and provide robust uncertainty estimates for each missing value which



Figure 1: Schematic of the augmented/AI process used to generate confident predictions for virtual compounds. Components are colour-coded as inputs (yellow), machine learning tools (purple), automated steps (green) and outputs (orange).

For most applications, the starting point is sparse and noisy raw experimental data for existing compounds and their chemical structures (Figure 1, top left)³. For a typical drug discovery project, these data could be a combination of experimental assays for activities and absorption, distribution, metabolism and elimination (ADME) endpoints⁵.

Data Preparation

First, we will follow the input data rightwards; the raw data are cleaned with automated routines and transformed into units that are more suitable for machine learning; for example, it is common to transform IC_{50} quantities to pIC_{50}^{-5} (the

is predicted^{3,5}. From this point, in Figure 1 we can immediately find high-potential compounds that are in the training set, but only have partially measured experimental data. We can also "confidently identify missed opportunities" as illustrated as an output in the schematic, which is a valuable positive outcome¹⁰. Examples of this could be incorrect or inconsistent experimental data in the inputs, which the deep imputation model can highlight that they lie outside of the expected range based on the error bars in the prediction, enabling them to be flagged for retesting. When training this deep imputation model, we can also build a virtual model³. This can make predictions for virtual



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Optibrium works at the forefront of decision-analysis and predictive modelling research, developing innovative products that enhance the efficiency and productivity of drug discovery compounds, i.e. those that have not yet been synthesised, with greater accuracy than the best QSAR methods⁵, while simultaneously providing robust error bars. This virtual model forms the explorative basis for the AI allowing it to judge new compounds which are generated by two methods.

Compound Generation

Broadly speaking, there are two kinds of approach for compound generation, a *bottom up* and a *top down* approach:

Bottom up: Start from known chemistry and optimise outward to explore related compounds to search for those that are likely to satisfy project requirements (activity, selectivity, ADME, etc.). This method closely resembles a human-led drug discovery programme, starting from known hits and performing synthetically accessible variations around promising compounds, but can explore many more, diverse ideas in a shorter time than even an expert chemist¹². In algorithmic terms, it can be slow to iteratively approach the goals, but the proposed chemistry will be familiar to project chemists and more likely to be synthesisable. In Figure 1, this is covered by the component 'Nova™', a module in StarDrop[™], which uses advanced evolutionary algorithms to generate libraries of virtual compounds using realistic chemistry transformations from the medicinal chemistry literature7.

Top down: This strategy attempts to generate descriptors for an 'ideal compound' which would be predicted to have the desired properties. The algorithm then generates a structure that matches these ideal descriptors. This method is an example of generative ML methods⁶ and is shown as 'Generative ML' in Figure 1. If the model predictions are accurate and a solution can be found, then the compound is likely to fulfil all of the project requirements. However, these methods often struggle to make synthetically accessible and drug-like compounds, and models without uncertainty estimates may give untrustworthy answers. The deep imputation method used in this work does provide uncertainty estimates, and these can be factored into the optimisation process. For our implementation, we solve for the ideal descriptor vector using a gradient descent optimisation layer over the Alchemite model. This layer varies the descriptor while minimising the difference in the predictions of the fixed model and

the desired properties for a compound. The solved descriptors are cleaned and minor variations are made about the solution. These idea descriptor vectors are subsequently entered into a recurrent neural network (RNN) decoder⁶ which is trained to write out SMILES representations as compound suggestions which meet the input descriptor profile. In our case, the StarDrop descriptors were generated for the original dataset alongside a large portion of the ChEMBL database. This meant the RNN would generate SMILES similar to ChEMBL compounds which also match the target ideal descriptors used as input.

Probabilistic Scoring

An important step is to take all of the virtual compounds generated from both methods, along with their predictions and uncertainties, and apply MPO to prioritise them for further consideration. This is because a high-quality compound must exhibit not only activity but also an appropriate balance of physicochemical and ADME properties. In this AI application we use the probabilistic scoring method⁸ in which an experienced user can define a profile of property criteria that represents the desired outcomes for an ideal compound. The algorithm estimates the likelihood of success of each compound, taking the uncertainties in the property values into account. This enables the generated compounds to be prioritised and the highest scoring shown to a human expert. The most promising can be taken forward for synthesis and experimental studies, or the expert can update the scoring profile or the design parameters for the Nova module to generate a new list of suggestions.

Application

A practical application of the AI process shown in Figure 1 was demonstrated for the Open Source Malaria (OSM) challenge, where various teams were invited to build predictive models for pfATP4 activity based on an open source dataset¹¹. The data were sparse and noisy and compounds had been measured across different

labs, protocols and sensitivities, and assays had been performed on different strains of drug-resistant Plasmodium falciparum (p. fal.) malaria parasites. The deep imputation model was able to impute this sparse and noisy matrix, while exploiting correlations between the strains, labs and associated measurements. The model also produced accurate error bars for both imputed results and virtual model predictions. A virtual library of approximately 1,000,000 structures was created through a combination of the two generative methods and the probabilistic scoring profile was defined to maximise activity in all assays, as well as increase solubility, while taking the confidence in each individual prediction into account. Figure 2 shows the four compounds most likely to succeed, generated by the two approaches. Upon review, compound a) was considered to have a reactivity problem that may result in HF production and was discounted. In addition, compound c) was considered to be potentially unstable.

The algorithms used could be improved to detect these high-level pitfalls and this reiterates the importance of the 'expert chemist verification' as depicted in Figure 1.

The compound most likely to succeed, the tert-butyl compound (b), had a predicted pIC_{50} value of 6.4 in the target assay. This was sent for experimental synthesis and, when tested, the experimental pIC₅₀ was 6.2, well within the uncertainties in both the experimental and predicted values. This activity met the project criteria for activity, which was a pIC₅₀ > 6.

Of the novel compounds proposed by four organisations in the project, this was the only experimentally verified active, illustrating that methods which cannot reliably consider uncertainty often struggle to filter the successful actives from noisy predictions. Furthermore, the project chemists considered that the tert-butoxy group on compound b) gives new directions in the SAR and it is unlikely that this compound would have been considered by a human. These are exactly



Chem Transforms

Figure 2: The most confident structures generated by the Al. Compounds a) and b) are from the bottom up Nova approach, compounds c) and d) were generated using the generative ML approach.

the kinds of benefits that an augmented tool will provide.

Additional insights were found in imputation of the original data in the context of the output 'confident identification of missed opportunities' in the process illustrated in Figure 1. Upon imputation, a compound with a single experimental "inactive" measurement ($IC_{50} > 10$) was proposed as being active in two other assays with a high degree of confidence (predicted *p. fal.* pEC_{50} of 7.2 and single shot inhibition of 96%). Upon digging deeper, the compound was found to be chiral (Figure 3). The compound was supposedly enantioenriched, but it was not known which enantiomer was more prevalent and the chirality had not been registered in the database. Upon experimentally resolving the enantiomers by chiral liquid chromatography, the enantiomer in Figure 3 was confirmed as inactive, while the other was confirmed as active. The AI was aware that there was a chance for activity and the active compound, which had been ruled out by a single datapoint, could have been a missed opportunity.



Figure 3: The chiral compound that was highlighted as a potential missed opportunity in the dataset.

Opportunities for Future Improvements

There are many further potential improvements than can be made to the process in Figure 1. We can combine additional data in the first instance to find correlations in public or private repositories. The descriptor generator used in the data preparation block could be upgraded to a machine learning tool such as a graph convolutional network. Further advances could be made to the optimisation steps, such as by employing reinforcement learning approaches. The RNN encoder could be replaced with a full generative adversarial network, which has been trained to produce drug-like and synthetically accessible compounds. The foundation developed here could easily grow into an even more powerful AI for drug discovery.

Conclusions

The combination of machine learning components can lead to an advanced system, which embodies a sophisticated AI tool. Using the Alchemite method, we are able to use all of the data available, even though it is sparse and noisy, and the resulting models output robust uncertainty estimates, which are essentially for later MPO and prioritisation of compounds. This concept was demonstrated through the efficient identification of a novel active antimalarial compound.

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Could Greater Diversity and Inclusion Improve Innovation in Pharma?

The past few weeks, and the response to the COVID-19 crisis, have shown not only how vital the pharmaceuticals (pharma) industry is to the global economy and society, but also the amazing collaboration and results it can achieve when it really puts its mind to it.

There can be no doubt pharma executives are committed to bringing drugs to market to improve the lives of patients, but when the pharma industry lacks diversity within, it underserves patients outside. A lack of diversity in decision-making leads to lack of insight that could otherwise contribute to improving and saving lives. Whilst the industry is certainly diverse, in terms of nationality and culture at least, there is no doubt it could be more inclusive. The problem stems in part from the industry's hiring practices: these tend to be too insular and there's also an over-confidence in the industry's own abilities.

The big question is whether the industry can really meet diverse, new patient and customer needs if it hasn't yet fully embraced inclusion amongst its own staff base. Innovation is about new ideas, or creative or different applications of existing knowledge or methods. It usually happens incrementally, using or redeploying existing technology, science and systems in pre-existing market conditions.

Incremental, disruptive and architectural innovation are probably already on the watching brief of pharma CEOs. However, Covid-19 has accelerated a new possibility – radical innovation. This is where the market and technology change fundamentally at the same time. The variables are many more to compute. The risks and the opportunities are beyond the capability of any one leader, any one company, to compute. This is where inclusion comes in.

Radical Innovation

Recently, AstraZeneca announced a

partnership with Oxford University to combat Covid-19 infection from SARS-CoV-2. In a move away from the usual linear process of bringing drugs to market, various workstreams and pathways will instead run alongside each other in parallel, enabled by the radical innovation circumstances we now find ourselves in. The university brings the vaccine, the pharma company brings the development, manufacturing and distribution machine. It's a creative and different application of academia, science and business partnering together in real time. The potential vaccine entered Phase I clinical trials in late April. Data could be available in June with advancement to late-stage trials occurring by late summer.

This didn't just happen overnight. Two months prior, during China's Covid-19 peak, AstraZeneca established a different approach in its China operations. Whilst not linked to the Covid-19 vaccine development, it highlights the importance of inclusion enabling innovation. Breaking down the usual hierarchy, over 20 online town halls were hosted across the organisation, where participants were encouraged to speak up on three dimensions: protecting employees, finding new ways to drive the business and supporting customers. This flat hierarchy and inclusive crowd-sourcing of ideas contributed to a fast and agile response. Over 220,000 masks and 40,000 vitamin C tablets were delivered to employees, online opportunities were captured through digital channels and there were no stock-outs.

In 2011, an AstraZeneca cancer drug programme was set to close after results from a Phase II trial. Susan Galbraith, SVP Early TDE in Oncology R&D, argued for further analysis of a particular genetic status. She had noted the multiple stories where patients had seen positive results from the cancer drug. Further analysis demonstrated the cancer drug substantially improved progression-free survival in a subset of patients with this mutation. The data subsequently led to approval, ensuring the cancer drug reached patients. Had Susan not spoken up, and had she not been heard, this opportunity to benefit patient lives would have been lost.

It is clear that there is a correlation between inclusive cultures and innovative outputs. We know that inclusive teams gain new perspectives, better avoid group think, and can be significantly more productive. When Pascal Soriot spearheaded an inclusive leadership culture change, he was aiming to improve psychological safety and encourage people to challenge the status quo. This had direct results in terms of innovation. For example, staff working on Calquence, a leukaemia drug, challenged norms and implemented a novel supply change design which resulted in a 70% reduction in batch cycle time and a 90% > 0% batch failure rate. In August 2017, Calquence was granted BTD and priority review for MCL by US FDA, and the overall development time was reduced from five years to 15 months.

How Diverse is Pharma?

The pharmaceuticals industry is certainly diverse, in terms of nationality and culture, but this masks two problems that need addressing. A lack of other types of diversity, and proactively including different perspectives. When Reshma Kewalramani was appointed Chief Executive of Vertex Pharmaceuticals, she become one of just two female CEOs in the top 25 pharma companies worldwide. Of the top 35 we have worked with, Emma Walmsley at GSK, Marie France Tschudin at Novartis and Heather Bresch at Mylan stand out joining Reshma as the only four female leaders. Compared with any other major industry, that level of gender diversity is low. Kenneth Frazier, CEO of Merck, is the only African American CEO in the top 35.

Cynthia Challener pointed out that the pharma industry features less gender and ethnic diversity than other industries in the Fortune 500, with one-third of the top 50 pharma companies having no women on their boards, and only 8% of board seats held by ethnically diverse directors, compared with 14% for the Fortune 500 overall. The board diversity that exists often relies on non-executive positions. The problem is the pipeline. Graduate programmes and lower management levels display more diversity but from middle management onwards it becomes a male game. If the industry still lacks diversity in its decision-making positions, can it truly claim to be inclusive?

Diversity Must be Accompanied by Inclusion

Every major pharma company undertakes some form of diversity and inclusion work. Inclusion can be measured by analysing those behaviours that contribute to or detract from inclusion. The majority of pharma companies are still reliant on 'pulse surveys' that are a poor indicator of inclusion. Instead, we have used an inclusion diagnostic in several organisations to do this. For example, if we measure psychological safety by asking whether employees feel they can speak up and challenge their boss without fear of retribution, we get an insight into whether pharma is cultivating an inclusive culture or not. Asking questions such as 'am I proud to work for the company?' offers very little actionable insight.

Inclusion diagnostics, on the other hand, have revealed poorer levels of psychological safety among those groups that are still under-represented in pharma. To increase inclusion, we need to improve their psychological safety and perceptions of fairness over a range of indicators. This is not only a moral question; it is directly related to the effectiveness of decision-making.

Take, for example, the Bank of England. Decision-making is core to the central bank's mission of mitigating risk in its decisions and the economy overall. Similarly, decision-making is core to pharma's ability to bring drugs to market to improve the lives of patients. However, the Bank of England instituted a policy of 'Author in the Room' in order to increase inclusion. It challenged the hierarchy by mandating that the most qualified person, of whatever level, should be in the senior meetings to inform the discussion, rather than the members relying on 'papers' that had passed up through the ranks. Many pharma companies would not even be aware of this because they haven't measured inclusion and they rarely look outside pharma for good practice.

Old Habits Die Hard

I recently spoke to 14 colleagues in diversity and inclusion roles in six European-based pharma companies and asked, "How much would you say the pharma industry is insular in its hiring practices?" 13 out of 14 said 'somewhat' to 'very'. Outside industry churn is a good measure of openness to new people and ideas. When compared to almost any other sector, pharma does not recruit from outside.

Perhaps more worrying than just the internal work, many pharma companies are not properly considering inclusion in their consumer work. Seven of our colleagues said their organisation considered the diversity of its customer

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base when discussing how best to meet consumer needs. However, six said the opposite. When a new pharma CEO was appointed, he privately acknowledged he wanted to use inclusion and diversity to provoke the executive team. In his view the executive was too comfortable, too insular and too resistant to change.

In my years working alongside executives in the industry I have personally witnessed brilliant innovation, excellent people management and the highest ethical standards. However, is its success part of the problem? When you have such an abundance of resources within, might you be less inclined to look elsewhere?

With an obvious scientific bias, there is less credence given to people's 'lived experience' because it's harder to quantify. This can result in an empathy deficit. When the diversity business case only offers correlation, not causation, many executives may dismiss its contribution to business and scientific outcomes. When many executives are working hard on complex briefs, there may be limited additional cognitive capacity available for empathy. When their companies are doing well, they may rely on their own view, rather than inviting challenge from the outside.

