EXPERT REPORT

Prepared By
Hedley Rees Managing Consultant
at
PharmaFlow Limited

Dated 17th December 2021

CONTENTS

Title

ABBREVIATED CV

Full CV available upon request

Name: Hedley Rees

Present Appointment: Hedley Rees is the Managing Consultant at PharmaFlow Limited, a UK based consultancy specializing in supply chain management within the pharmaceutical and life science sectors. Clients range from large pharmaceutical companies to emerging biotech, and also include investors, lawyers, other consultancies, facility design & build specialists and third-party logistics providers (3PLs). Assignments span preclinical, clinical, and commercial supply chains up to complex multi-product networks covering global territories.

Qualifications: B. Eng. (Tech) Hons Production Engineering, University of Wales;
Executive MBA, Cranfield University School of Management.

Previous Appointments:

Senior positions at Bayer UK, British Biotech, Vernalis, Ortho-ClinicalDiagnostics and OSI Pharmaceuticals (now Astellas).

Affiliations and qualifications:

- Author, *Supply Chain Management in the Drug Industry: Delivering Patient Value forPharmaceuticals and Biologics, Wiley, 2011*
- Advisory Board Member, International Institute, Advanced Purchasing & Supply (IIAPS).
- Editorial Board Member GMP Review (GMP = Good Manufacturing Practice).
- Former consultant to Oxford BioMedica on UK Government funding call *AdvancedManufacturing Supply Chain Initiative (AMSCI)*, resulting in funding of £7.1M.
- Former Advisory Board Member to Marken, 2011 - 2012 (now a UPS company).
- Founding Member of Expert Industry Panel for CPhI Worldwide (UBM plc)
- Former member of the UK Bio-Industry Association's (BIA) Manufacturing AdvisoryCommittee, 2007 – 2011

Conference Speaking Engagements:

"Why patient-specific (autologous) therapies need hospitals to manufacture; and how to go about it", National Healthcare Expo, 26th November 2019, ARENA MK, Milton Keynes.

"How Whole Systems Thinking Will Transform the Pharma Supply Chain", Making Pharmaceuticals, Coventry Ricoh Arena, April 30th, 2019.

"Building Robust Advanced Therapy Value Chains with Rapid Prototyping and Systems Thinking", Making Pharmaceuticals, Coventry Ricoh Arena, April 25th,2018

"A practitioners view on supply chains in Pharma & Biotech", Pharmaceutical Licensing Group (PLG), at Fasken & Martineau LLP, London, October 23 2014

"A Provider Perspective on Building Patient-Centric Supply Chains", UPS EUHealthcare Annual Conference, Hungarian Academy of Science, Budapest,
October 1 2014

"*De-risking the Pharma Supply Chain from Day 1…*" Jardine Lloyd Thomson(JLT) Insurance Annual Conference, Windsor, UK May 16 2014

"*Implementing QbD like other industries – successfully!*" FDA/Xavier University PharmaLink Conference, Cincinnati, March 13th 2013.

"*Is the Pharma Supply Chain a Lost Cause?*" QUMAS CONNECT, Tampa, Florida,Feb 4th 2013.

"*The Power of Integrated Supply Chains, by Design*" 36th International GMPConference, University of Georgia March 14th 2012.

"*Good Distribution Practices: What do they mean to you*?" International Society for Pharmaceutical Engineering (ISPE) Annual Conference, San Francisco, November 14th 2012.

"*Building, Managing and Continuously Improving Clinical Supply Chains*", IQPCClinical Trial Supply Europe, Basel, February 1st 2012.

"*The Power of Integrated Supply Chains, by Design*" FDA/Xavier UniversityGlobal Outsourcing Conference, Cincinnati, October 4th 2011.

"*Building Supply Chain Transparency and Pedigree*", FDA/Xavier UniversityGlobal Outsourcing Conference, Cincinnati, June 16th 2010.

"*The Importance of Quality by Design in Biotherapeutic Development*", BioIndustry Association,London June 4th 2009.

"*Building, Managing and Continuously Improving Outsourced Value Chains in Biotech*", Next Generation Pharmaceutical Summit, Evian, Lake Geneva, May 7th2008.

"*Building, Managing and Perfecting Supply Chains in Pharmaceuticals*", TheManuPharma European Summit, Noordwijk aan Zee, Netherlands, 18th May2005.

Publications:

Supply Chain Management in the Drug Industry: Delivering Patient Value for Pharmaceuticalsand Biologics, J Wiley & Sons, Hoboken, NJ 2011

What Patients Need to Know About Pharmaceutical Supply Chains, KDP, March 2021

Various journal articles on supply-chain management and industry modernisation published in:

- Chemistry Today
- GMP Review
- Industrial Pharmacy
- Pharmaceutical Technology
- Pharmaceutical Journal (PJ),
- Pharmaphorum
- European Biopharmaceutical Review

Background:

Hedley's skill set covers the range of competencies from strategic procurement, production and inventory control, distribution logistics, information systems and improvement. His early career was spent as an industrial engineer in the automotive, consumer durables and FMCG sectors.

As an expert in production systems and industrial improvement methods, Hedley is a zealous advocate of the regulatory modernization frameworks of FDAs 21st Century Modernization and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidances Q8 – Q12.

Hedley regularly delivers podcasts, webinars and presentations at international conferences. He was co-chair of the highly regarded FDA/Xavier University sponsored PharmaLink Conference (formerly FDA/Xavier Global Outsourcing Conference) held in Cincinnati annually, from 2011 - 2013.

He is focusing his time now on developing and delivering digital education programmes for various stakeholders in the pharmaceutical industry, believing education is the only route to long term, sustainable resurgence for the industry.

GLOSSARY OF TERMS

Advanced Therapy Medicinal Products (ATMPs): These are biologic in nature and cover somatic cell therapy, gene therapy and tissue engineering. These use the body's own healing mechanisms and often target conditions associated with a patient's genetic make-up.

Biologics (large molecule): These are essentially made from living things, such as animal and human cells. A monoclonal antibody is an example. There has been a rapid growth of biologics in recent years.

CDMOs: Contract Development & Manufacturing Organisations

CMC: "chemistry, manufacturing and controls" data. This requires immense detail about every aspect of the end-to-end supply chain, for review by the relevant regulatory authority.