Change is often driven by underperformance. Many cash-rich, highmargin pharma businesses simply lack the external pressures many other sectors experience. This might go some way to explaining a reluctance to really address insularity and make the necessary changes.

Making Progress

Of the 14 diversity and inclusion professionals we surveyed, all of them said their work had been at least somewhat effective in changing culture. Examples included employee resource groups and internal communications, participation in external benchmarks, celebrating dates, for example raising the Pride flag on IDAHO day and training, specifically unconscious bias training. Others went further, to have diversity strands in the core business (e.g. research policy) and work closely with patient advocacy groups and have diversity-focussed clinical trials. However, all admitted there was much still to do, especially going beyond gender, including disabled people, and more customer segmentation.





Collaboration around Covid-19 has shown what the industry is capable of: opening up labs for rapid testing, co-operation between firms, and release of staff for medical duties. Diversity is now featuring in clinical trials. The next challenge is to move from diversity to inclusion. The industry needs to start measuring inclusion and start embedding it throughout. Inclusion offers insight leading to innovation and multiple benefits. The scientific bias needs to be challenged head on, with an appreciation that inclusion is more than technical; it's a behavioural methodology. The fact is without it the industry misses out on insights that would help it save lives.

The good news is diversity is now high on the agenda. We just need to progress to more inclusion. The future of medication is individualisation – without realising the "diversity" of people/patients, pharma companies will not be able to provide future medication. Without being inclusive, pharma would only provide medication of the "standard male person". It is not an exaggeration to conclude that tackling insularity in pharma would lead to fewer Covid-19 deaths, better drugs, and better lives for patients.



Stephen Frost

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Dissolution Specifications for Oral Drug Products (IR, DR, ER) in the USA – A Regulatory Perspective

Abstract

The development of a dissolution method with suitable specifications is a key part of any oral drug product control strategy. Dissolution testing is a highly important in vitro technique for pharmaceutical dosage form in development and formulation; under certain specified conditions, the *in vivo* dissolution test can be replaced by an *in vitro* dissolution test. The important point of the present article is that the drug release rate is identical batch-tobatch. For those batches proven to be bioavailable and clinically effective to facilitate generic drug manufacturers in the arranging of dissolution limits for IR, DR and ER solid oral dosage form for in vitro purposes, USFDA had revealed some guidelines. The principle is to derive the drug product specification on the basis of the biobatch quality features. This article helps during dissolution development by providing an overview of dissolution specifications and acceptance criteria that should be considered for IR, DR and ER dosage forms.

Key Words: Dissolution testing, USFDA, IR, DR and ER

Introduction

In all development phases, the dissolution test was used for product release and stability testing and also for all types of solid oral dosage forms as a prerequisite. To detect physical changes in active pharmaceutical ingredients (APIs) and in the formulation of drug, the dissolution test was used as a key analytical test. At the initial stages of development, to optimise the drug release from the formulation in vitro a dissolution test was used. For the past 50 years, to identify the effect of crucial manufacturing variables and comparative dissolution studies for IVIVC (in vitro - in vivo correlation), a dissolution test was used as a quality control technique. The FDA guidance on dissolution testing for immediate release solid oral dosage forms includes the use of the Biopharmaceutics Classification System (BCS) guidelines for biorelevant dissolution tests, which is based upon solubility and permeability of the API. As per BCS classification for potentially decreasing the bioavailability/bioequivalence study number and analysing the in vivo performance of drug products, the most useful test is the *in vitro* dissolution test. To specify post-approval changes for immediate release oral dosage form, the in vitro dissolution test is used depending upon the FDA guidelines on SUPAC. The test must be robust and reproducible, revealing or distinguishing major product performance changes. The proposed dosage form characteristics and route of administration drug can be used to determine the given dissolution test.1

Dissolution Test

USP classified apparatus 1 or 2 can be used.

The dissolution medium must be used which was given in the individual monograph. The pH of the solution should keep below 0.05 units as specified in the monograph.²

Time

As per the monograph specifications, the test may be completed if the least amount of drug was dissolved within a short period of time which represents the single time point. If the test may not be completed, then two or more time points are considered, with an acceptance of \pm 2 %.

Assemble the apparatus and warm up the dissolution medium to 36.5° to 37.5°C unless specified otherwise in the individual monograph. Withdraw a specimen from a zone midway between the surface of the dissolution medium and the top of the rotating blade or basket, not less than 10 mm from the wall of the vessel, within the time period defined or at each of the times specified. When samples are withdrawn from the dissolution basket, except in the case of single sampling, add a dissolution medium volume equal to the volume of the withdrawn samples. Do the analysis as directed in the individual monograph.³

Purpose of Specification

- In process controls, design, good manufacturing controls and process validation, development and necessities applied to the manufacturing and development of the drug product are used in the determination of drug product quality.
- To make sure the drug product efficacy, quality and safety are validated by selecting certain requirements.
- To ensure uniformity in manufacturing of quality of the product.

Conventional / Immediate Release and Modified Release Drug Products

Maximum immediate release drug compounds, i.e. tablets and capsules are prepared to produce the active drug instantly after oral consumption. No deliberate effort is made in preparing conventional drug products to alter the rate of compound produce; they immediately produce a common outcome in fast drug absorption, and start concomitantly with pharmacodynamic effects.⁴

If in case of conventional oral compounds having compounds, the pharmaodynamic action may be slow because of conversion by hepatic or intestinal metabolism of the active drug. Alternatively, conventional oral compounds which have very low solublility of the drug substance may be gradual because of slow dissolution in the gastric tract, and also conclude in a slow-dawning period. To accomplish a desired therapeutic objective or enhance patient comfort, the design of drug produced from a modified release (MR) formulation form is consciously alternated with that of a

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conventional dosage form. Modified release compound types contain delayed release, extended release, and orally disintegrating (ODT) tablets.

MR drug compounds are compounds that adjust the drug substance timings and release amount. The MR dosage form is a formulation where the drug releases over a personalised period and the site is selected to accomplish a therapeutic purpose not given by the conventional dosage form – solutions, ointments, or prompt dissolution forms. Modified-release oral drug compounds are divided into many types:

- Extended-release drug compound: A formulation which allows for at least a double debasement in dosage frequency as related to that drug in conventional dosage form.
 Example: Controlled release, sustained release.
- Delayed-release drug compound: A formulation that produces a separate product over a period rather than immediately following consumption. After consumption of an initial dose it may be released promptly, enteric coated drug compounds are popular delayed release compounds.
- 3. Targeted-release drug compound: A formulation that produces the drug action near the intended location. It may have personalities of neither immediate nor extended release.
- 4. Orally disintegrating tablet (ODC): After oral administration these disintegrate quickly into saliva, so ODT can be utilised with no water added. The compound is dispersed in saliva and swallowed along with a small amount of water, or no water.

Already the phrase 'controlled-release drug compound' is utilised to explain the different varieties of oral extendedrelease-rate dosage forms containing sustained-release, sustained-action, prolonged-action, long-action, delayrelease, and programmed drug delivery.

Retarded release is a former word for a slow-release drug compound. Drug companies have introduced varieties of words for modified-release drug compounds to reflect a special pattern to an extended-release drug compound, or to utilise in marketing.

Modified-release drug compounds are patterned for various routes of consumption depending on the drug's physicochemical, pharmacodynamic and pharmacokinetic characteristics, and on the properties of the materials used in the formulation. Now various words are described to explain the types of modified-release drug compound available, depending on the drug release peculiarities. test conditions, basket method – 50/100 RPM / paddle method – 50/75 RPM, in 15 minutes. If the dissolution test was performed for rapid dissolving drugs, a sufficient sampling profile must be generated. For BCS class I (highly soluble) and class III (rapidly soluble) drugs and batch-to-batch consistency, there should be a single point specification, i.e. not less than 85% of the drug dissolved in 60 minutes. A single point dissolution test specification of NLT 85% (Q = 80%) in 60 minutes or less is suitable as a standard QC test. For BCS class 2 (poorly water

USP APPARATUS	DESCRIPTION	ROTATION SPEED	DOSAGE FORM
Type I	Basket	50-120 RPM	IR, DR, ER
Type II	Paddle	25-50 RPM	IR, DR, ER
Type III	Reciprocating cylinder	6-35 RPM	IR, ER
Туре IV	Flow through cell	N/A	ER, POORLY SOLUBLE API
Type V	Paddle over disk	25-50 RPM	TRANSDERMAL
Type VI	Cylinder	N/A	TRANSDERMAL
Type VII	Reciprocating holder	30 RPM	ER

Where, IR= Immediate Release, DR= Delayed Release, ER= Extended Release

Table 1: Classification of USP Apparatus and Agitation Criteria⁵

Drug Release – Types⁶

- 1. Immediate-release dosage forms
- 2. Delayed-release dosage forms
- 3. Extended-release dosage forms

Specifications for Different Dosage Forms

1. Immediate-release Dosage Forms

The dissolution profile was produced under certain conditions such as: mild

soluble) drugs in order to classify product quality, a two-point dissolution specification was suggested, i.e. one at 1 minute to include the dissolution range and the rest at a later point (30, 45 or 60 minutes) to make sure of 85% dissolution.⁷

If the dissolution characteristics of the drug product vary every time, whether or not the requirements should be altered will depend on the



Figure 1: Graph Showing IR Tablets Drug Release (%) in Time (min)

bioequivalence of the product being altered to the first biobatch or pivotal batch being demonstrated. The dissolution profiles will remain similar to those of the standard biobatch or pivotal clinical trial batches to ensure batch-to-batch equivalence of the drug after SUPAC is placed in the market.⁸

reading of the six single samples separately.

The feasibility of pooled samples is the lesser samples and greater outcome in the lab, i.e. less time for the analysis. The drawback of this method is that it does not provide particular and specific averages.



The below table shows confirmation of a minimum quantity of active substance released from the dosage units tested. Until the results match at any point of S1 or S2, the test should be done by the three levels.

The amount of active substance dissolved was given in terms of Q, which was expressed as a % of the labelled content; the 5%, 15% and 25% values are percentages of the labelled content in the given table, so that the given value and Q are in similar terms.

Pooled Sample

Pooled sample is a method performed with a single point time infra-red method by converting the six individual samples of equal capacity at a given time into one sample, which will replace the individual



Is dissolution

meth

The acceptance criteria or the limits of the pooled samples are many, and a few acceptance limits are given in the table below.10

Comparative Dissolution Profiles

Model-dependent or -independent procedures are required for calculating the CDP (comparative dissolution profile). A simple model-independent approach utilises a difference and similarity factor (f1 & f2) in order to define dissolution profiles.¹¹

The standard method to differentiate the similarity and difference factors as follows:

$$f_1 = \{ \left[S_{t=1}^{n} \left(R_t - T_t \right) \right] / \left[S_{t=1}^{n} R_t \right] \} + 100$$

 $f_2 = 50 \cdot \log \{ [1+(1/n)S_{t=1}^n (R_t - T_t)^2]^{0.5} \cdot 100 \}$

The two product dissolution profiles, i.e. test product and reference product, must be determined.

The above given equations along with the mean values of dissolution are used in calculating the difference and similarity factors (f1 and f2) for both curves at a single time interval. For similar curves, f1 values must be near to 0 and f2 values must be near to 100. Basically



Figure 2: IR Dosage Form Drug Release

values of f1 ending with 15 (0-15) and f2 values > 50 (50–100) confirm sameness or equivalence of two curves.¹²

> This model-independent procedure is more appropriate for CDP when three to four, or more than four time points of dissolution exist.

> The given suggestions must be followed:

Stage	Number Tested	Acceptance criteria
S_1	6	Each unit is not less than Q +
		5%
S_2	6	An Average of 12 units (S1 +
000		S2) is equal to or greater than
		Q, and no unit is less than Q -
		15%.
S ₃	12	An Average of 24 units (S1 +
		S2 + S3) is equal to or greater
		than Q, not more than 2 units
		are less than Q - 15%, and no
		unit is less than Q - 25%.

Table 2: Acceptance Table of IR Drug Products

Drug Discovery, Development & Delivery

Stage	Number Tested	Acceptance criteria
S_1	6	Average amount dissolved is not less than $Q + 10\%$.
S_2	6	Average amount dissolved $(S1 + S2)$ is equal to or greater than
		Q + 5%.
S_3	12	Average amount dissolved $(S1 + S2 + S3)$ is equal to or greater than O

Table 3: Acceptance Table for IR Pooled Sample Drug Products



Figure 3: Graph Showing DR + IR & DR + ER Tablets Drug Release (%) in Time (Min)

Stage	Number Tested	Acceptance criteria	
A_1	6	No individual value exceeds 10% dissolved.	
A ₂	6	An average of the 12 units $(A1 + A2)$ is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.	
A ₃	12	An average of the 24 units $(A1 + A2 + A3)$ is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.	

Table 4: Acceptance Table for Delayed-release Drug products (Acid Stage)

Stage	Number Tested	Acceptance criteria
B 1	6	Each unit is not less than Q + 5%
B_2	6	An average of the 12 units (B1 + B2) is equal to or greater
		than Q, and no unit is less than Q - 15%.
\mathbf{B}_3	12	An average of the 24 units (B1 + B2 + B3) equal to or greater
		than Q, and not more than 2 units is less than Q - 15%, and no
		unit is less than Q - 25%.s

Table 5: Acceptance Table for Delayed-release Drug Products (Buffer Stage)

Dissolution Release Profile¹⁵



Under similar conditions, measurement of the test and reference batches must be made. The time points of dissolution for the both the profiles must be similar. The reference batch utilised must be the new product manufactured.

After the dissolution of 85% just one measurement should be taken of both the products.

The % coefficient of variation at the advance time points (e.g. 15 minutes) must not be > 20% and at other time points must not be greater than 10% to allow use of mean data.¹³

2. Delayed-release Dosage Forms¹⁴ Acid Stage:

The below table confirms the amount of active substance dissolved from the dosage units tested to confirm whether the requirements are met or not.

Until the results conform at any of the acid or buffer stages, the test should be continued for three levels.

Buffer Stage:

The below table confirms the amount of active substance dissolved from the dosage units tested to confirm whether the requirements are met or not.

Until the results conform at any of both acid or buffer, the test should be continued for three levels.

The Q value in the below table is 75 per cent dissolved unless otherwise specified. The quantity Q is the given total amount of active substance dissolved in two stages, i.e. acid and buffer, expressed as a labelled content percentage.

The 5 per cent, 15 per cent and 25 per cent given values in the following table are percentages of the labelled content, so that Q values are in the same terms.

3. Extended-release Dosage Forms

The below table confirms the amount of active substance dissolved from the dosage units tested to confirm whether the requirements are met or not.¹⁶

Until the results conform at any point of L_1 or L_2 , the test should be continued for three levels.

The minimum limits on the amount of active substance dissolved are given





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in terms of the % of labelled content. The amount of drug dissolved at every particular fractional dosing interval was given by Qi, i.e. the limit holds each value. The acceptance criteria are related separately to a particular range, in case greater than one range is given.

Graph Showing IR, ER, MR Tablets Drug Release





Conclusion:

The above theory and discussion proves dissolution testing is an important specification test. By collaboration with departments like analytical, pharmacokinetic, formulation, regulatory and CMC, the dissolution specifications are established. There are different dissolution media when taken into consideration regarding the testing of dissolution of the conventional and the modified release dosage form.

The above methods and media of dissolution are intended to be used in development and research mostly, but not in regular quality control. The acceptance criteria which were provided in the above discussion will help in the selection of a suitable dissolution apparatus along with the dissolution media. The dissolution test for oral products was considered as an important in vitro tool for performance measurement. The specifications that are provided above and discussed should be followed by the industry and the regulatory authorities should also try to abide by these guidelines. The industry and the regulatory authority need to focus on the standards of 'acceptance criteria'. In the aspect of product performance and quality, in vitro dissolution is the major impact. Properly designed dissolution tests will speed up the development of drugs, accelerate the



Figure 5: Graph Showing ER Tablets Drug Release (%) in Time (Min)

Stage	Number Tested	Acceptance criteria		
L ₁	6	No individual value lies outside each of the stated ranges		
		and no individual value is less than the stated amount at the		
		final test time.		
L_2	6	The average value of the 12 units $(L1 + L2)$ lies within each		
		of the stated ranges and is not less than the stated amount at		
		the final test time; none is more than 10% of labeled content		
		outside each of the stated ranges; and none is more than		
		10% of labeled content below the stated amount at the final		
		test time.		
L_3	12	The average value of the 24 units $(L1 + L2 + L3)$ lies within		
		each of the stated ranges, and is not less than the stated		
		amount at the final test time; not more than 2 of the 24 units		
		are more than 10% of labeled content outside each of the		
		stated ranges; not more than 2 of the 24 units are more than		
		10% of labeled content below the stated amount at the final		
		test time; and none of the units is more than 20% of labeled		
		content outside each of the stated ranges or more than 20%		
		of labeled content below the stated amount at the final test		
		time.		

Table 6: Acceptance Table for Extended-release Drug Products



post-approval change validation and reduce the unnecessary human studies.

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Barriers in Medical Device Innovation

Abstract

Every day, innovative new technologies can and do transform industries, and due to the massive technological innovations like the web, smartphones and communication technology, the rate of change has increased. But not all companies are created equal as regards creativity. The healthcare industry is extremely complex and due to rising costs and patient demands, the medical care delivery environment is under growing pressure. Such stresses and the industry's inherent existence itself make healthcare development more complex than it is in the consumer products market. To break through the complexities of medicine and drive science forward, inventors and medical testing and production firms must first resolve the many obstacles to the creation of healthcare products. Knowing how medical devices interact with humans is a critical problem that influences both the design and acceptance of innovative new technologies and their regulation. The FDA classifies medical devices

in three classines medical devices in three classes. The first two classes do not have many regulatory requirements, but class 3 has many hurdles to passing the regulatory requirements for marketing of the product. During the early generations, the regulatory requirement for marketing of medical devices was much less compared to the present situation: now they need to pass many regulatory hurdles, which is a very big barrier for medical device innovation because there is no proof that will it pass through the regulatory hurdles.

Key Words: Medical device, Innovative Barrier

Introduction

A medical device is described as a medical product which, via pharmacological,

immunological or metabolic means, achieves its primary intended effect in or on the human body; or a tool intended for internal or external use in human or animal disease or disorder, diagnosis, treatment, mitigation or prevention.²

Example

Substances used for *in vitro* diagnosis and surgical dressings, surgical bandages, surgical staples, surgical sutures, ligatures, blood and blood component collection bags with or without anticoagulant, and substances like mechanical contraceptives (condoms, intrauterine devices, tubal rings), disinfectants and insecticides.

History

The first "medical device" invented was the thermometer in 1603 by Galileo. In 1819 the stethoscope (wooden) was invented by Rene, and the real breakthrough was the discovery of X-rays in 1895, then the invention of the ECG in 1903, which is still used in all hospitals. There are more than 14,000 different products, according to Global Medical Device Nomenclature.

There are four types of classification of medical devices in India and Japan:⁴

CLASS	RISK	EXAMPLE
Class A	Low risk	Thermometer
Class B	Low -moderate risk	Hypodermic needle
Class C	Moderate- high risk	Lung ventilator
Class D	High risk	Heart valves

But according to some countries like Europe and the USA, there are only three classes:¹

for the broader society. The cost of such studies is often the liability of the fabricators of products.⁵

familiar with the issues that need to be

addressed. Most ideas are received from

clinicians and healthcare providers to

solve their problems by innovating new

Barriers to innovation of medical

devices cause a massive problem

globally. For example, if a medical

device is not on the market and the

treatment for some disease or disorder

is not available, most barriers relate to

medical efficacy review, distribution

of the product, and manufacturing of

the medical device with good quality,

Another hurdle is questions relating

to intellectual property rights (IPRs).

The extensive testing that the US Food

and Drug Administration (FDA) or the

European Notified Bodies require

represents large and risky financial

commitments. The final financial out-

come of investments may be uncertain

even after positive clinical testing, as

payments for products and services

are not assured by reimbursement

mechanisms. Reimbursements may

require more research, recording a

beneficial cost / benefit analysis for

patients, healthcare providers, or even

regulatory oversight.

products.

CLASS	RISK	EXAMPLE
Class A	Low risk	Thermometer
Class B	Medium risk	Lung Ventilator
Class C	High risk	Heart valves

Innovation is not only about introducing something new but also adding value to it. It should be useful and feasible. Innovation and new product development are the lifeblood of the R&D department of an industry.

Ideas for change also come from consumers and experts who are most



Barriers in Medical Devices:6

The following topics will be discussed herein in an attempt to give a brief overview of barriers in medical device innovation: pacemaker and the requisite charges for implantation and monitoring cannot be managed. This can be partially understood as an inefficiency for medical devices firms in emerging



Medical Practice Patterns and Education

While medical practice is changing rapidly, there is an underlying tradition in medicine which supports the status quo. New methods are often, and often correctly, adopted only after the "medical establishment" has completed and accepted controlled studies. Randomised trials and meta-analysis are needed for new procedures and technologies to become a standard of care. Even upon completion of such studies, years can pass before a tool or procedure is commonly used. This is a challenge for designers of devices who spend enormous resources to sell a product. The duration of the new product's high-income potential may be short, making it less desirable for new technology to be the first out. The method of introducing new technologies in hospitals is often difficult and relies on physician-administrative consensus.

Market Size and Penetration

The global market for medical devices is rising, but substantial maldistribution exists between rich and poor countries. The disparity is apparent and important as applied to the consumer technology industry such as mobile phones. Although cell phones are available to most people, there are few cardiac pacemaking agents, and the number of patients killed each year by a lack of pacemaker and defibrillator care is estimated at 1–2 million. While ordinary Africans can afford a cell phone and pay the subscription services, a lifesaving markets and a lack of healthcare services and skills. Device manufacturers may be hesitant to offer the emergent market lower-priced products, believing their own goods could be cannibalised and profit margins eroded.

Research and Development (R&D) and Device Failures

Medical device R&D and sales are high-risk projects. It's a long and expensive process from proposal to practical medical implementation. Traditionally, early research is conducted in educational institutions, while in the corporate environment software creation, evaluation and development occur. Systems are expensive and often drag on for years. Despite extensive product evaluation both ex vivo and in vivo, the manufacturer's risk of later failure of new products will cause severe medical problems for the consumer and economic disaster. The Christiansen hip prosthesis and the "Björk-Shiley" heart valve, as well as the silicone breast implants in France, are leading examples of failed products. The future legal and financial consequences of such failures represent a major investment risk. As an example, with the problem of the "Björk–Shiley valve", where welded valve struts split and caused embolisation of the leaflet, the production company went bankrupt because of allegations of personal injury. The "Björk-Shiley" experience has resulted in more stringent testing practices and medical follow-up for heart valve products, which is helpful to patients, but acts

as an innovation barrier as new claims will emerge more than 20 years after medical devices barriers to product development implantation. Initial acceptance and successful implantation of a device is definitely not a guarantee against future complications. It may be unrealistic for developed and poor countries to assume the same degree of complexity and safety features of medical devices as those requested by Western regulatory bodies. Most poor countries' gross domestic product could not afford the implantation of costly implants even for life-threatening diseases for the people, and it may be fair to permit simple, perhaps even less stable devices in such markets. At present, advanced computer therapy is open only to wealthy and government leaders in poor countries. Implantable devices pose risks to patients and are known as Category III products requiring premarket approval. In the US, the FDA, a government agency, oversees this procedure.

IPRs, Patent Issues, and Publication

New medical technologies are often the product of academic-commercial collaboration. This may create contradictions between the willingness to publish and the interest in patenting and obtaining IPRs. Previously, researchers and healthcare employees' IPRs may have been poorly secured, leaving the scientist with the choice of keeping or publishing an invention secret, risking the latter's loss of privacy. Technology transfer organisations, while increasing this obstacle, promote collaboration between companies and institutions. Small businesses, creating new technologies, may be in an adverse position to protect their IPR from the enormous legal and financial assets of corporations. Big companies often use large and general patents to protect their goods and services, preventing new development. Medical professionals are essential contributors to product innovation, and insufficient IPR regulations pose yet another obstacle to advanced innovative development unless technology transfer organisations actively help protect IPRs. A doubleedged sword may be the question of patent law and practice. Gaining a patent will promote creativity by granting exclusivity to the patented item for the length of the patent. Patents, on the other hand, raise product costs dramatically and may reduce creative efforts in the relevant field. Gold *et al.* provide a careful analysis of the importance and drawbacks of existing patent law practices. The consumer limitations on modern devices or drug therapies in the developing world is a particularly serious problem that has been proposed as an alternative to the current patent procedure.

Reimbursement and Pricing

Healthcare service fee is based on clinical classification in many countries and may not include the cost of new advanced tools. Methods involving new devices for healthcare providers can pose a financial pressure or loss. The lack of innovative technology payments will hamper the implementation of new technologies and thus product innovation. Legislation can vary considerably in different countries, and the lack of predictability is an apparent obstacle to innovation. Reduced payment options on emerging markets are seriously obstructing the introduction of new technologies. As noted earlier, patent regulations may further hinder the growth of low-income countries, even though these countries may be able to use the reversing design technique to manufacture out-of-patent products.

Ethical Considerations

The World Health Organization considers access to healthcare to be a human right, but this right remains a myth for most of the global population. Although the health problems are different, the richest countries are also struggling with delivery and access to care. Transplantation and use of existencesupport equipment, such as dialysis and circulatory aid devices, should be in theory open to everyone in need, but provision, in fact, is severely restricted globally. In many countries, insurance may not cover existence-supporting devices such as pacemakers, and treatment is thus restricted to monetary rather than clinical indications.

Conclusion

As the world is moving very fast, innovation of medical devices will provide better lifestyles for patients. Innovation in medical devices has given enormous benefits to patients, particularly in the developed world, while there has been much less benefit to the population in emerging and poor countries. Because of the obstacles to technology, the production and adoption of novel medical devices was slower than for some consumer goods. The combination of medical and technical expertise will contribute to faster and more efficient growth, thereby enhancing investment capital availability. Early R&D will take place across consortia like education, manufacturing companies, and government agencies, thus increasing shareholder aversion to risk. Streamlining clinical trials, including a more consistent method to the process of evaluating health technology, can accelerate the implementation and spread of price-effective devices. While the current business model for computer manufacturers may be threatened by lower prices, increased sales may make up for them economically by establishing a real global market. Medical devices often have excessive pricing and it is undoubtedly true that this innovation will make it much easier for the medical field to stick to its basic moral principles when interacting with medicine and technology. Changes in patent laws and the way such laws are practised may decrease cost and increase competition.

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Expiry Dating: A Complex Mathematical Puzzle

Many times, during the course of a pharmaceutical clinical study, expiration dating and the extension of clinical product beyond the original date becomes a critical need for sponsors. Ongoing stability trials may not be at a specific point in time such that real-time data is available to make an informed decision as to whether the product is still viable and whether the product expiration can be extended to maintain product in the clinics. Through statistical analysis based upon both first-order kinetics and the use of the Arrhenius Equation, Sharp Clinical Services (SCS) can offer this rationale to clients in an effort to provide scientific reasoning that can reasonably extend the expiry of the product. The focus of this paper is to describe methods which provide this scientific rationale to evaluate and potentially extend expiry.

Puzzles

Do you like puzzles? Specifically, mathematical puzzles. Here's one: Three (3) is to twelve (12) as six (6) is to twentyfour (24). I have always loved math puzzles, from my earliest memories of 7th grade math class, when my math teacher would save a few complicated "puzzles" for myself and a few of my classmates. We'd spend hours after class, using up every inch of the chalkboard trying to solve the problem. She was, in her own way, trying to stretch our brains and hoping to have us "connect the dots". Within the pharmaceutical development cycle of drug products, expiry dating and even more so extensions of expiry are very complex mathematical puzzles. This paper hopes to shed some light on how to better connect the dots to provide sound reasoning in solving these complex puzzles.

Stability and Expiry – A Complex Puzzle Going back to my original puzzle above in which three (3) is to twelve (12) as six (6) is to twenty-four (24), puzzles are nothing more than an effort to find some solid connection between what appear to be separate and distinct pieces. Find the connection, solve the puzzle. Imagine that 1000-piece Ravensburger puzzle in which you try to find the connections, which might be sorting the pieces into shapes, series of similar colors, looking at the picture on the cover or just plain sitting there trying to fit one into another.

In the first puzzle above, the connection seems obvious that the answer is just a multiple of the first value. Thus 12 is a multiple of three and 24 is a multiple of six. The connection appears to be the multiplier of four (4). However, what if we complicate the puzzle further. In stability testing of a pharmaceutical product, the rule of thumb has been that a material on stability at an accelerated condition (e.g. 40°C/75%RH) which remains stable for three months is a predictor of 12 months of expiry of the same material kept at the long-term storage condition (e.g. 25°C/60%RH). The extension of this becomes that six months accelerated can predict 24 months of product expiration at long-term conditions. To be clear, this rule of thumb is the basis of why regulatory agencies request accelerated storage data during pharmaceutical development, as it would take an inordinately long period to generate real-time data during these early clinical stages. However, remember that real-time stability storage and testing must continue, as this data is critical. Those predictions of product expiration are just that predictions.

Thus, while similar, these puzzles are completely different and complicated by the fact that we have added additional variables. In the first example, no variables were provided. Now, we have introduced time, temperature and even humidity. So, in the second case, how did we arrive at this connection? That is where Arrhenius enters the picture.

A Physicist Named Arrhenius

The Arrhenius Equation¹ described by Nobel laureate Svante Arrhenius

(1859–1927) expresses the relationship of temperature dependence on the rate constants of chemical reactions. The equation is written mathematically as:

$k_{T} = Ae^{Ea/RT}$

where k is the rate constant at a specific temperature expressed in degrees Kelvin (°K), Ea is the activation energy, R is the universal gas constant and T is temperature (°K). Simply, assuming that most of the elements of this equation are fixed constants, the variation of temperature provides the key to how much the rate of change occurs with temperature. For example, assuming a change of 10°C from 20°C to 30°C and by substitution into the equation using 293°K and 303°K, the difference in rate constants k293K and k303K would change by about a factor of two. This doubling effect is the typical value applied as the standard rule of thumb in simple rates of reaction².