Conditional Marketing Authority (CMA): The MHRA has introduced a national Conditional Marketing Authorisation scheme for new medicinal products in Great Britain (England, Wales and Scotland) effective from 1 January 2021. The scheme has the same eligibility criteria as the EU scheme and is intended for medicinal products that fulfill an unmet medical need. Examples would be for serious and life-threatening diseases where no satisfactory treatment methods are available or where the product offers a major therapeutic advantage. The MHRA may grant a CMA where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

CTA: Clinical Trial Application

CTS: Clinical Trial Sponsor

eCommon Technical Document (eCTD): This is the template that must be used to submit a licence application to market any medicine, and therefore applies to vaccines. It is the basis of the approval of the drug for sale.

EMA: European Medicines Agency

FDA: US Food and Drug Administration

GDP: Good Distribution Practice

GMP: Good Manufacturing Practice

GMDP: Good Manufacturing and Distribution Practice

IMPD: Investigational Medical Product Dossier

MAA: Marketing Authorisation Application

MAH: Marketing Authorisation Holder

MHRA: Medicines and Healthcare Products Regulatory Agency: the competent authority responsible for medicines and healthcare products in the United Kingdom

PMDA: Japanese Pharmaceuticals and Medical Devices Agency

Product: The product is the final result of both the manufacturing and distribution supply chain. It is the medicine that is administered to the patient.

REMS: Risk Evaluation and Mitigation Strategy

Small Molecule: This means that they are molecules made using industrial chemistry. Aspirin is an example. The pharmaceutical industry was mainly founded on small molecule products.

ULT: Ultra low temperature

SUMMARY

Introduction

S1 This report has been requested by pjhlaw relting to:-

S2 Injections to reduce the symptoms of Sars-Cov-2 have been developed by Astra Zeneca, Johnson & Johnson, Pfizer and Moderna. Astra Zeneca and Johnson & Johnson are Adenovirus vector injections and Pfizer and Moderna are mRNA injections. The development and manufacture of the Sars-Cov-2 injections have been carried out by various Contract Development & Manufacturing Organisations (CDMOs) These products have been given approval in Great Britain by the Medicines and Healthcare Products Regulatory Agency (MHRA) under Conditional Marketing Authorisations (CMA).

S3 The companies named above will have done the laboratory experiments only. What enters the patient's body is the fully developed and produced Product. The companies named above simply submit the application for a Conditional Marketing Authorisation and then market the product and collect the profits. The development and manufacture of all the Sars-Cov-2 injections is carried out by Contract Development & Manufacturing Organisations (CMDOs). The company sponsoring any clinical trials (CTS) or holders of the marketing authorization (MAH) has total responsibility for what happens in the supply chain, even if they have outsourced to third parties.

S4 There must be a written agreement between the CTS/MAH and any company carrying out the work on the product, known as the Quality & Technical Agreement (QTA) which sets out the steps required to develop and manufacture the Product. Normally the CMDOs will have a regulatory inspection history that regulators can use to assess the suitability of a facility to manufacture a particular kind of product. There could be no such history in this situation as the products are so new which would mean that the regulators would have no idea what was happening inside a production plant. Virtual inspections would not work.

S5 The development of new medicines takes many years. On average it takes 11.5 years for a new medicine to progress from drug discovery to preclinical testing through clinical trials and regulatory review to approval. Advanced Therapy Medicinal Products (ATMPs) require the most rigorous approval of all. The Sars-Cov-2 injections were authorized for use in less than a year from the time Sars-Cov-2 was identified as a threat to public health. In my opinion this process could not safely be carried out in such a short time frame.

S6 There are various stages involved in developing a new medicine. Pre-clinical trials involve small quantities and a small supply chain. If the product seems to be safe, then it progresses to clinical trials where larger quantities and a larger supply chain is needed. Finally, after authorization the production will be scaled up again. At each stage it is vital to assess the product in great detail as each time production is scaled up the product can change and may become toxic. The public has repeatedly been told that the trials for the Sars-Cov-2 injections took place in parallel instead of in series in order to speed up the process. It is my opinion that by developing the injections in this way, without following the accepted protocols, and proceeding through the steps in order, the vital checks on scaling up the

product will have been missed. It is possible that the finished product will be toxic to the recipient. In my opinion, this is dangerous and leads to serious safety concerns.

S7 Pfizer's own report Document 5.3.6 Cumulative Analysis of Post-Authorization Adverse Event Reports of PF-07302048 (BNT162B2) Received Through 28-Feb-2021 (*annexed* to this statement) shows a shockingly high rate of death and injury. This should be compared to the Swine Flu vaccine. The rollout was halted after no more than 50 deaths attributed to the vaccine.

S8 Until Brexit new medicines used by consumers in Great Britain were authorized by the European Medicines Agency (EMA), headquartered in London from 1995 - 2019. The EMA is now situated in the Netherlands and the authorization of new medicines in Great Britain is now carried out by the Medicines and Healthcare products Regulatory Agency (MHRA), albeit there has been no apparent recruitment of staff with the skills and qualifications in assessing safety, efficacy, and quality of new medicines.

S9 This leaves me wondering how MHRA has been able to approve SARS-CoV-2 vaccines for conditional use (under a Conditional Marketing Authorisation scheme which came into effect on 1 January 2021).

S10 I am therefore concerned that any authorization which has been given will not be of the standard required.

Safety of Final Product and Supply chain

FP1 The safety and quality of any medicine must be assessed on the final Product of the manufacturing and distribution supply chain, before use in humans. This applies to both clinical trials and marketed products. This is important as many factors including but not limited to production in different facilities, component parts from different sources, scaling up of quantities and differences in packaging could change the Product that is ultimately administered to humans. Any undetected error or omission could cause considerable patient harm or even death.