Using this rule now allows us to apply a more practical equation in determining shelf-life. Using an "Accelerated Aging Time (AAT)" as defined within ASTM document F1980-02³, "Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices", the ASTM defines the use of accelerated aging as follows with respect to real-time shelf-life testing. Section 4.3 indicates: "...Real-time aging programs provide the best data to ensure that package materials and package integrity do not degrade over time. However, due to market conditions in which products become obsolete in a short time, and the need to get new products to market in the shortest possible time, real-time aging studies do not meet this objective. Accelerated aging studies provide an alternative means..."

Accelerated aging is based on the earlier assumption that the rate of reaction doubles or decreases by half with each 10°C increase or decrease in temperature, respectively. Thus, expressing this mathematically, the following equation for the Accelerated Aging Factor (AAF) is:

$$AAF = Q_{10} AA BT^{[(T - T)/10]}$$

where: Q_{10} is typically "2" based on Arrhenius equation, T_{AA} is the considered accelerated temperature and T_{RT} is the ambient starting condition. However, while Q_{10} can be estimated to be equivalent to "2", more aggressive factors can be scientifically determined based on the actual rate of reaction curves of time versus temperature. Values upwards to 2.5 or 3 for AAF can be applied if supporting data is generated. Q_{10} values can easily be calculated as the slope of logarithmic evaluation of time vs. temperature.

Accelerated Aging Time (AAT) is defined as a function of this AAF and the desired (required) shelf-life. This is expressed as:

For purposes of discussion let us assume that TAA is 40°C and TRT is 25°C. By substitution, the AAF would equal 2^[(40-25)/10] or 2^{1.5}, which is 2.828. If an AAF value of 2.5 is applied, the AAT becomes 4. So, in using this predictive tool, a desired real-time study of 12 months at 25°C should be able to be effectively estimated through an accelerated study conducted at 40°C in either three to four months depending on how aggressive an aging factor is applied. Hopefully, based on these assumptions, it has now become obvious to the reader as to the solution to our earlier puzzle: 3 is to 12 as 6 is to 24. The factor was four. Using an aggressive aging factor of 2.5, this would now explain this stability concept better.

First-order Kinetics (Rate of Decay)

While the above expressions can describe an estimation of shelf-life based on a change in temperature, many requests for expiry dating and extensions are based only on materials kept at a single temperature (room temperature). Thus, another method to evaluate shelf-life to be considered can be based off data collected during real-time stability studies. The evaluation of the rate of decay from simple first-order kinetics can be used to extrapolate data to points at and well beyond the shelf-life desired.

A similar concept was described above for estimating the AAF at different

rates relative to time and temperature. First-order kinetics describes the relationship between concentration changes over time. The equation for 1st order kinetics is well described within literature and can simply be expressed as:

$$\ln \begin{bmatrix} A_0 \end{bmatrix} = -kT$$
$$\begin{bmatrix} A \end{bmatrix}$$

where: k is the rate of decay, T is time, [A0] is the initial concentration and [A] is some observed concentration at a distinct time T.

As shown below in Figure 1, this logarithmic relationship of concentration (%Assay) over a period of months of storage at $25^{\circ}C/60\%$ RH can be expressed as a linear equation of the form Y = mx + b, where the slope of the line equation is equivalent to the rate

constant (k). The tabular data for this plot is shown in Table 1. The % Assay values for this product can easily be converted to the natural log (ln) and plotted versus time (months).

The key to this data is two-fold, in that first the regression line of the data can be used to generate a real rate constant to estimate Q₁₀, but also the data can be extrapolated to a point where an extended line can be used to predict where the product may degrade to an unacceptable potency (in this case 90.0%). At that point, a reasonable estimate of shelf-life could be estimated. In Table 1, the log value for 90.0% become 4.500 and this can easily be extrapolated from the regression line to a future point. This projected value in the example presented for shelf-life is about 42 months.



Figure 1. Estimate of Expiry (Active DP) – 25°C/60%RH

Time (months) Ln(Y) %Assay 0 4.578 97.3 4.572 96.7 1 6 4.557 95.3 6 4.551 94.7 6 4.561 95.7 6 4.560 95.6 9 95.2 4.556 9 95.5 4.559 9 4.560 95.6 9 4.558 95.4 9 4.555 95.1 9 4 5 4 6 94.3 12 95.0 4.554 18 4.544 94.1 18 4.540 93.7 ? (42M) 4.500 90

Table 1 – Experimental Expiry Data – (Active DP) – 25°C/60%RH

Fortunately, through the use of Excel and the "*Trend*" function, a simple table can be developed in which the trend line can be expressed to determine this relationship easily.

Further Applications

Using all of the above considerations, this paper looked to determine if these previously discussed concepts could be applied to other products such as placebos which would not provide quantitative data (e.g. assay) for this type of trending or statistical analysis. In the case of placebos, the use of some qualitative type analysis has been considered, such as disintegration as a potential tool to provide clients with the ability to predict when placebo product may expire or provide the ability to



Figure 2. Estimate of Expiry (Placebo) – 25°C/60%RH

extend the expiry dating based on some statistical supporting evidence. As shown below in Figure 2, a simple placebo tablet formulation was monitored for a period of 18 months at 25°C/60%RH and then tested for disintegration of the tablets. The placebo's acceptance criteria for disintegration had been established at a period of 30 minutes prior to stability initiation. To be clear, the product would remain within criteria if as per USP<701>, sixteen (16) of eighteen (18) units fully disintegrated within the specified time.

To better explain how this statistical approach was developed, the data in Table 2 displays two sets of data with regard to time in minutes. To permit the use of the rate of decay, the observed disintegration time in minutes would increase typically as the product approaches the expiration. Thus, the actual observed value(s) were subtracted from the acceptance criteria (in this case 30 minutes) so that the resulting curve would generate a negative slope.

The resulting data reported in Table 2 was plotted and the trendline generated would appear to support that the product would not meet acceptance criteria at about 14 months. The actual data shown in Table 2 indicates that the product did not meet the criteria at 12 months. Thus, by converting a qualitative test into a quantitative analysis through some simple manipulation, the concepts discussed above appear to support use in the prediction of expiry for non-active ingredient products such as placebos.

Summary

We began this discussion on the concept of solving complex puzzles. Through the use of statistical analysis and some basic understanding of rate constants and rates of decay, the application of expiry dating was shown to be nothing more than an effort to find some solid connection between what appear to be separate and distinct pieces. Through the generation of data for both active pharmaceutical products and even placebos, these types of mathematical tools and concepts to help clients find the connection and solve the complex puzzle that is expiry dating, are being used.

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Time (months)	Ln(Y)	Observed Disintegration Time (min)	Time Corrected (30-Actual)
0	2.708	15	15
1	2.708	15	15
3	2.398	19	11
5	2.197	21	9
6	2.398	19	11
9	2.079	22	8
12	(-9.2)	>30	0
18	(-9.2)	>30	0

Table 2 – Experimental Expiry Data – (Placebo) – 25°C/60%RH

basicrates/arrhenius.html

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The Rise of Al in Pharma

Over the last few years, the use of Artificial Intelligence (AI) in the pharmaceutical industry has gone from a promising prospect to an indispensable and proven tool. Largely driving the use of AI is the digital transformation that is occurring in the industry. Digital transformation is enabling pharmaceutical companies to innovate in new ways to drive scientific discoveries and get life-transforming treatments into the hands of patients more quickly.

Digital transformation in the pharmaceutical industry is a strategic imperative for companies to maintain market competitiveness. Pharmaceutical executives are noticing the impact of digital initiatives and are realising the crucial need to implement business strategies around these rapidly evolving technologies. The application of Artificial Intelligence (AI), cloud technology, informatics platforms, machine learning, the Internet of Things (IoT) and other tools of the big data era are enabling pharmaceutical companies to build their own digital ecosystems. These ecosystems are creating infrastructures from which strategies can be implemented to successfully manage and execute the copious amounts of multi-factorial data generated during the drug discovery and development process.

A Growing Field: Artificial Intelligence

In 1958, Frank Rosenblatt's "perceptron" was unveiled, a machine that has now been acknowledged as the world's first neural network. Rosenblatt demonstrated that artificial neurons could learn from data, laying the foundations for AI as we know it today¹. The real boom in the field of AI came in the early 21st century, with the advent of more affordable computing, access to large datasets, and advanced machine learning techniques.

Al includes its subfields of machine learning (ML) and deep learning (DL).

ML refers to computer programs that learn from input data, environment, and feedback, and then generalises this data to perform tasks with increasing efficiency. DL is a further subset of machine learning that mimics the human brain: artificial neural networks are linked together like a web and combined with immense computing capacity to create powerful models for the non-linear processing of data.

AI has been quietly revolutionising market sectors in a growing range of fields. Today, AI systems are fully operational in a diversity of applications, such as warehouse management, forecasting demand in the power industry, monitoring agricultural land for precision spraying and soil restoration, and autonomous vehicles. Moreover, there's no sign of a slowdown in AI implementation: entrepreneurial activity related to AI in 2016 drew investment in the range of 26 to 39 billion dollars, triple the amount generated three years earlier².

One industry in particular that has seen an increased use in AI is the pharmaceutical industry. Given the results already achieved by earlyadopting companies, the notion that AI has the potential to revolutionise the pharmaceutical industry in terms of more rapid and lower-cost drug discovery cannot be regarded as hyperbole. Behind the use of AI in drug discovery and development is the implementation of a platform technology. Platform technologies connect all the various technologies that exist within the digital ecosystem and enable AI platforms to work. Laboratory information management systems (LIMS) are largely facilitating this process. LIMS completely aggregate laboratory data and feed it into a data lake, which then allows AI systems to mine through that data and make accurate predictions. The enormous costs faced by pharmaceutical companies in turning candidate therapies into approved drugs represent a wide window of opportunity for AI to bring major improvements. Last year's announcement that ten pharmaceutical

companies were collaborating to train their drug-discovery machine learning algorithms with each other's data³ proves that Al's potential advances outweigh the need for commercial secrecy.

Breaking Bottlenecks, Conquering Challenges

Digital ecosystems and technologies are making inroads throughout the pharmaceutical industry for numerous applications, improving existing business and operational models, as well as creating new ones. The announcement earlier this year of what is the world's first Phase I clinical trial of a drug candidate created entirely by AI has provided a clear illustration to a global audience of the power of the technology⁴.

Inevitably, as with any advancement capable of triggering a genuine paradigm shift, the advent of Al in drug discovery is not without challenges. How do companies ensure the proper implementation of a digital ecosystem? How do companies ensure that their data lakes and Al systems are secure? To address these types of questions, pharmaceutical companies are implementing a new role to oversee the implementation of a digital transformation, a chief digital officer (CDO).

A CDO oversees the implementation of short- and long-term digital strategies, including collaboration with a chief security officer to ensure that the strategies being implemented are safe and secure. The involvement of a CDO also provides the opportunity for department heads to work with them to determine where efficiencies can be made to make a company more agile and competitive. Leadership teams play a critical role in not only providing funding, but also changing corporate culture towards a greater appreciation of the value of digital strategies.

Applying AI at the Frontline

Most of the major pharmaceutical companies, if not all, have now formed partnerships with at least one Al-based

HOW AI, ML AND DL RELATE TO EACH OTHER IN A VENN DIAGRAM FORMAT:



drug development company. We focus here on two examples of such collaborations to gain an insight into the reality of the digital transformation, and how it is advancing healthcare.

Cyclica, a Canadian company aiming to decentralise drug discovery using Al and computational biophysics, has developed powerful software to match the biophysical and biochemical properties of millions of molecules to the structures and properties of approximately 150,000 proteins. The objective is to uncover molecules that are likely to bind to a target⁵. This critical first step in the drug discovery process is becoming ever more important as researchers continue to decipher the complex mechanisms of diseases. such as Alzheimer's and cancer. For these multifactorial disorders, AI has a huge potential due to its ability to screen vast numbers of compounds at much faster speeds and with greater certainty than previously attainable. While sophisticated screening is nothing new in pharma, AI represents a sea change because it has the innate ability to learn which elements of the data are important, and to use this information to make highly accurate predictions.

Global pharmaceutical companies, such as Bayer and Merck, are among the companies that have formed

partnerships with Cyclica to harness its AI software for their drug discovery efforts, and Cyclica has already announced the successful identification of a key target protein for systemic scleroderma (an autoimmune disease which damages connective tissue under the skin and around internal organs) and Ebola, both of which are linked to already-FDA-approved drugs⁵. Given that these drugs are FDA-approved for HIV and depression, respectively, extending their application could be a relatively rapid process, if and when research efforts demonstrate their suitability for treating other disorders.

Al is also demonstrating its effectiveness in cases where researchers already know the target protein but need to discover molecules that will bind with the target. Companies such as Celgene, GSK, Sanofi, and Sunovion have partnered with Exscientia, an Al-driven drug discovery company with UK-headquarters, to solve this problem. Exscientia has created an algorithm that compares information about a target protein with a database of around a billion interactions, to focus on the possible compounds that may meet the criteria. Moreover, this AI tool also generates information on what additional data could help further reduce the list of possible compounds. The process is repeated until a manageable list of favourable drug compounds is generated. The CEO of Exscientia, Andrew Hopkins, claims that their specialised process can reduce the time spent in drug discovery from 4.5 years to as little as one year, and decrease discovery costs by 80 per cent.

GSK has reported that its partnership with Exscientia has led to a promising molecule targeting a novel pathway to treat chronic obstructive pulmonary disease (COPD)⁶. COPD is a progressive lung disorder with debilitating health impacts, which affects around 384 million people worldwide. There is, therefore, an urgent need for new and more effective treatment options. The highly potent, in vivo active lead molecule was identified using Exscientia's Centaur Chemist Al-driven automated drug discovery platform after testing only 85 compounds, and was synthesised and tested within five iterative design and screening cycles. The first results of the Exscientia-GSK collaboration are very promising in terms of alleviating the burden of this disease.

Conclusion

Digital transformation is a watershed that must be addressed by businesses across all sectors, and pharmaceutical companies are no exception. Drug development is an inherently dataintensive process which strongly lends

MACHINE LEARNING CONSISTS OF THE FOLLOWING STEPS:



itself to AI and machine learning techniques, and the companies that have started implementing digital strategies are already seeing dividends.

Exscientia and Cyclica are just two examples of companies that are joining forces with pharmaceutical companies to improve the drug discovery process, helping to ensure that life-transforming treatments are made available to patients more quickly. In the research laboratory setting, a key aspect of facilitating AI is making sure that all research data is readily available in a secure, centralised location to ease machine-learning processes. This can be achieved using centralised data management systems and LIMS, platforms that enable the direct communication between laboratory instruments and software. With integrated, modern technologies, pharmaceutical companies can take advantage of the data available to them to optimise their processes, and ultimately, accelerate drug discovery.



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Establishing a Sound Data Footing for Al

Emerging, smart technologies offer a means of delivering more value and better business outcomes in many industries, not least life sciences. But the transformation potential relies on the quality, credibility and completeness of the data these intelligent systems are working from. Here, Steve Gens of Gens & Associates and Remco Munnik of Iperion Life Sciences Consultancy offer five best practice tips for achieving a definitive, trusted regulatory and product information asset base capable of supporting intelligent process automation.

Life sciences companies, in common with peers in other industries, are aware of the huge potential of emerging technologies including artificial intelligence/machine learning (AI/ML). Opportunities range from complex trending and scenario analysis, and delivery of rapid snapshot insights, to transforming process delivery through intelligent workflow automation.

Yet, in their keenness to harness these options, many companies try to run before they can walk, not realising the potential of AI/ML is wholly dependent on the credibility of the data available. Having trusted data is a substantial and essential first step in delivering AI/automation-based innovation and operational transformation. And this requires an ongoing 'data quality sustainability' programme to be successful: companies need to be continuously checking/reviewing and enhancing the quality, integrity and completeness of the data sources that key processes rely on.

So what are the critical considerations and steps companies must take before they can progress to the interesting part – the application of AI to drive new insights and facilitate transformational process change?

Here are five critical data governance elements companies must have in place

before they can attempt to become smarter in their use of data.

1. Assigned Roles and Responsibility around Data Quality

Unless organisations assign clear and precise responsibility for ensuring consistent data quality, the integrity and reliability of the information available in the systems will suffer. Although this does not need to be a full-time undertaking, having someone whose remit clearly includes maintaining the integrity and value of data is the only way to ensure that any future activities drawing on these sources can be relied upon, and will stand up under regulatory scrutiny.

A 2018 study of regulatory information management by Gens & Associates¹, which polled respondents from 72 companies internationally about their associated plans and practices, found that confidence in product registration, submission forecasting, and regulatory intelligence data quality was not high. When 'confidence' is low or moderate, organisations spend considerable time 'verifying' and remediating this information, with a direct negative impact on productivity.

Building confidence must start with imposing rules and procedures around data entry, to ensure that there is no risk of individual interpretation of the data requirements. Ongoing oversight over data quality is critical too, to ensure human errors do not build over time, eroding confidence in system data.

Data quality sustainability should be an organisation-wide concern, necessitating a culture of quality and clear accountability for this as part of people's roles – as appropriate. Allocated responsibilities should ideally include:

Quality control analysis. Someone who regularly reviews the data for errors – for example sampling registration data to see how accurate and complete it is. This role typically includes establishing quality control routines, managing predetermined metrics, and reporting weekly or monthly on conformance (or not) to naming conventions; workflows that are stuck; incomplete data; and how different regions are performing against agreed data-related KPIs.

Data scientist. Someone who works with the data, connecting it with other sources or activities (e.g. linking the company's regulatory information management (RIM) system into clinical or ERP systems), with the aim of enabling something greater than the sum of the parts - such as 'big picture' analytics. This person would play an important role in the design and proof-of-concepts for a data warehouse or Al project, with an eye towards discovering any data quality issues as part of the integration/data consolidation activity. Data quality needs to be closely assessed and reported on before anything more ambitious is done with the combined information, or before rogue data fields from one system can contaminate another.

Chief data officer. With a strategic overview across key company data sources, this person is responsible for ensuring that enterprise information assets globally have the necessary governance, standards and investments to ensure the data they contain is reliable, accurate and complete – and is monitored and maintained consistently over time.

2. Quality Control Routine

To steadily build confidence and trust in data, it is important to set down good data hygiene habits and build these into everyday processes. By putting the right practices into place, companies can avoid the high costs and delays caused by data remediation exercises, which can run into millions of dollars or euros. Spending just a fraction of that amount on embedding good practice and dedicated resources pays dividends in the long run and is cost-effective.

Operationalising data quality standards is important. Naming conventions, data standards, data links with related content, and data completeness guidelines need to be applied consistently on a global basis. And of course not all data quality errors are equal. Successful companies apply severity levels, to flag issues for urgent action and tracking of error origins, so additional training or support can be provided. To inspire best practice and drive continuous improvement in data hygiene, making data quality performance visible can be a useful motivator: drawing attention to where efforts to improve data quality are paying off. This is critical for our next point.

3. Alignment with Recognition & Rewards Systems

It is important to recognise people/ teams/countries/regions making the biggest contribution, or who have made the biggest transformations, in their data quality and upkeep. Recognition, via transparency, will continue to inspire good performance, accelerate improvements and bed in best practice, which can be readily replicated across the global organisation to achieve a state of continuous learning and improvement.

Knowing what good looks like, and establishing KPIs that can be measured against, are important too. Where people have had responsibility for data quality assigned to them as part of their roles and remits, it follows they should be measured for their performance, with reviews forming part of job appraisals, and rewarded for visible improvements.

4. A Mature and Disciplined

Continuous Improvement Programme Continuous improvement is a learning process that requires experimentation with 'incremental' improvements. Over time, many small improvements lead to high-performing organisations.

Gens & Associates' 2018 research found that life sciences companies with a regulatory 'continuous improvement programme' (CIP) have 15 per cent higher data confidence levels, 17 per cent are more likely to have achieved real-time information reporting, and 21 per cent have higher efficiency ratings for key RIM capabilities.

As the US management consultant Peter Drucker famously said, "If you can't measure [something], you can't improve it." We recommend collating multiple ideas from across the organisation, performing root-cause analysis, and agreeing KPIs that help people focus on the main priorities for change.

Establishing good governance, and measuring for and reporting on improvements and net gains and how these were achieved (what resources were allocated, what changes were made, and what impact this has had), are critical elements too.

5. Data Standards Management

Intensifying international regulatory and safety initiatives are resulting in whole rafts of new specifications about how data should be captured, categorised, formulated and applied – to create greater harmony in information handling, and comparable product insights within organisations and across global markets.

Too often today, data is *not* aligned and standards vary or simply do not exist. Ask representatives from Regulatory, Pharmacovigilance, Supply Chain, and Quality how they define a 'product' or how many products their company has, and no two answers will be the same.

The more that all companies keep to the same regimes and rules, the easier it will become to trust data, and what it says about companies and their products – as it becomes easier to view, compare, interrogate and understand who is doing what and how at a community level.

Evolving international standards such as ISO IDMP and SPOR (specifications around how information about substances, products and associated manufacturers/partners/systems must be captured and reported) mean that companies face having to add and change the data they are capturing over time. To stay ahead of the curve, minimise the impact of changes, and avoid the risk of non-compliance, life sciences companies need a sustainable way to keep track of what's coming, and a plan for adapting to and managing any new requirements.

It may be prudent to seek external help here, *i.e.* with how to strike the optimal balance between regulatory duty and strategic ambition.

Effective AI Depends on a Solid Data Bedrock From all of this, the important takeaway is companies cannot assume they will be able to innovate and transform their operations with AI and process automation relying on the data that is not properly governed tactically and strategically. With emerging technology's potential continuing to grow, it is incumbent on organisations to formalise their data quality governance and improve their ongoing data hygiene practices *now*, to ensure these assets will be capable of supporting their ambitions for AI-enabled process transformation when appropriate.

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Adopting More Agile Process Management and IT Advancement: The Need for Speed

External demands from regulators and the wider market are evolving at an accelerating pace, which is challenging life sciences firms' ability to respond. Project cycles of 12–24 months are no longer practical, especially given that new or updated requirements may have entered the frame along the way. In this article, Romuald Braun, VP of Strategy for Life Sciences at Amplexor, discusses the need for greater responsiveness from IT teams and suppliers to the changing needs of the business and how they might achieve that.

Without question, life sciences organisations, in common with other businesses more generally, need to be more nimble, agile and responsive to the changing market conditions they are operating in. More often than not, they look to technology to help make this possible. So when 'transformational' projects look set to take 12–24 months – or longer – before business owners are likely to see any benefits, this can feel quite jarring.

In a regulatory context, this is particularly the case given that global compliance is a moving target. Requirements are being updated and supplemented continuously. This makes it impractical to try to define all probable needs up front, then lock down an IT project and go through all the rigorous sequential stages of designing, approving, developing, validating/testing, piloting and rolling out. By the time that end point comes, there is a strong possibility that needs will have changed and new regulatory requirements will be coming through. This then necessitates a new round of modifications and additions - incurring more delay, cost and frustration.

There has also been a growing realisation that major IT investments can and should deliver more than the immediate specific requirement. Where possible, new systems should feed into and contribute towards bigger transformation ambitions – those geared to improving operational transparency globally, for instance; and/ or cost-efficiency and speed to market. These strategic plans may involve harnessing some degree of smart process automation, using the latest Al capabilities as these emerge and become more reliable and affordable. At the very least, they should take into account a broader view: for instance how the new system will connect with, draw from, and add value to other core business systems.

So what does all of this mean, practically?

Improved agility – whether through adoption of accelerated, technologyaided processes, or the ability to roll out and exploit new IT capabilities more swiftly – is not something companies can achieve overnight. It might appear to be the case with so many out-of-thebox, cloud-based software solutions now available, but these can be a compromise too far and still demand a hefty amount of data preparation and migration before they are ready to use, and before they can be trusted.

Rather, business and IT teams need to adopt a more iterative and collaborative mindset and culture as they approach new system requirements, because there are ways to accelerate even fairly bespoke projects if all of the stakeholders involved are prepared to plan and manage developments in new ways.

Agile software development typically involves a much closer and more continuous engagement with the IT supplier – including monthly meetings to discuss progress and feedback; suggestions of tweaks to keep the evolving system tightly aligned with the latest needs of the business.

In a regulatory information management (RIM) scenario, this regular dialogue would provide an opportunity to feed in the latest authority guidelines and data standards as these are announced and firmed up. Since agile development happens as a series of short'sprints', a continuous collaboration ensures that no part of the project can go too far along one path without reconfirmation that this remains the right course.

Another feature of agile development projects is that different aspects of the work can be progressed in parallel. In the case of a first formal RIM system, when there is so much contributing data to locate, verify and clean up/prepare, it makes practical sense for this work to be happening alongside the system development/configuration process. This will help ensure that by the time an approved system is operational, it can be populated fairly swiftly with a reliable master resource – one that multiple applications and types of document will be able to draw from.

This concurrent activity is important also because software release models are more fluid and continuous in an agile development environment. Startup application companies will often talk about putting a 'minimum viable product' (MVP) into users' hands, so that people can start to interact with the product and check that it works well for them. The thinking is that it is far better to discover at an early stage that improvements could be made, than to expend time and budget finessing a system that has inherent design or functionality flaws.

Shorter, iterative release cycles – a prominent characteristic of collaborative, agile development processes – will ideally be supported by convincing, meaningful data so that users have a realistic picture of what they'll be able to do once the new system is more fully formed. The more they can visualise what the finished product will look like and what it will do for them, the greater the chance that users will accept and embrace the system and use it to its full potential. While much of the direction and synchronisation of the agile process will be down to the technology vendor, internal IT teams, business sponsors and user groups will need to be primed to support the agile development process. This needn't take up huge amounts of their time: actually key representatives are more likely to be involved at just the stages that are relevant to them. But success and speed of delivery (the ultimate goal here) will depend on everyone's mental preparedness – their proactive involvement and commitment to being part of the whole journey.

IT teams are likely to have a good understanding of agile delivery, and associated methodologies and tools. However, other parts of the organisation may need bringing up to speed on the benefits of the approach and what it



means for them. Quality teams, for example, may be concerned at any deviation from the traditional V-model/ linear development approach, and the implications for rigour around defining and validating requirements. If so, it will be worth involving them in discussions about how that same rigour can be carried across to a more incremental, iterative development cycle, which features all of the same checks, just on a more frequent basis and smaller scale.

Certainly few stakeholders across the organisation would deny the need to rethink approaches to new system provisioning, as the traditional two-year cycle just isn't practical given today's speed of change. Even if the resulting system will be fairly custom-configured, and irrespective of whether it is run on premise or hosted in a remote data centre or cloud facility, adopting an agile development practice could result in a good 50 per cent reduction in time to deployment, while consuming less of people's time, and ensuring higher user acceptance. With so many new technology advances coming down the line that companies will want to exploit to improve their everyday operations, that's a pretty powerful case for change.



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How Aseptic Nanomilling Can Provide a Solution for Today's Insoluble Compounds Including HPCs

High-energy media milling (nanomilling) has become an increasingly popular drug delivery technique and for good reason; it is suitable for oral, injectable, topical, and inhalable applications.

Appropriate for complex solid drug products of all kinds, nanomilling continues to prove its viability as an efficient, reliable and validatable approach to enhancing the bioavailability of poorly watersoluble active pharmaceutical ingredients (APIs), as well as minimising undesired side-effects.

Virtually agnostic and appropriate for most indications, nanomilling offers drug developers a number of flexible attributes, including organic solventfree processing, relatively high drug loading, and tunability. Furthermore, its inherent compatibility with a broad variety of today's insoluble APIs and highly potent APIs being developed to treat or cure chronic disease is another advantage.

Nanomilling's applicability and utility is increasingly recognised by pharma and ongoing development of the methods and technologies behind it are providing new opportunities for more effective delivery of complex, insoluble, and increasingly potent APIs.

However, the key to commercialising an array of complex drug products being developed now or on the horizon may hinge on accomplishing high-energy nanomilling aseptically, with the ability to manage and control complex high-potency compounds (HPCs) in these drug products.

Offering an expert's review of the method's great potential, Dr Robert Lee, president, CDMO Division of Lubrizol Life Science Health (LLS Health) explains how aseptic nanomilling (AN) can help to successfully develop and commercialise complex drug products.

Nanomilling: A Pathway for All Delivery Routes

For most small-molecule compounds and a growing number of large-molecule therapeutics, nanomilling is a popular, reliable methodology, with wellunderstood chemistries and physiologies to achieve bioavailability goals or desired delivery routes. It is also a proven means to provide parenteral administration routes for generally insoluble drug products in solution. As it stands, nanomilling, aseptic or non-aseptic, is an ideal pathway for all delivery routes:

- Parenteral
- o Ocular
- Mucosal
- Topical
- Oral

Aseptic Nanomilling for Complex Drug Products

The majority of today's nanomilled APIs are not amenable to terminal sterilisation. While the preferred option is to terminally sterilise nanomilled drug products, there are fewer options for sterilising insoluble and highly potent nanomilled formulations. Although sterile filtration is an alternative, it is tough to do at commercial scale and is estimated to be applicable to an even smaller minority of insoluble compounds in suspension.

In general, and depending on the indication, the vast majority of new chemical entity (NCE) APIs are BCS Class II & IV (water insoluble). As little as 5–10% of nanoparticulate suspensions in these classes are amenable to terminal sterilisation (gamma radiation) with only about another 5% amenable to sterile filtering. In these cases, AN is the only alternative.

The fact is, the majority of new APIs require nanomilled particulates in their formulations to function therapeutically but also require an aseptic process to assure sterility, especially for parenteral and ocular therapeutics.

For insoluble solid compounds and HPCs, nanomilling offers great advantages, but

its broader application in the aseptic manufacture of these kinds of drugs may be stymied because there are few economically or technically feasible options to sterilise products after milling operations.

The Aseptic Nanomilling Method

Drug developers have been applying nanoparticulate technologies to their products for decades, and many of today's most familiar therapeutics have employed the methodology. The efficacy of the method continues to deliver therapeutically effective drug products and the list is sure to grow with access to the aseptic, high-energy nanomilling required by today's complex drug products.

Colloids, Nanoparticles, and Bioavailability

Colloidal particles are present in a broad variety of pharmaceuticals. Colloids can range in diameter from 1–1,000 nanometers and can be solid, liquid, or gaseous. For most pharmaceutical applications however, colloids in 1–100 nanometer range (nanoparticles) are used.

Particle size distribution (PSD) directly affects the bioavailability of APIs and the safety of intravenous lipid emulsions. As with suspensions, nanoparticle dispersions can contain a range of particle sizes which define the PSD.

When the particle size of an API is reduced, the surface area increases exponentially, and the particles exhibit a higher surface-area-to-volume ratio. More surface area allows smaller API particles to have greater interaction with surrounding water and a higher dissolution rate in the human body. The same logic applies to dissolving sugar cubes vs. powdered sugar. Because the powdered sugar has significantly higher surface area, it dissolves much faster in tea or coffee.