FP2 An example of this would be the tragic event described in a report from PEW Health in 2012, titled *Heparin: A Wake-Up Call on Risks to the U.S. Drug Supply*.[i]

Below are some extracts:

FP3 *The adulteration of heparin, a widely used blood thinner, is a tragic example of the risks resulting from an increasingly globalized and complex pharmaceutical manufacturing system…*

FP4 *…as a result of the heparin adulteration, dozens of patients in the United States suffered adverse events, and several lost their lives. Investigations into this occurrence have revealed a number of systemic failures, including inadequate oversight and supply chain management…*

FP5 *…investigation revealed that a synthetic adulterant with toxic effects, over-sulfated chondroitin sulfate (OSCS), had been introduced during heparin's manufacture in China. OSCS costs nearly 100 times less to produce than heparin and is so similar to the actual drug that it was undetected by standard tests…*

FP6 *…dozens of Americans suffered adverse reactions, including death. Baxter Healthcare, the major U.S. manufacturer of heparin, along with 14 other U.S. companies recalled at least 11 drug products and 72 medical devices containing heparin…*

FP7 *…according to local health agencies and news reports, heparin products were also recalled in Australia, Denmark, France, Germany, Italy, Japan, Sweden, and Switzerland.*

FP8 Despite intense activity by multiple stakeholders in the pharmaceutical industry, this could still happen today, or any time in the future. This is because the safety measures that have subsequently been implemented since, including the *Falsified Medicines Directive (FMD) 2011*, only apply to movement of the manufacturer fully finished products to wholesalers and then on to community and hospital pharmacies.[ii]

FP9 Any material or product adulteration occurring and incorporated into the upstream supply chain, would appear genuine, as was the case with heparin.

Non-compliance with GMDP

NC1 To carry out the development and manufacture for SARS-CoV-2 injections in less than 12 months, many critical non-compliances with GMP and GDP would have to have taken place.

NC2 Below is an example of the regulatory requirements from Chapter 5 'PRODUCTION' of the Orange Guide:

"Principle

Production operations must follow clearly defined procedures; they must comply with the principles of GMP in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisation.

Validation
5.23 Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated."

NC3 The upshot of this regulation is that a master validation protocol (MVP) must be compiled for any new process or piece of equipment, to define the activities required to prove it produces what it is supposed to produce.

NC4 This is typically authoured in draft by the quality department, and goes through a number of reviews by staff involved. Once agreed, it is signed off and then needs to be implemented. The timeframe for completion is measured in weeks and months. For a biologic/ATMP product, it would take considerably longer.

NC5 For a new product, this applies to every stage of production, from starting materials to finished product (see Figure 3); and for every process and piece of equipment involved.

NC6 For each process change, such as scale-up, it would need to be done again.

NC7 Note also that production must "be in accordance with the relevant manufacturing and marketing authorisation." Since approval has been under a conditional authorisation only, there will be no marketing authorisation to refer to.

NC8 Please refer to the section below, SUMMARY OF GMP OBLIGATIONS OF A CLINICAL TRIAL SPONSOR (CTS) OR MARKETING AUTHORISATION HOLDER (MAH) for more details on areas of potential non-compliance. Examples can be provided if required.

Conflicts of Interest and lack of experience in the MHRA

C1 See Board Member profiles in Annex 1. Many of the non-executive directors appear to have conflicts in their previous and current relationships with pharmaceutical companies.

C2 On further review of the profiles of MHRA Board members with executive roles at MHRA, I can comment as follows:

C3 Dr June Raine CBE, Chief Executive, MHRA, has medical experience in her background. However, having spent 10 years in her previous position at MHRA as Director of Vigilance and Risk Management of Medicines, she would not have been operating in the field of scientific assessment and review medicines.

C4 Dr Marc Bailey, Chief Scientific and Innovation Officer, Claire Harrison, Chief Technology Officer and Dr Glenn Wells, Chief Partnerships Officer are listed on the website without a biography.

C5 Jon Fundrey, Chief Operating Officer, has a financial background with no experience of medicines.

C6 Dr Laura Squire OBE, Chief Healthcare Quality & Access Officer, has a large portfolio that includes scientific advice, clinical trials/clinical investigations, licensing assessment, marketing authorisations and device registrations, inspections, enforcement and standard setting through for example the British Pharmacopoeia and Target Product Profiles.

C7 Dr Squire's biography shows little or no experience of the disciplines within her portfolio, and during her time at MHRA has only worked on the SARS-CoV-2 programme , nothing else.

C8 Dr Alison Cave, Chief Safety Officer, although having an academic qualification in a relevant discipline, pharmacology, her biography shows no evidence relating to the assessment and licensing of medicines.

C9 From the above, I conclude that MHRA executive leadership team is not sufficiently competent to license medicines, especially SARS-CoV-2 injections that are both biologics and ATMPs.

Steps for MRHA to take

M1 MHRA should urgently and immediately arrange physical GMDP inspections of all Contract Development and Manufacturing Organisations (CDMOs) producing bulk active substance, part finished and fully finished SARS-CoV-2 injections intended for use in humans, according to Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017 (Orange Guide), with special reference to:

CHAPTER 5 PRODUCTION

ANNEX 1 MANUFACTURE OF STERILE MEDICINAL PRODUCTS

ANNEX 2 MANUFACTURE OF BIOLOGICAL ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS FOR HUMAN USE

M2 Also, refer to EU "The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Product", as they must also be applied in the UK.

M3 Inspection reports should be written according to regulatory authority protocols, identifying initially 'critical' observations that would require immediate remediation or even cessation of production activity.

https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing

M4 **Pharmacovigilance**

Pfizer et al have the obligation to collect their own safety data, aside from the yellow card system, and they should have a Qualified Person dedicated to that – they should declare their data.

M5 See further: https://www.gov.uk/guidance/guidance-on-qualified-person-responsible-for-pharmacovigilance-qppv-including-pharmacovigilance-system-master-files-psmf

STAGES INVOLVED IN DEVELOPING A NEW MEDICINE

NM1 The development of a new medicine is time consuming and very, very few drugs make it through the lengthy trial and regulatory process to be approved for the market.