Additionally, as material is broken down, the internal surface becomes exposed, bringing a change in the number or type of surface chemical sites

and groups. Large increases in surface area can also affect the interaction between particles and system properties, including suspension rheology, coating, and adhesion. In general terms, smaller particles dissolve more quickly and, therefore, exhibit higher bioavailability. Overcoming poor bioavailability is one of the great formulation challenges facing the pharmaceutical industry. Poor bioavailability results in ineffective treatments, higher costs for patients (more medication required to treat the condition), and unpredictable dose delivery, which often leads to an increased risk of side-effects and poor patient compliance.

Fighting Insolubility

Pharmaceutical companies estimate that approximately 60% of the NCEs synthesised each year have an aqueous solubility of less than 0.1mg/mL. This low solubility is a significant cause of failure for discovery phase compounds. Poorly b-soluble compounds are both difficult to formulate and analyse in humans or animals and are often discarded.

Additionally, the synthesis of watersoluble analogs often results in decreased bioactivity when compared to their insoluble counterparts. A significant number of the "Top 200" drugs exhibit clinical or pharmacoeconomic limitations that arise from their poor water solubility.

Technical Innovation to Address Insolubility Challenges

High-energy milling is central to manufacturing nano-sized particles. LLS Health has decades of experience with the technology and has been a leading force advocating the methodology's potential.

For example, to meet a significant market need for delivery of poorly water-soluble drugs, we were early developers of highly refined crystalline particles made by wet-milling APIs, water, and stabilisers to create a colloidal dispersion in the size range of 100 nanometers to 400 nanometers.

One benefit of the process is that, due to the non-covalent adsorption of stabilising polymers onto the surface of the particle, they do not aggregate, which helps decrease the surface-free energy. Furthermore, the hydrophilic polymers used to stabilise colloidal dispersions are found in numerous marketed products and involve Generally Recognized as Safe2 (GRAS) materials.

These particles can be further processed into all dosage forms traditionally used to administer drugs via oral, parenteral, inhalation or topical routes. The applicability of this technology is defined solely by the drug candidate's aqueous solubility and is not constrained by therapeutic category or chemical structure.

Aseptic Nanomilling Opens New Drug Development Opportunities

The most practical approach is to process sterile ingredients in sterile equipment in a sterile environment, but access to aseptic nanomilling capability is not widely available on a contract outsourced basis. In many cases, pharma has had to develop its own aseptic nanomilling expertise in-house, which may be providing a significant barrier to entry for certain drugs being considered for development.

With the intention of providing pharma's innovators with the best tools to create more effective treatments, CDMOs need to continue investing in advancing nanoparticle processes and formulation development.

With access to high-energy aseptic mills and media, drug developers can leverage advanced milling methods and flexible scalable cGMP production capabilities to accommodate all phases of drug development. With aseptic nanomilling available on a contract manufacturing basis, pharma has the opportunity to forego the risk and investment required to bring this capability in-house to meet their development plans.

Ready for the Challenges Ahead

The challenge for traditional pharmaceutical companies is to deliver the right therapeutic to the right target at the right time. Nanoparticles help achieve this goal through improved bioavailability, controlled dosing, and precise targeting. Nanoparticle technology is versatile and can be applied to emerging routes of administration including drug-eluting devices (DEDs) and inhalants – the advent of aseptic nanomilling only extends its utility and versatility.

Enhanced drug delivery is a critical area of pharmaceutical research and one

where nanoparticles have proven useful. When designing nanoparticulate systems, a formulator can consider specific particle properties and manipulate these to influence the overall system. With a clear understanding of the established science behind nanotechnology, developers and scientists will continue to use this versatile and now aseptic process to improve the therapeutic performance and value of today's most advanced and complex drug products.

Opportunities for Oncology

One of the more useful aspects of nanoparticles is that they can be sized and shaped to support the permeation and retention of APIs in proximity to the preferred site of treatment; the location of a tumour, for example. For today's chemotherapeutics this is an especially important effect, because it allows pharmacologists more precise delivery control of cytotoxic ingredients and therefore better control of undesired side-effects that commonly accompany chemotherapy.



Before joining the CDMO division of LLS Health, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He holds BSs in biology and chemistry from the University of Washington and a PhD in physical bioorganic chemistry from the University of California, Santa Barbara. Rob has published articles in numerous peer-reviewed journals and five book chapters, and holds 12 issued patents and 14 provisional or PCT patent applications. He has nearly 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. Rob maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in early 90s, and serving as a reviewer for both the International Journal of Pharmaceutics and the Journal of Pharmaceutical Sciences.



Greening Up Our Act to Secure Supply: The Push for Pharma to Move Towards More Environmentally-friendly Propellants

Global warming accelerated by increased consumption of potent greenhouse gases has become a serious public concern and triggered initiatives to further reduce the carbon footprint of all industries. Over recent decades, there has been a transition to more environmentally responsible industry practices. For example, replacement of chlorofluorocarbons (CFCs) with hydrofluorocarbons (HFAs) or F-gases following the 1987 Montreal Protocol has successfully recovered the ozone layer. However, these F-gases have also been shown to have an impact on global warming due to their high global warming potential (GWP) and long atmospheric life (AL). To resolve the issues, a Kigali Amendment to the Montreal Protocol was agreed by the United Nations (UN) countries in 2016, which aims to phase down global HFA consumption by 80-85% by 2047.1

This decision will no doubt affect the inhalation industry and respiratory healthcare sectors where pressurised metered dose inhalers (pMDIs) utilising HFAs as propellants are produced and prescribed. In this article, Lei Mao, Ph.D., Director of Inhalation Science and Product Development, Ron Roscher, Head of Engineering and HSE and Mark Knowles, Head of Product Engineering - Bespak at Recipharm discuss how the inhalation industry should be prepared and ready to adopt new propellants in order to guarantee the continued, reliable manufacture and supply of vital medicines.

pMDI and Impact from Potential HFA Phase Out

pMDIs have become one of the major inhalation dosage forms for respiratory disease treatment since the first epinephrine and isoproterenol inhalers launched (Medihaler Epi and Medihaler Iso) in 1956.

Using the UK as an example, in 2017, approximately 50 million inhalers were

dispensed, of which 70% (35 million) were pMDIs and 30% (15 million) were dry powder inhalers (DPIs). From a patient compliance perspective, it is critically important to sustain supply of pMDIs, since not all patients are able to use other inhalation products such as DPIs because of their compromised lung function and breathing capability. In fact, the need for pMDIs is expected to grow by 6.5% annually between 2017 and 2023.²

Current pMDIs use HFAs, namely 1,1,1,2-tetrafluoroethane (HFA-134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea) as propellants to deliver and aerosolise medicines. Although the amount of HFAs used in pMDIs is only a very small portion (1Mt or 0.2% of the annual CO₂ emission) as reported from a survey conducted in the UK in 2017,³ there are other challenges that mean the pharmaceutical industry should be actively looking at propellant alternatives. As other industries phase out the use of HFAs, limited supply could result in a situation where products are no longer available to patients. It is, therefore, important to ensure that equivalent pMDIs with new propellants are available.

Potential New Propellants

Several aspects need to be considered when selecting alternative propellants. These include safety, compatibility between the new propellants and container closure systems such as MDI valves and cans, and the medicines to be formulated. It is also important to consider the evaluation of optimal vapour pressure for respiratory delivery, optimal molecular weights to reduce diffusion through solids (leakage), low GWP and low toxicity. It is of course vital that any propellant is safe for human ingestion and that there is no detrimental impact/interaction with drugs.

There are at least two potential alternatives – 1,1-difluoroethane (HF – 152a) and 1,3,3,3-tetrafluoropropene (HFO-1234ze(E)) – currently being

developed by Koura⁴ and Honeywell.⁵ Both products are going through safety evaluation.

Both HFA-152a (GWP:124, AL: 1.5 years)^{6,7} and HFO-1234ze(E) (GWP: 6, AL: 18 days)^{6,8} have a lower GWP and shorter AL compared to the existing propellants HFA-134a (GWP: 1430, AL: 14.6 years)^{6,9} and HFA-227ea (GWP: 3220, AL: 33 years),^{6,11} and therefore are more environmentally-friendly.

In addition to the safety and impact on the environment, the physical chemical properties of the propellants are important when formulating medicines into MDIs. Fortunately, both HFA-152a and HFO-1234ze(E) have similar properties to HFA-134a and HFA-227 in terms of the vapour pressure, density, and compatibility with surfactants and solvents such as ethanol, which means there are limited issues in terms of formulation development.

Compared to inert HFO-1234ze(E), HFA-152a is more flammable, which means more attention should be given to engineering control during process development, scale-up and commercial manufacturing of MDIs.

Technical Challenges in Applying the New Propellant

As far as technical challenges are concerned, compatibility between the propellants and container closure systems such as cans and valves, compatibility between the propellants and actives, and how to develop a process and scale up manufacturing in a safe way, become the key factors to be considered.

Compatibility between the new propellants and container closure systems is ensured by maintaining the seal integrity and valve delivery performance through the product shelf life. Acceptable levels of leachables and extractables are also key.

Propellant vapour pressure and molecular weight are two key factors



determining the propellant leak rate, which can be evaluated by exposing the filled canisters to extreme temperatures and pressures, testing them at different time points. Calculations for propellant leakage can then be generated to understand and predict the leak rate, as well as establish the root cause of any deviation from the acceptance criteria. In detail, an example of a best practice approach for a successful evaluation would be:

- Understanding the essential requirements for propellants to be successfully used in inhalers and key aspects of product performance to be achieved.¹⁰
- Risk assessment/understanding of the product performance that will be affected by a propellant change.
- Risk assessment of the wider impacts on manufacturing, assembling and testing.
- Evaluating the impact of the new propellant by running product performance tests and comparing results against a control/acceptance

criterion.

First principle assessment (e.g. building a model) to identify the root cause of the product performance tests and identify and predict any potential improvements to current design.

While exploring and anticipating the potential industry changes around the application of existing propellants and the introduction of new alternatives is complex, companies need to actively work to prepare so that they can tackle these hurdles head on. By starting to work with these potential propellants and documenting preliminary findings, supply chain partners can work to determine next steps which will allow the industry to secure the supply of these essential medicines, while addressing the demand for environmentally-friendly solutions.

<u>Compatibility between the actives,</u> <u>formulation and new propellants</u> is determined by the physical chemical properties of the new propellants and all formulation components. Using suspension MDI products as an example, compatibility of micronised actives, selection of proper surfactants and necessary co-solvents must be considered along with container closure selection during initial formulation screening. Special considerations such as use of a gasket with less permeability or secondary packaging may be necessary if the active particles are sensitive to moisture ingression, i.e. tend to form agglomeration.

Process development, scaling up and commercial manufacturing need to bring safety, process design and risk control into consideration. Commercial manufacturing facilities must follow specific guidance such as European Aerosols Federation's Guidelines on Basic Safety Requirements in Aerosol Manufacturing, The Dangerous Substances and Explosive Atmospheres Regulations 2002, and Directive 99/92/ EC & Directive 94/9/EC on operating aerosol manufacturing.

In terms of safety, occupational exposure limits (OELs), lowest-observedadverse-effect level (LOAEL) and acute inhalation toxicity need to be evaluated.

For process design, vapour/liquid pressure, the upper exposure limit (LEL and UEL), and temperature relationship of the new propellants, suitable equipment contact materials, pressure containing systems, e.g. vessels, pipework and relief stream etc. need to be fully assessed and design changes may be required if necessary.

In terms of risk control, a different approach needs to be taken when handling flammable propellants such as HFA-152a. This includes but is not limited to evaluation of the minimum ignition energy, the lower and upper flammable limit (LFL/UFL)/lower explosive limit, auto ignition temperature (AIT), velocity of detonation (VoD), and rate of pressure rise. Corresponding measures such as ATEX certification of electrical equipment, special design of isolated storage/mixing, filling areas and leak detection can then be taken.

Development of MDI Products with New Propellants

No specific regulatory guidance has been issued regarding the use of new



Lei Mao

Lei Mao is the Director of Inhalation Science and Product Development at Recipharm Laboratories. With over twenty years of experience, Lei has a wealth of knowledge in formulation and inhalation product development within the pharmaceutical industry. He started a career working as a senior scientist, where he developed particulate formulations for inhalation applications and has since held managerial positions for big pharma companies. He also holds a PhD in pharmaceutical sciences and a degree in pharmacy. propellants in MDIs. However, from safety and efficacy standpoints, it is important to follow the latest FDA guidance on MDI and DPI Products – Quality Considerations¹¹ when determining a development strategy. It is advisable to match the performance to that of existing MDI products as much as possible. This not only ensures the safety and efficacy of the products but also will make it easier for patients to adapt to the new product versions.

Looking Forward

There is a need to adopt more environmentally-friendly propellants, not only to reduce carbon footprint but also to mitigate any supply issues that result from the decline in the use of existing options. HFA-152a and HFO-1234ze(E) are two potential candidates. It is important that drug developers and manufacturers prepare their facilities for the use of these propellants, considering factors such as container closure compatibility, flammability and process development and scale-up challenges. Those that prepare now will futureproof their operations, meaning they can continue bringing MDIs to patients that depend on them.

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Printer Validation Packs: Don't Leave Compliance to Chance

Validation impacts every process and component of pharmaceutical production, including machines, systems, equipment and computer systems. Part of the validation process is in the documentation – there needs to be integrated support for documentation with 100% clarity and traceability.

In today's supply chain, the printer is arguably the final key element in the validation process, and with regulatory complexity increasing – not to mention industry-wide moves towards just-in-time production processes – no organisation can afford to omit this final stage of compliance.

Yet, the unfortunate reality is that many organisations may not realise that their printer validation packs are incomplete and therefore not meeting the FDA regulatory requirements. With the considerable risk and implications of noncompliance, Bart Vansteenkiste, Life Science Sector Manager, Domino Printing Sciences, outlines how pharmaceutical companies can ensure their user requirement specification (URS) covers the final element of the production process.

Market Context

Good Manufacturing Practice (GMP) validation is an essential element of quality assurance underpinning the safety of pharmaceutical and biotech products and processes as set out, initially, by the US FDA and now widely adopted by regulatory bodies globally such as Europe's EMA and the UK's MHRA. Increasingly, other international regulators have followed suit, including Australia's TGA and India's Schedule M, with new regulatory requirements around pharmaceutical serialisation due to come into force in Russia (1st July 2020), Brazil and Indonesia, (2021) and China (2022) that will further impact the pharmaceutical supply chain.

The risk of non-compliance is significant, albeit difficult to measure. From the potential regulatory fines and loss of brand reputation, to the temporarily forced shutdown of a full production line and the cost of remedying the situation, not having validated systems and processes in place could adversely impact any business.

Every pharmaceutical manufacturer will be aware of the requirement for GMP validated products and processes, whereby the company has to demonstrate in a documented form that the processes, methods, tests, activities and equipment they deploy are capable of repeatedly producing the desired product. Therefore, each critical step in the manufacturing process must be validated to perform as intended under defined conditions.

The documentation associated with validation includes:

• Standard operating procedures (SOPs)

SOPs are used to ensure that production processes are consistently and repeatedly executed exactly in accordance with a proven methodology. SOPs must be available for every task that is used in the manufacture or testing of a regulated product.