NM2 Figure 1 shows a diagram reproduced from the US Government Accountability Office Report GAO-07-49, published November 2006, titled *NEW DRUG DEVELOPMENT: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*[iii]

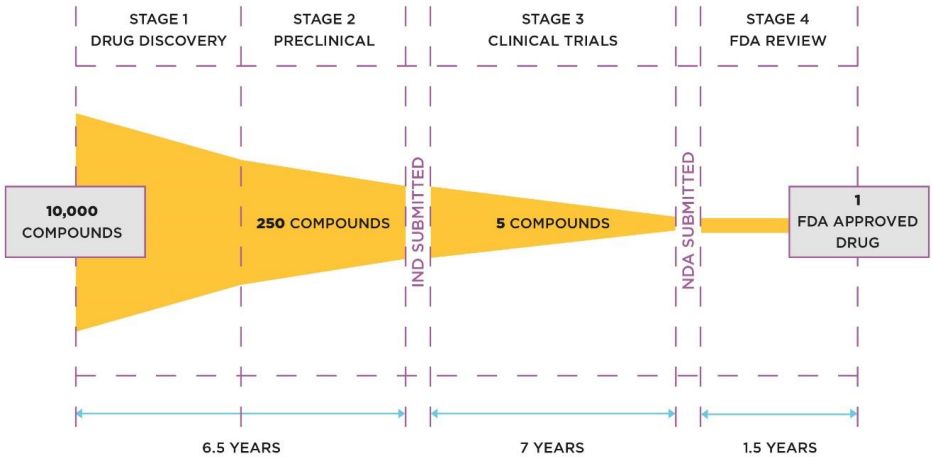


Figure 1: US Government Accountability Office Report GAO-07-49 Diagram

NM3 The failure rates and timelines are generally regarded as being unchanged today, and while this is US data, the global nature of product launches in pharmaceuticals means this reflects a worldwide picture.

NM4 In summary, for every 10,000 screened molecules, 250 are selected as candidates for preclinical development. 245 fail to satisfy regulatory requirements. Of every five to enter clinical trials, just one is approved for market.

NM5 In terms of timelines:

- Preclinical testing, and manufacture of the molecular compound for preclinical testing, takes about 3 years.
- Clinical trials take 7 years on average.
- Regulatory review and approval take 1.5 years.

In total, that is an average of 11.5 years.

NM6 It is hard to see how, even with unlimited funds being applied to the Sars-Cov-2 injections, how a medicine, especially an ATMP, could complete this process in such a reduced timescale. It is extremely difficult to obtain authorizations for ATMP products.

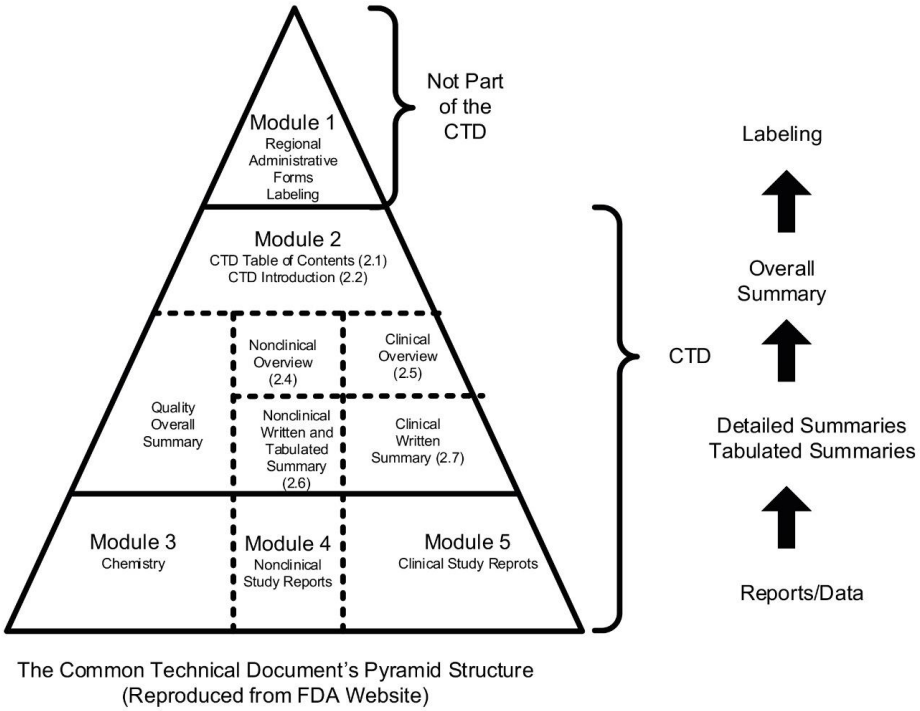
NM7 The claim that manufacturing activities had been carried out in parallel to account for the speed of innovation doesn't hold up.

NM8 There is a Regulatory limit on the multiples of a batch size can be scaled up – SUPAC, at 2.5 times the existing batch – molecular structure can change during scale-up, and become toxic, termed a polymorph.

GLOBALLY HARMONISED PROCESS FOR DEVELOPING A NEW MEDICINE

GH1 The process for developing a new medicine, and the data required, has been established by Governments and regulatory bodies over decades, responding to real-world events demanding improvements in safety, efficacy, and quality of medicines

GH2 Figure 2 shows the electronic Common Technical Document (eCTD) format that has been agreed by the three major regulatory bodies around the word – FDA (US), EMA (EU), and PMDA (Japan), following regulatory collaboration and the work of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for human use.



The Common Technical Document's Pyramid Structure
(Reproduced from FDA Website)

Figure 2: electronic Common Technical Document (eCTD)

GH3 The three required modules are at the bottom of the pyramid are:

- Module 3: Chemistry (short for CMC - 'chemistry, manufacturing, and controls') or also termed 'Quality'
- Module 4: Nonclinical Study reports
- Module 5: Clinical Study Reports

GH4 The sections above the modules provide overviews and summaries.
The CMC section is where all the details of suppliers, including site(s) of manufacturer and inspection history, material and product specifications, analytical test procedures, and process development protocols, must be submitted for review by regulators.

GH5 There is an amount of regulatory flexibility when it comes to standards in the supply-chain for producing preclinical test material, given the early stage of development.

GH6 However, for trials in humans, which is what the current rollout of the Sars-Cov-2 injections is, production in the supply-chain must comply with GMP and GDP.

ADVANCED THERAPY MEDICINAL PRODUCTS

ATM1 Most medicines, such as Aspirin, are Small Molecules.
SARS-CoV-2 injections are Biologics.

ATM2 They are also classed by regulatory authorities as Advanced Therapy Medicinal Products (ATMPs). ATMPs are defined as medicines for human use that are based on genes, tissues, or cells.[iv]

ATM3 SARS-CoV-2 injections fall under the heading of gene therapy, with the following description:
"*…contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer, or long-term diseases*."

ATM4 "*A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources."*

ATM5 It is generally accepted the regulatory terrain for ATMPs is in its infancy, and very few ATMPs have received regulatory approval.

ATM6 For example, a leading therapy area in ATMPs is CAR-T, a treatment for blood cancers.

ATM7 First to market was Novartis' Kymriah[v], launched August 2017. This is the warning on the labelling:

ATM8 ***Warning: Cytokine Release Syndrome and Neurological Toxicities***
Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab, or tocilizumab and corticosteroids.

ATM9 *Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.*

ATM10 Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah Rems.

ATM11 It is interesting to note that Oxford BioMedica manufacturers the viral vector for Kymriah (Lentiviral vector) as well as the vector for AZ/Oxford University.

ATM12 ATMPs have their own GMP regulations. The full extent of the regulatory requirements can be viewed here. They are extensive, and far more challenging to implement in practice than any other medicine. Given the known dangers of ATMP products, it is clearly vital that procedures for development and testing are followed in full.

THE PROCESS OF LICENSING

PL1 The process consists of licensing companies to undertake clinical studies in humans, and, if successful, licensing the company to sell the approved product(s) under strict terms of the license. In each instance, companies in UK/EU must

comply with the *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017 (The Orange Guide).*[vi]

PL2 The licenses are awarded by the competent authority responsible for medicines and healthcare products in each country or region. In the United Kingdom, this is the Medicines and Healthcare-products Regulatory Agency (MHRA).[vii]

PL3 In applying for a license to undertake clinical studies in humans, the company must submit a clinical trial application (**CTA**).[viii] The application must include an investigational medical product dossier (**IMPD**), with details of the supply chain that will be employed to manufacture clinical trial supplies.[ix]

PL4 **1. Preclinical development and Preclinical development supply chain**

Patients receive injections that are produced by the supply chain, so it is crucially important that safety testing is carried out on the batches produced.

PL5 Figure 3 shows the preclinical supply chain required to assess the safety of the compound under development.
The diagram depicts the production of the active pharmaceutical ingredient (API) and onward shipment to the company responsible for carrying out the safety testing (typically a contract research organisation, or CRO). Even though this appears to be a simple supply-chain to produce 5 – 10 litres of API for testing in animal models, there is already an array of suppliers and service providers involved, often spanning the globe.

PL6 Raw and starting materials are sourced primarily from China, so ex-Asian countries are operating a long way from home, limiting the necessary due diligence and oversight required.

PL7 There is also the question of supplier/service provider (CDMO/CRO) selection.

PL8 CMC data and safety data must be collected by the company sponsoring the clinical trial and included in the regulatory filing. The sponsor company can then submit a clinical trial application (CTA), and, if approved, they can move onto trials in humans.

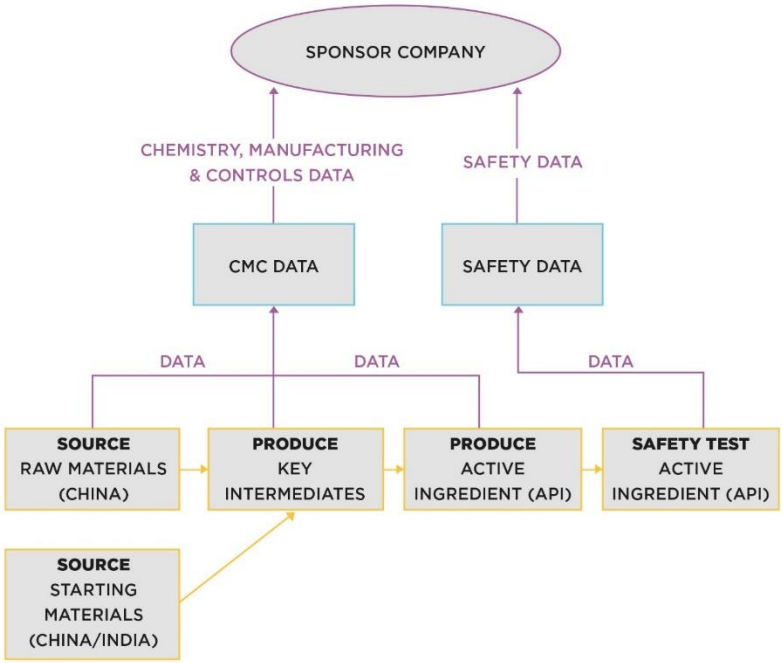


Figure 3: Supply chain for preclinical safety evaluation

PL9 **2. Clinical development and Clinical development supply chain**

When the time comes to submit the regulatory filing (MAA for MHRA/EMA), assuming clinical trials have gone to plan, the Competent Authority mandates the data be submitted using a common technical document (eCTD) as above.

PL10 Figure 4 shows the clinical supply chain and the three modules of data that must be collected and included in the licence application.

PL11 The sponsor company can then submit a marketing authorisation application (MAA), and if approved, they are able to market the product under the terms of the licence.

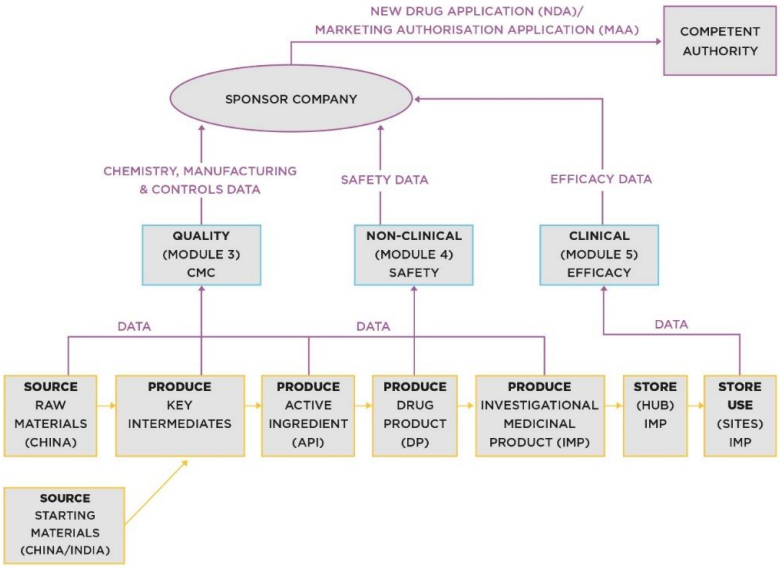


Figure 4: Clinical Trial Supply Chain

PL12 On approval, the supply chain for all future production must comply with the registered information, as established during phase 3 clinical trials, is as shown in Figure 4 above. The marketing authorisation holder (MAH) must ensure that all further production meets the terms of the licence and is carried out in compliance with Good Manufacturing and Distribution Practice (GMDP).