- SOPs are written step-by-step procedures that quality control (QC), quality assurance (QA), and production units use in order to assure that the accuracy and precision of the original product development is maintained in the transformation from small trial and batch work to full-scale production of the product. SOPs are an essential part of the consistent replication of the tasks that are used to produce a regulated product to a pre-approved quality specification.
- SOPs are active documents that are routinely reviewed and amended as production processes

are repaired, altered or replaced. Having defined all the appropriate standard operating procedures, they are then used as audit standards to ensure that these defined methods are meticulously followed and adhered to.

Specifications

Documents that list the requirements that a supply, material, or product must meet before being released for use or sale. The QC department will compare their test results to specifications to determine if they pass the test.

Validation master plan (VMP)

The validation master plan is a high-level document that establishes an umbrella validation plan for the entire project and summarises the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

- Qualification protocols and reports Key sets of protocols within validation include installation qualification (IQ), operational qualification, (OQ) and performance qualification (PQ).
- IQ, OQ, PQ protocols are methods for demonstrating that equipment being used or installed will offer a high degree of quality assurance, such that production processes will consistently manufacture products that meet quality requirements.
- Validation protocols and reports A validation protocol is a plan written to describe the process to be validated. This includes production equipment and how validation will be performed. Such a plan would address objective test parameters,

product and process characteristics. Predetermined specifications, and also factors that will determine acceptable results, are included.

Title 21 CFR Part 11

Part 11 is the part of Title 21 of the Code of Federal Regulations that establishes the United States Food and Drug Administration (FDA) regulations on electronic records and electronic signatures (ERES).

Part 11 applies to drug makers, medical device manufacturers, biotech companies, biologics developers, CROs, and other FDA-regulated industries, with some specific exceptions. It requires that they implement controls, including audits, system validations, audit trails, electronic signatures, and documentation for software and systems involved in processing the electronic data that FDA predicate rules require them to maintain.

Validation is the first requirement identified in Title 21 CFR 11 for compliance.

Critical Components

Labelling and label printing are critical final components of the validation process. In 2018, 9% of all medical device recall events, and the return of over a million units, were due to labelling issues, with printing errors undoubtedly a factor. It only takes one stray label, IFU or printing error to cause a product recall. A trivial issue like a faulty print ribbon, for example, can lead to missing, unreadable or misinterpreted content. When this goes undetected and products reach the supply chain, regulations are breached and patient safety is put at risk. Moreover, with an increasing move towards just-in-time production processes, organisations need to ensure they have robust mechanisms in place to assure batch integrity. Concerningly, most organisations are unlikely to realise that their printing systems don't comply, until the regulators come knocking.

Error-free Coding

On modern production lines, handling multiple products for consumers worldwide, accuracy is crucial. Errors in



product identification and coding is one of the top reasons for product recalls – which can be costly for manufacturers, and harm brand reputation.

Utilising automated product coding solutions alongside code validation systems is the most effective way of ensuring that production lines are kept error-free and help ensure 21CFR Part 11 compliance. Coding automation software, integrated with existing ERP and MES systems, can handle product message changeover, and work in unison with external vision systems for message validation.

Having the ability to transmit and share data between systems and software providers is essential for pharmaceutical manufacturers looking to maximise their efficiency. It is important to find a partner that has experience in integrating systems, and working together with other companies and integrators easily and efficiently.

Conclusion

The most reliable suppliers will be proactive in ensuring system validation, checking that what is required in the user requirement specification (URS) is delivered without errors; providing a risk assessment; providing a test strategy; providing good document standards, including customised FS, IQ, and OQ documentation; and providing training protocols. A dedicated, GAMP V trained expert will know exactly what is needed to achieve validation in a pharmaceutical production environment, including validating any additional systems integration – such as labelling or ERP systems – and will provide the validation pack to support that.

It's ever more important that a company's printing systems' rationale can stand up to the scrutiny of an audit. So why leave the compliance of the final component of the validation process to chance?



Bart Vansteenkiste

Domino's Global Life Sciences Sector Manager, Bart Vansteenkiste, has a 19-year history with the company, focusing on EU FMD legislation since 2011. He works with Domino's European OEM partners and trade associations, including the European Federation of Pharmaceutical Industries & Associations and Medicines for Europe. A Dutch, English, French, and Spanish speaker, Bart presents at conferences worldwide.

Polymer Syringes Plus Functional Labels – A Combination with Added Value

Prefilled syringes (PFSs) are continuously gaining market share as a convenient form of administering drugs. In particular, PFSs made of high-quality polymer such as cyclic olefin copolymer (COC) have become a well-established alternative because they offer greater design flexibility while reducing the breakage rate throughout the value chain. Due to its properties and manufacturing process, COC is heavy metal- and tungsten-free and also exhibits low or no siliconisation. This makes it an attractive choice for a wide range of applications. However, the polymer also has a different E&L profile and a lower oxygen and gas barrier threshold than borosilicate glass, which increases the potential for drug interaction.

These barrier properties are of concern when it comes to labelling. Labels are an approved and well-established form of providing the required information about the pharmaceutical product directly on the primary packaging. However, as adhesive labels are affixed directly to the container, there is a potential risk of adhesive migration into the polymer. This can be overcome by using functional labels, which even have the potential to enhance the primary packaging by adding specific functionalities - from overt or covert as well as analogue and digital security features to effective first-opening indication – or specific protection through UV-blocking or enhanced gas barrier properties.

Matching Syringes with Labels Offers High Potential for Synergies

In order to exploit the full potential of functional labelling and to provide pharmaceutical customers with a comprehensive rather than a partial solution, it is necessary to match the label with the primary container. A key aspect to be considered in this context is that the label has to fit the container and can be processed in the packaging line without any problems. As part of a joint approach pursued by global pharma packaging specialist SCHOTT and speciality labels and self-adhesive marking solutions specialist Schreiner MediPharm, COC syringes and label solutions were examined with a particular focus on evaluating:

- The combination of a low-migration label with COC syringes
- The addition of an oxygen barrier to COC syringes
- The addition of UV protection to COC syringes
- The addition of first-opening indication to COC syringes

Combining a Low-migration Label with a COC Syringe

Although labels are not considered part of the primary packaging (i.e. there is no direct contact with the drug product), they are a potential source of drug impurities via migration through the primary packaging into the drug product. Knowledge of label and adhesive technologies – combined with in-depth understanding of the physical properties of polymers that may affect the extent of label-adhesive migration - is the key to understanding the risks associated with this phenomenon. Schreiner MediPharm and SCHOTT initiated a study of leachables to investigate the migration properties of two different label concepts with SCHOTT TOPPAC® COC PFS syringes.

Leading global provider of laboratory testing, Nelson Labs, compared the profiles of labelled syringes with the profiles of the respective non-labelled (reference) syringes in terms of leachable chemical compounds. Sample syringes were filled with water for injection (WFI), sealed, labelled and then stored for a total of 36 months under wellcontrolled room temperature conditions. By choosing a challenging environment with a temperature scenario of 25°C, all storage conditions at lower temperatures (i.e. 2-8°C) are covered from the perspective of migration. After the 36 months, the syringes were emptied and the contents submitted to multiple

analytical methods in screening mode to detect all possible compounds. The analytical methods allowed screening for volatile organic compounds, semi-volatile organic compounds, and non-volatile organic compounds.

The results of the two label-syringesystems show that, after 36 months of aging, no additional compounds were found compared to the reference sample. This means that the barrier properties of the COC syringe combined with specific label concepts involving a low migration profile guarantee that there is no migration of chemical components from the label.

Addition of an Oxygen Barrier to COC Syringes Using Functional Labels

Oxidation can significantly affect the shelf-life of pharmaceutical products, particularly of those based on large and complex molecules such as biologics and biosimilars. Therefore, pharmaceutical packaging has to provide sufficient protection against oxidising factors. Accordingly, an oxygen barrier is a crucial functional feature of primary containers in this context. As discussed above, primary containers made of polymer show a significantly lower gas and oxygen barrier compared to glass, which could be a reason to exclude their use for oxygen-sensitive drugs. There are solutions on the market to overcome this issue, such as the addition of an inorganic layer based on silicon oxide, onto the polymer layer by chemical vapour deposition, for example. Triple-layer constructions, in which a polyamide barrier layer is sandwiched between two COP layers, are another solution for primary COP-based containers. These approaches provide an excellent oxygen barrier, but are complex and cost-intensive, and require major changes to existing processes.

Therefore, SCHOTT together with Schreiner MediPharm tested a different approach. Functional labels made of gas barrier films were used to provide an additional oxygen barrier for COC prefilled syringes. The label design



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covers as much of the syringe surface as possible for maximum protection. Various barrier films were tested for suitability as label material, printability, combinability with pressure-sensitive adhesives and effectiveness as an additional oxygen barrier. For the test, a COC prefilled syringe (Type 1 ml long with Luer Lock closure) was used without the plunger. The syringe samples with various barrier labels were flushed with nitrogen and, using duroplastic adhesives, sealed on the back with a glass plate inside a glove box. Afterwards, the samples were exposed to the standard atmosphere at 23°C and 50% relative humidity. The oxygen content within the syringes was measured by a conventional oxygen sensor.

possibility to add the barrier functionality by means of a functional label without additional needs for process changes, high capital expenditure or modifications of the primary packaging. To increase the effect and adjust the barrier level to specific customer-driven use cases, further analyses are still required.

Addition of UV and Light Protection to COC Syringes Using Functional Labels

Ultraviolet as well as visible light can have a serious effect on light-sensitive drugs. One way to protect the drug is by choosing primary packaging of coloured glass (amber glass). Coloured glass, however, makes an inspection of substances difficult or even impossible. Especially for biologics and biosimilars, visual inspections with unadulterated



Figure 1 shows the oxygen content within the syringes as a function of time and the significant effect of barrier labels on oxygen permeation. The green curve (syringe with standard label) is almost identical to the blue curve (syringe without label). The curves of the variants with a barrier label ("label 2" and "label 3") show a considerably smaller slope, with barrier label 2 (orange curve) showing a clearly higher effect compared to the other tested barrier label ("label 3", violet curve). In this test, a partial pressure of 100 mbar in the syringe labelled with barrier label 2 would only be reached after more than 80 days. This period of time is more than twice as long as for the syringe without extra barrier protection. These initial results show that barrier labels have the potential to significantly reduce oxygen permeation and therefore might be an interesting option for drugs that are oxygen-sensitive but do not require a 100 per cent gas barrier. The key advantage of this approach is the

results are indispensable in order to identify discolouration, turbidity or particles. Therefore, primary containers made of fully transparent materials are preferred for biological formulations. In a new approach, labels made of UV and light barrier films were used to add specific UV und light protection to transparent containers. In order to enable a full true-colour inspection, the labels can be provided with a re-sealable inspection window, which allows for easy examination of the substances through the transparent primary container.

Various barrier films were tested for suitability as label material, printability, compatibility with pressure-sensitive adhesives and effectiveness as additional UV and light protection. In a transmission test, it was found that the test samples selected as suitable films demonstrated the possibility of providing a defined protection level (Figure 2). In this graph, the translucence of a standard transparent film (grey curve), a transparent UV protection film (blue curve), a semi-opaque yellow printed UV protection film (orange curve) and a fully opaque film (green curve) are displayed.

A standard transparent PET film shows a high light transmission rate, even in the ultraviolet light (< 380 nm) range, and therefore does not provide a relevant protection level. The transparent UV protection film tested shows very low translucence in the UV range (< 1%) with a sharp threshold at 380 nm. The yellow printed semi-transparent film provided significant protection against UV and blue light (< 480 nm) and the totally opaque film blocked the entire light spectrum tested. This test showed that using a UV protection film optionally combined with colour printing allows for a tailored protection level against ultraviolet and visible light. These results can now be used to develop customised label concepts for prefilled syringes adding extra UV and light protection according to specific use cases.




Figure 3: The label with integrated perforation extends to the adapter and is irreversibly destroyed when opening the syringe cap. The adapter and primary closure are interlocked, thus preventing additional waste.



Figure 4: Adapter is snapped onto the primary closure to compensate for the difference in diameter of the primary closure and the syringe body

Addition of Tamper-evident Features to COC Syringes Using Functional Labels

The sealing of a primary container is a valuable step in proving the integrity of the closure of primary packaging up until the point of use, visibly exposing a potential tampering attempt or preventing the re-use of a primary container in the context of product counterfeiting. Functional labels are a practical and efficient means of adding a tamper-evident feature to the syringe whenever this function is required. There are various options available for sealing a syringe with a label. Figure 3 shows a solution for a 5 ml SCHOTT TOPPAC[®] syringe. In this example, the main label reaches up to the primary closure. An adapter (Figure 4), which is snapped onto the primary closure, levels the diameter-difference between the primary closure and the syringe body to make labelling possible up to the top. A perforation within the label will result



[®]SCHOTT AG, SCHOTT TOPPAC[®] syringe

in a defined partial destruction of the label, which clearly indicates the first removal of the cap.

Summary and Outlook

The joint approach and test results show that matching COC PFS with functional labels can result in enhanced pharmaceutical containers with additional features. The study found that the barrier properties of the COC syringe tested combined with label concepts featuring a low migration profile result in no migration of chemical components emanating from the label. Moreover, through the use of tailored label solutions, a COC syringe can be enhanced with an oxygen barrier, UV protection or a first-opening indicator. Hence, pharmaceutical labelling offers a solution to provide more than just the required information on the primary container. SCHOTT and Schreiner MediPharm are exploring further steps to solve pharmaceutical packaging challenges by means of solutions that can be integrated easily and in a modular approach.



vation and Strategic Partnerships at Schreiner MediPharm, a business unit of Schreiner Group GmbH & Co. KG



Stefan **Krauss**

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Fake Coronavirus Medicines, Tests and Protective Equipment – Proof of Originality More Important than Ever

The demand generates the offer. Where there is an acute lack of protective equipment, testing and medication in the fight against the coronavirus, product fraud is already growing rapidly.^{1,2,3} Even in exceptional times like these, criminals do not shy away from putting counterfeit and inferior goods into circulation, directly putting the public, healthcare workers and patients in harm's way. Often, in the race against time, less attention is paid to where the goods have come from. For controls and authentication of products, therefore, simple and quickly verifiable indicators are needed to determine where the goods come from and whether they are genuine.

Special care should be taken when buying products on the internet, a popular platform for selling counterfeit products. Here you can also encounter companies that do not deliver the goods after prepayment, or simply put unsafe replicas or completely ineffective products on the market.

Especially now, when drastic measures are being taken to stem the spread of the virus, safe protective equipment that meets the prescribed standards is essential. Nobody wants to



Technically highly complex labels encourage the user to check the authenticity of products in a user-friendly way, and it is intuitive and motivating to do so. For instance, this label changes irreversibly when it is peeled off from a package, uncovering an additional code. The user, equipped with a smartphone, is guided through the verification in a self-explanatory manner.



The FMD requires a unique identifier to verify the authenticity of each medicine plus an anti-tampering device – in this case a VOID label.

imagine what will happen if counterfeit protective equipment does not have the promised properties to intercept the viruses. Especially when they are used in hospitals, where staff have daily direct contact with infected persons.

Fake tests that give false or unreliable results prevent containment of the virus. People who are thought to be healthy can transmit the virus unhindered and the spread cannot be stopped. Devastating consequences that would overwhelm even the best healthcare systems would result.