PL13 For a typical MAA, the regulatory review takes over 12 months, and includes a series of questions and answers that the applicant must satisfy the regulator on before approval. This could not have happened given the accelerated timescale of conditional approval.

PL14 The regulatory review also involves assessment of the inspection history of, at the very least, manufacturers (CDMOs) of the active substance and the Product filled into vials, capped, and sealed in unit doses; also, the manufacturing license of the manufacturers need to have that specific product added to their license before commencing manufacture.

PL15 Regulatory inspections typically include two scientifically qualified inspectors spending 3 or 4 days at a facility, going through all the critical aspects of the manufacture, then writing a detailed report of observations, categorised under minor, major, and critical.

PL16 Because of SARS-CoV-2, the only inspections were carried out virtually. This would be totally inadequate.

PL17 **Supply chain management**

Management of the supply chain begins with the CTS /MAH producing 12-48 month forecasts of finished product required and making them available to the finished product manufacturer (CDMO). That information must be cascaded down through the lower tiers of the supply chain – downstream processing, upstream processing, starting and raw material suppliers.

PL18 Significant supply lead-times are involved for each tier in the supply chain, and it is not unusual for raw material suppliers to be producing for finished product demand three years into the future. Along with this is all the negotiation of commercial and technical agreements that must be established between actors along the supply chain, including those storing and transporting product around the globe between the various stages of production.

PL19 The other thing to bear in mind is that while forecasts can change very quickly, increases in manufacturing capacity takes investment and long lead times to install.

PL20 I cannot envisage any circumstances where such a dramatic ramp up in demand and requirement for new facilities, fully compliant with GMDP, could be achieved in anything less than 3 – 5 years.

SUPPLY CHAIN FOR DISTRIBUTION OF SARS-COV-2 INJECTIONS

SCD1 The SARS-CoV-2 vaccines are classed as Biologics, which means the active component is a living thing that must be kept alive and in good condition throughout its lifecycle.

SCD2 Figure 5. shows the stages involved in producing and supplying a biologic. The overall development programme will span continents, with a plethora of companies at widely different geographic locations involved.

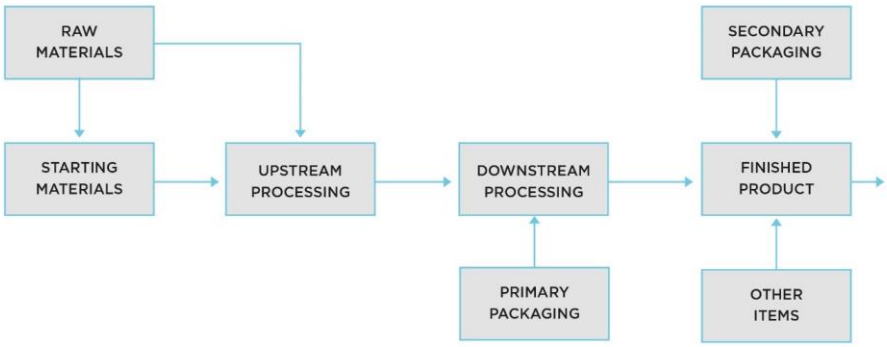


Figure 5. Stages in the production supply-chain for biologic (large-molecule) products

SCD3 *Raw Materials*: a large number of suppliers and geographic locations will be involved, sourced from anywhere in the world, although typically they come from China and other Asian countries. Examples of the materials are:
Serum, plasma, reagents, commodity chemicals, antibodies, antigens, hormones.

SCD4 *Starting Materials* will be animal or human cell lines. This stage is where Regulatory Authorities stipulate the company developing any medicine, including vaccines, must operate to Good Manufacturing and Distribution Practice as set out in the Rules and Guidance for Pharmaceutical Manufacturers Distributors

(2017), the Orange Guide. This applies to both clinical trials (development) and the supply of approved Product for sale. Starting materials are therefore difficult and time consuming to source, as the regulations demand significant control over the quality of the processing operations.

SCD5 *Upstream Processing* is where biomolecules are grown, usually by bacterial or mammalian cell lines, in bioreactors. Inputs are raw materials and starting material(s). When they reach the desired density, they are harvested and moved to *Downstream Processing*.

SCD6 The purpose of *Downstream Processing* is to isolate, purify and concentrate the drug substance (DS) received from upstream processing, and fill & cap in a primary container, such as a vial.

SCD7 Conventionally, the filled vials are secondary packaged to form the finished product, ready to ship into the distribution system. With frozen vaccines, this is not possible as they are packaged, part-finished, into trays for shipment to various storage locations that would not have been licensed to carry out GMP operations.

SCD8 Upstream and downstream processing is being carried out by contract development & manufacturing organisations (CDMOs), working on a fee-for-services basis, under a supply agreement.

SCD9 A variety of companies are involved in the development and manufacture of COVID vaccines. These include:
OXFORD BIOMEDICA
LONZA
COBRA BIOLOGICS
WOCKHARDT
CATALENT PHARMA SOLUTIONS

SUMMARY OF GMP OBLIGATIONS OF A CLINICAL TRIAL SPONSOR (CTS) OR MARKETING AUTHORISATION HOLDER (MAH)

O1 **Organisation** - the regulations require that a quality control unit be established whose responsibility it is to approve or reject materials and check and approve relevant documentation.

O2 There must be a clear organizational reporting relationship that allows the quality unit to be independent of the production function so that no undue influence can be brought to bear when difficult decisions about product disposition must be made.

O3 **Quality Management System** - the regulations require that SOPs be established for all aspects of GXP. These SOPs, together with policy and guidance documents, should make up a fit-for-purpose management system to assure product quality. These must be carefully documented and controlled, made available to all relevant

staff, who must be trained and confirm that they are competent to work under the SOPs.