Criminals target all types of products, knowing that the profit margins will be high – fake airbags and unsafe toys, to name but two areas. It has been said that to sell fake medicine is 20,000 times more profitable than selling narcotics on the street and with laws that mean punishments are far less severe, it is no wonder that this sector of healthcare is targeted so frequently.

All types of medicine, for example, counterfeit spare parts for medical devices or respiratory equipment might fail to fulfil the desired function, if they are of insufficient quality.

And it is important to kill the myth that it is only lifestyle medicines that are bought online. That is not the case at all. Looking at 2300 respondents to a survey carried out by ASOP EU⁴, when asked what medicines they wanted to buy, their answers revealed that all types of medicine are being bought. So we are talking about antibiotics (which is very concerning when linked to the rise of antimicrobial resistance), anti-cancer treatments and blood pressure-lowering medication, to name just three. So it is clear that ALL types of medicines are being bought online.

So what are the health consequences and impact on the hundreds of thousands of individuals who are buying medicines online?

The WHO in 2017 characterised these and stated that adverse events due to incorrect ingredients gave rise to:

- A failure to cure or prevent future disease, thereby increasing mortality, morbidity and the prevalence of disease,
- The progression of antimicrobial resistance and drug-resistant infections,
- A loss of confidence in healthcare professionals, health programmes and health systems,
- An increase in out-of-pocket and health system spending on healthcare,
- Lost income and productivity due to prolonged illness or death.

In recent years, therefore, numerous



Opened locks visuals appear when the user opens the medicine. Language-free, self-explanatory symbols document the initial opening. The security printing uses VOID technology and the hologram, as on banknotes, also makes the originality obvious.



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regulations have been rolled out across many countries that enable authentication traceability of individual serialised prescription medicines. In addition, these regulations often insist on tamper-evident devices to give double the protection.

In Europe, the Falsified Medicines Directive¹, since February 2019 requires every prescription pack to be uniquely serialised with a barcode, as well as having a tamper-evident seal. At point of dispensing, the pharmacist then checks the pack to be authentic and also checks that the tamper-evident seal has not been compromised.

So this important Directive greatly enhances the security and integrity of the legitimate supply chain. In addition, the Directive obliges every Member State in the European Union to sell "medicines at a distance" and the retailer (in most cases pharmacy shops) have simply to register with their national health authority.

And if they are selling medicines via the internet, then each page of their website must display a logo which is described as the common logo which, when clicked on, routes through to a page that shows it has been registered.

Each Member State is legally obliged to inform the public of the purpose of this common Logo and to explain exactly what a falsified medicine is.

ASOP EU has held a number of meetings with the Member States to share the various advertising campaigns, but it soon became clear that many



VOID tapes ensure that a shipping carton can be checked to ensure that the contents have not been opened in transit. This ensures that the original contents cannot be replaced with counterfeit products.

Member States are not carrying out public-facing information campaigns. And so we would urge governments to address this issue and create campaigns to raise awareness.

In response to the newly released report by the European Union Intellectual Property Office (EUIPO) and the Organisation for Economic Cooperation and Development (OECD)⁶, entitled "Illicit Trade in Counterfeit Pharmaceutical Products", Mike Isles, Executive Director of ASOP EU – a non-profit patient safety organisation dedicated to making the internet a safe place to buy medicines (where it is legal to do so) – said at the launch conference that:

"Demand is fuelling the supply."

After all, it is you and I that are going online to buy medicines. If we did not then there would be no market, and no need for criminals to supply. With medicines being sold via social media and with 96% of the 35,000 websites



When users scan products for authentication or other attractive applications, valuable statistical information can be collected. Rights-holders receive early warning indicators when, e.g., products deviate from their destiny markets, opening a gap for falsified products to enter the supply chain. selling medicines worldwide operating illegally, it is a problem that urgently needs solutions.

"There is no one silver bullet so it requires many silver bullets and coordination amongst myriad publicand private-sector partners. And with an estimated 130 million people potentially buying medicines across Europe, urgent action is needed. This is especially important as we see false and predatory promises and misguided advertisements around potential treatments or cures for COVID-19, as well as fake tests [and] medical devices."

It follows, therefore, that manufacturers and users should protect themselves equally by means of good identification marking, proof of originality and protection against tampering of the packaging, and by paying attention to secure distribution channels.

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Where demand is greater than supply, product fraudsters are attracted. The penalties for putting life-threatening counterfeits into circulation are low when compared with other types of criminality, such as narcotics being sold on the street, despite the fact they can be deadly.

medicines bought, reasons for buying, knowledge of internet and pharmacy – data on file

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Dr. Marietta Ulrich-Horn

Dr. Marietta Ulrich-Horn holds a PhD in philosophy from the University of Vienna, and an MBA from the Vienna University for Economics and Business and the Carlson School of Management, Minnesota. She is co-founder and CEO of SECURIKETT®, a company offering a wide range of product protection solutions: complex security labels for physical product protection, and the digital cloud solution CODIKETT® for track & trace in global applications. MILLEPEDIA®, one of the latest IT product developments, makes interoperability possible. The motto is: authenticate, identify and locate the original. Marietta has been delegated by the Austrian Standards Institute to actively contribute to the emergence of European and International standards on authentication, traceability by UIDs (unique identifiers), tax bands and tamper evidence.



Mike is the Executive Director for the Alliance for Safe Online Pharmacy in the EU (www.asop.eu), a non-profit Community Interest Company (CIC). With over 30,000 fake pharmacy websites targeting Europe on any given day, this multisectoral organisation's mission is to enable patients to buy their medicines online safely - where it is legal to do so. Its Members and Observers involve many key internet stakeholders. Its aim is to produce concrete voluntary actions that will make a real difference and ultimately benefit the health and safety of patients. Mike is Executive Director of the European Alliance for Access to Safe Medicines (www. eaasm.eu). Mike is also European Medicines Partnership Director for International Health Partners (www.ihpuk.org).

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The Evolution of Clinical Trial Supply Chain Flexibility

The drug development industry of yesteryear was heavily reliant upon manual processes and typically characterised by singlearm, single-country trials. As such, it was relatively simple to manage from a clinical supplies, cost and compliance perspective.

Things look a little different in today's clinical trials landscape. In a bid to respond to the increasingly complex challenges modern drug development brings, do things better by adopting true patient-centricity and reducing waste in all its forms, flexibility is now king and innovation must reign supreme.

When it comes to clinical supply chain management, the need for greater flexibility feeds innovation and can be seen in the emergence of intelligent IRT systems, personalised packaging and labelling and direct-to-patient distribution. But why is flexibility so coveted within clinical supply chain management? Where did the concept come from? What benefit does it deliver? And what role does it play in shaping the drug development landscape of tomorrow?

Drivers for Change

Several factors contribute to the need for sponsors to operate with greater flexibility. Clinical trials are no longer the relatively straightforward entities they once were and, increasingly, IMP is no longer the robust, easily replaceable commodity it once was either.

Many traditional, chemically synthesised pharmaceuticals are slowly but surely being replaced by large molecule alternatives. In fact, biologics grew at almost twice the rate of traditional pharmaceutical products between 2012–2016, with billions invested by the top 10 pharmaceutical giants over the past five years. The biologics wave is expected to continue, as market analysts predict it will remain the fastest growing segment until 2025.¹

The personalised medicine market is also growing at rapid pace, partially in



response to the increasing prevalence of cancer and rare diseases. The key advantage of precision medicine is its ability to be tailor-made to suit different needs and conditions.

Yet there are inherent challenges with biologics and personalised medicines. Not only are biologics IMP and comparator products incredibly expensive, which significantly reduces margin for error, but they typically possess a lack of stability data, which necessitates end-to-end temperature management and frequent retesting.

Biologics can also be notoriously difficult from a blinding perspective because of the small size of primary packaging containers and the oftenultra-low temperature handling requirements, which can render certain materials and adhesives useless. Add to this the low product yield synonymous with biologics, the fact that many are being developed for trials involving patient-centric dosing, and the short expiration dates that impose limitations on building stock, and it's easy to see why many sponsors struggle to balance timely supply to sites and patients with effective cost control.

The geographical shift in clinical trial supplies from developed nations to emerging countries is also having an impact. These emerging study locations are especially attractive to biopharmaceutical companies studying rare diseases, due to the greater disease variations available, coupled with lower operating costs. Globalisation of clinical trials undoubtedly brings opportunity but isn't without obstacle. Importation into many emerging study locations can incur long logistical lead times that require a presence of in-country depots to successfully navigate the license, importation and transport processes. Regulatory requirements can also be more challenging to understand and properly implement.

Standard Manufacturing's Place in New Era Drug Development

Traditional manufacturing approaches to clinical supply chain management still have an important place within modern drug development. That said, they will need to be scrutinised against a trial's protocol, and perhaps used in conjunction with more flexible supply models, to create a bespoke, hybrid approach that delivers flexibility and value to supply chain operations.

Batch manufacturing, a technique where drugs are made, packaged and labelled before being added to inventory over several workstations to produce set demand, has typically been the standard approach for sponsors. Operations can start and stop to meet varying needs.

However, batch manufacturing can present numerous disadvantages against the context of new era drug development. With medication becoming more personalised, a 'one size fits all' approach to clinical supply chain management isn't always compatible. When dealing with biologics, for example, the shorter shelf-life heightens the risk of fully assembled kits surpassing expiry dates, while waiting to fulfil notoriously unpredictable enrolment demand. The fact that sponsors are dealing with expensive, limited supply product can also make bulk manufacturing risky business.

Tactics often used as part of a batch manufacturing approach include pooled inventory and the use of booklet labels. When demand forecasts are uncertain, pooling supplies can help meet the needs of multiple studies and reduce the risk of negative patient impact. However, pooled inventory isn't appropriate for all supply scenarios and will typically require IRT customisation and present additional import/export challenges.

Booklet labels represent another method of increasing supply flexibility within global studies. Incorporating extensive regulatory information, warning statements, directions for use and multilingual instructions into one label can help manage uncertain demand and reduce the risk of stockouts for certain kinds of trials. Yet booklet labels aren't appropriate for patientor site-centric protocols and will likely create longer lead times and additional expenditure, compared with singlepanel labels that are less complex.

With the clinical trials landscape continuously evolving, it's vital that all supply chain approaches are understood and evaluated during a trial's planning phase so that the most appropriate strategy, or combination of strategies, can be selected.

Adapting Clinical Supply Models to Deliver Greater Flexibility

As drug development complexity grows, harnessing supply flexibility in a bid to deliver the right drug to the right patient at the right time (and in the correct condition) becomes even more vital. Clinical trials have evolved and so too must the strategies we adopt to assure timely and cost-effective supply.

For studies involving expensive IMP and/or comparator products, including gene therapies, rare or orphan disease, oncology and immunotherapy; for patientcentric trials that necessitate patientspecific labelling and kit configuration; for trials operating a pooled supply strategy; and for trials involving drugs with short stability and a need for frequent retesting, just in time manufacturing (JTM) provides essential flexibility.

JTM can be practised on its own or as part of a wider LEAN initiative (a systematic and strategic approach that maximises value by removing or minimising waste from processes and typically involves reduced timelines, smaller batches, less complex kit and more frequent operations that reduce risk of waste). JTM refers to full late-stage customisation of clinical kits that makes it possible for stock materials, such as bottles, wallet cards, vials, ampoules and pre-filled syringes, to be packaged and labelled just prior to shipment in order to effectively meet varying global need, once demand is known.

This approach better supports variable demand and patient-specific requirements, while mitigating the risk of IMP exceeding its expiry date, while awaiting distribution. Implemented appropriately, JTM can reduce the need to pre-package bulk supplies before a study commences, facilitate pooled supply across protocols and reduce instances of over-production. Sponsors can also better cultivate patient-centricity through responding quickly and effectively to individual patient need, as individual kits are packaged, labelled and shipped on demand. This final benefit is something that will play an increasingly important role in the future of drug development, as the industry continues to invest in precision medicine, the market for which is predicted to be worth \$85 billion by 2025.2

Another approach that is becoming more common is just in time labelling; the partial late-stage customisation of clinical kits just prior to shipment. With this approach, kits are packaged and labelled in advance and added to inventory. Once clinical need is identified and a distribution order placed, kits can be further modified with the application of an auxiliary label to the exterior kit container. This might be the addition of a protocol number, revision of expiration date, or update of non-critical data such as an investigator's address.

Implementing Flexible Supply Strategies

Planning for JTM studies requires sponsors to approach supply chain planning slightly differently. Once adaptive supply strategy is decided upon, several core areas will need to be explored, discussed and planned for from the outset. For instance, will IRT customisation be set for dispensing visits pre-randomisation or post-randomisation? Or will dynamic randomisation be more appropriate? How will shipment timelines and visit schedules impact protocol development? How will kit customisation (kit configuration and label design) need to adapt to facilitate JTM strategy? How will storage processes need to adapt? This is particularly important as sponsors may be dealing with an ultra-low product that can only be taken out of conditions for a very brief period, so it's essential to scrutinise product stability programmes and storage requirements early on.

Quality endorsement is so key to success for any supply strategy but also needs to be approached differently when operating a JTM model because the timeframes are much reduced. Creating bulletproof quality processes, such as SOP alignment and audits, must be considered with the JTM model in mind. Aspects like end-to-end risk assessment and mitigations, system validation and random qualification of records, a well-defined quality agreement and early engagement to align processes with vendors, will facilitate a best practice approach to quality, despite the added complexity that JTM can bring.

Safeguarding Patients, Streamlining Efficiencies

As the challenge of operating a compliant, cost-effective and patient-centric clinical

trial intensifies, investing additional overheads in flexible manufacturing strategies may seem counterproductive but it's important to consider the bigger picture.

The initial overheads required to implement JTM may be higher than standard batch manufacturing but JTM delivers cost savings through waste reduction, shortened timelines, minimised overage, optimal use of drug product across multiple studies, and far fewer returns (and therefore significantly lower investment in accountability and destruction activity).

For instance, it is estimated that 50% of clinical sites fail to recruit patients in line with estimates.³ If sponsors are utilising a batch manufacturing approach, a significant quantity of seeding stock is likely to remain unused and will either require replacement, due to expiration, or destruction, due to unrealised demand.

Contrastingly, JTM supports variable demand and patient-specific requirements, while mitigating the risk of IMP exceeding its expiration date, while awaiting distribution. The approach also removes the need to pre-package supplies before a study commences and facilitates efficient use of pooled supply across protocols. Waste management becomes even more vital when considering the expensive nature of biologics and often in limited supply and the industry-wide supply shortage of many commercial comparator products.

The shortened timelines associated with JTM also offer bigger picture cost efficiencies. JTM has been shown to reduce the average timeline of study start-up by up to 50% for initial supplies and by up to 60% for resupplies, compared with standard batch manufacturing.⁴ Arguably, this cultivates enhanced patient-centricity and overall experience; mitigating missed patient visits, supporting retention and fast-tracking study completion.

Finally, because clinical supplies are customised and distributed to fulfil a precise and immediate need, less product requires return and destruction. This incurs significant savings in courier costs, administration time and the expense of physically transporting and incinerating product.

The continued evolution of clinical trials, and the complex challenges it brings, demand greater flexibility in clinical supply chain management. By considering all appropriate approaches at the earliest opportunity and partnering with supply chain experts, sponsors can create innovative and adaptive supply models that safeguard patients, while streamlining efficiencies and better controlling costs.

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