O4 **Quality and/or Technical Agreement** - the regulations require that a written contract is in place between companies where services are provided by any third-party undertaking activities that may affect GXP.

O5 **Validation -** confirms and documents that the output from a process or operation is as specified. In the case of a press producing tablets, for example, the producer must prove that under defined and documented production conditions, the tablets manufactured will consistently meet specifications. There are several stages to validation that follow the development life cycle:

- Design qualification: confirms that the design meets requirements
- Installation qualification: confirms that the installation meets requirements
- Operational qualification: confirms that the operation meets requirements
- Process qualification: confirms that the entire process meets requirements

O6 Validation must be carried out to a protocol, termed a master validation plan. FDA defines a validation protocol as: "a written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and/or operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results."

O7 **Change Control** - changes to any aspect of the supply chain must be carefully controlled. This involves assessment of the impact of any proposed change on safety, efficacy, and quality of the product. Companies are required to have a standard operating procedure that defines all the responsibilities and activities involved. Many companies form a change control board, so that assessment can be made more easily with all the key personnel present. The main stages are as follows:

- Define the change clearly.
- Perform an impact or risk assessment.
- Make a cross-functional review.
- Identify needs for validation, verification, and other risk mitigations.
- Sign-off on the implementation plan.
- Implement change according to the plan and document accordingly.

O8 **Stability** - products tend to degrade over time under the ravages of temperature and humidly effects, for example. Stability is a measure of how quickly or slowly that happens. Some compounds are as "stable as old boots," as the term goes. Others may last only days or weeks. In general terms, biological compounds are far more sensitive than small molecules to temperature and humidity. This means that cold chain storage and transportation is a major consideration in biologics.

ICH Q1A(R2) defines stability testing requirements to support allocation of shelf life.

ICH Q5C Stability testing of biotechnological/biological products should be found here, but the page no longer exists.

O9 **Investigations and CAPAs** - any out-of-specification result or unplanned deviation must be investigated to find the root cause, which must then be corrected through corrective and preventive actions (CAPAs). Pharmaceutical companies are required to document the investigation carefully and not close the file until a satisfactory solution to the quality issue has been identified, approved, and implemented. It is the responsibility of the CTS or MAH to ensure that this happens.

O10 **Customer Complaints** - companies must monitor records and respond to customer complaints relating to products. They should then have a process of correcting any deficiencies identified and reporting any matters relating to safety to the appropriate competent authority.

O11 **Traceability and Recall** - traceability and recall are classic supply chain concerns. As a product is made and distributed, it is possible that quality defects could be identified in one of two ways:

1. A finished product in the marketplace could be found to cause adverse patient events or to exhibit some other unacceptable problem.
2. A constituent material in the product could be identified (by a supplier of manufacturer) as being of suspect quality.

O12 In either case, the supply chain must be halted while investigations take place.

O13 This requires identification of all the batches of product that could be involved and taking them out of the system by quarantining them. To do this, there needs to be forward (in case 1 above, where did the product go to) and reverse (in case 2 above, where did it come from) traceability.

TRANSFER OF OWNERSHIP TO THE DISTRIBUTION CHANNEL

T1 Following production of finished product by the pharmaceutical company, it is purchased by wholesalers in the distribution channel. At that point, ownership transfers to the wholesalers, and their role is to supply pharmacies in compliance with Good Distribution Practice (GDP). They also handle cash collection and administration of the NHS payment system. Figure 6 shows the basic flows.

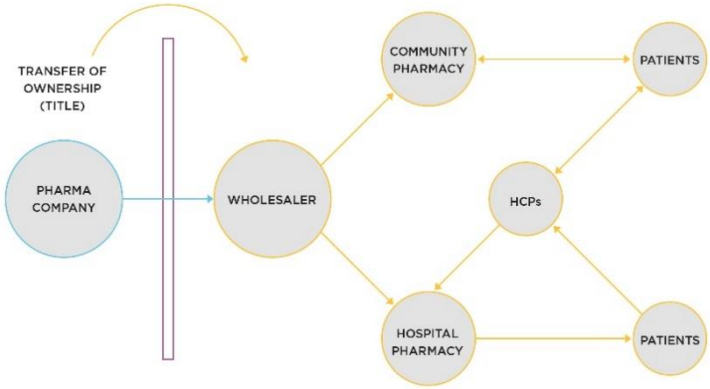


Figure 6: Transfer of ownership from pharmaceutical companies to the distribution channel

T2 There is no two-way communication between the pharma company and the wholesalers, even though, as MAHs, the pharma companies are still responsible for pharmacovigilance. It seems now that MHRA is depending on yellow cards reporting of SAEs and the MAHs have waived their responsibility.

T3 Good Distribution Practice places the obligation on wholesalers to check bona fides of all the suppliers they purchase medicines from.

T4 With the frozen vaccines, wholesalers were not able to handle them as their vehicles are only geared up for room temperature or refrigerated products (2^{o} – 8^{o}. That left two major issues. CDMOs making the frozen vaccines were only able to part-finish up to vials containing 5 doses, packed into trays in bulk and then frozen to either -70^{o} or -20^{o}. They were not finished products and they had to be converted into unit doses in the vaccination centres. This is gross contravention of the regulations that require to maintain GMP at all times. Risk in thawing and dose titration.

INITIAL FURTHER ASSESSMENT OF ISSUES AND CONCERNS

C1 **SARS-COV-2 injections challenging to develop and manufacture** - Biologics are an order of magnitude trickier to produce than medicines made using industrial chemistry (small molecule).

C2 Small molecule products can be reproduced reasonably accurately, independent of the facility and equipment used to make them. In biologics, the molecules are so large and complex that it is often impossible to define their molecular structure by analysis. All that is known is that a particular process has produced something that has a particular biological effect on a patient.

C3 Other manufacturers may not be able to replicate that product and its clinical effect, even if the process appears to be the same. That has led to the industry mantra for biologics supply chains that "the product is the process." See extract from link:

C4 *However, unlike small-molecule drugs, which are one-dimensional and chemically defined molecular entities, biologics are much larger in size and have greater structural complexity, including primary, secondary, tertiary and, possibly, quaternary structures. Their biologic activity is notably defined by their structure and by the cell-based manufacturing process that is used to produce them.*

C5 This is evidenced by the comparatively few copies of biologic products (biosimilars) approved for market compared with small molecule generics. To gain approval of a biosimilar, the company has to prove it is interchangeable with the originator product, and given the above, it is problematic, see here.

C6 **Sensitivity to environmental factors** - another complication is the sensitivity of biologics to temperature variation and other environmental factors (remember they are living things). The exact temperature range products and materials must be stored and transported at must be established, registered, and proven to have been maintained throughout any journey. Temperature data loggers are used to monitor temperatures in storage and transportation. Excursions outside a given range, say minus -80°C to -60°C, must be investigated and corrective action taken.

C7 Below is quote from Biopharma Cold Chain 2011 Sourcebook, Healthcare Commerce Media Corp. P.19:
Below is quote from Biopharma Cold Chain 2011 Sourcebook, Healthcare Commerce Media Corp. P.19:

"Biological products are essentially perishable because they consist of organic matter and are therefore influenced by extremes of temperature and the actinic effect of light.

C8 *Carelessness in the handling and storage of smallpox vaccine, for example, often results in such injury to the product that it becomes inert, although physically it may appear to be in perfect condition and is of recent manufacture.*

C9 *Smallpox vaccine should be stored in a refrigerator or someplace where the temperature does not exceed 50°F." (Parke, Davis & Co. 1919)"*

C10 **Input materials can be problematic** - they can dramatically affect yield, potency, and quality of output, as the strength (titre) of each new supply of materials can vary widely, depending on factors that are not always obvious to the acquiring company. Obtaining pedigree information from suppliers, especially when the upstream supply chain leads to seemingly anonymous donors, can be a nightmare, and sometimes even impossible.

C11 I conclude from this background that the development and manufacture of COVID -19 vaccines has created a supply chain that involves a huge number of actors working in a heavily regulated global environment; also, it should be noted that GMDP has been progressively tightened over several decades, to protect patients being harmed by errors in the supply chain caused by lack of proper process and procedures.

C12 The risks of undue haste to move materials and products through the end-to-end supply chain cannot be overstated.

C13 **On this basis, I am concluding that the Conditional Marketing Authorisation (CMA) used by MHRA to approve SARS-CoV-2 vaccines in the UK does not sufficiently protect patients from harm, or even death.**[x]

C14 **Furthermore, multiples of injections, covering a large percentage of the UK population is still ongoing and the risk could involve thousands if not millions of people.**

Annex 1: Profiles of MHRA Board Members

A1 *Dr June Raine CBE*

June qualified in medicine at Oxford University and undertook postgraduate research leading to an MSc in pharmacology. After general medical posts and Membership of the Royal Colleges of Physicians (MRCP), she joined the then Medicines Division in 1985, and has worked in several licensing areas including the Review of Medicines, new drugs and abridged.

Prior to becoming Chief Executive, June was Director of Vigilance and Risk Management of Medicines from 1999 to 2019.

As Chief Executive, June chairs the Executive Committee, which is the highest decision-making body in the agency.

A2 *Jon Fundrey, Chief Operating Officer*

Jon joined the MHRA as Chief Operating Officer in 2016, prior to which he was Financial Controller at the Department for Work and Pensions. He has been in the civil service since he joined HMRC in 2007. Prior to joining the civil service, Jon held a number of senior Finance, IT and global programme management roles at a FTSE50 company, The BOC Group Plc, during a seventeen-year career there.

A3 *Dr Laura Squire OBE, Chief Healthcare Quality & Access Officer*

Laura oversees a large portfolio that is designed to ensure the quality and access of products to the UK market - this includes scientific advice, clinical trials/clinical investigations, licensing assessment, marketing authorisations and device registrations, inspections, enforcement and standard setting through for example the British Pharmacopoeia and Target Product Profiles.

Laura started her career as a post-doctoral research assistant looking at resistance to anti-malarial drugs at the Liverpool Institute of Tropical Medicine following her PhD and BSc in Biochemistry and Physiology. She has spent most of her career as a Civil Servant. After many years in operational work Laura moved into government policy in 2014. In parallel, she went back to university, gaining an Executive Master's degree in Public Policy from the London School of

Economics. Laura has extensive experience of regulatory and organisational transformation through her wider policy and operational work in other major government departments.

She joined the Medicines and Healthcare products Regulatory Agency from the Department of Health and Social Care, where she worked extensively on the COVID-19 vaccine deployment programme.

A4 *Dr Marc Bailey, Chief Scientific and Innovation Officer*

The Chief Scientific Officer leads the scientific, research and innovative work of the agency.

A5 *Claire Harrison, Chief Technology Officer*

The Chief Technology Officer leads the work of the agency in using technology to help us deliver the best for patients.

A6 *Dr Alison Cave, Chief Safety Officer*

Alison is a pharmacologist with a PhD in biochemistry. Her long career includes significant academic and regulatory experience, the latter initially at the Medicines Control Agency and then in senior roles within the Vigilance and Risk Management of Medicine Group at the MHRA and the European Medicines Agency (EMA). In addition, she was Head of Cellular, Developmental and Physiological Sciences at the Welcome Trust and most recently an Industrial Strategy Challenge Fund Director at UK Research and Innovation.

A7 *Dr Glenn Wells, Chief Partnerships Officer*

The Chief Partnerships Officer leads the work of the agency in building and developing partnerships to deliver the best for patients.

Declaration of Responsibilities

I understand that my overriding duty is to the Court, both in preparing reports and in giving oral evidence and I have complied with this duty.

I confirm that I am aware of the requirements of Part 35, practice direction 35 and the Protocol for Instruction of Experts to give evidence in Civil Claims.

I have set out in my report what I understand from those instructing me to be the questions in respect of which my opinion as an expert is required.

I have done my best, in preparing this report, to be accurate and complete. I have mentioned all matters which I regard as relevant to the opinions I have expressed. All of the matters on which I have expressed an opinion lie within my field of expertise.

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Wherever I have no personal knowledge I have indicated the source of factual information.

I have not included anything in this report which has been suggested to me by anyone, including lawyers instructing me, without forming an independent view of the matter.

Where, in my view, there is a range of reasonable opinion, I have indicated the extent of that range in the report.

At the time of signing the report I consider it to be complete and accurate. I will notify those instructing me if, for any reason, I subsequently consider that the report requires any correction or qualification.

I understand this report will be the evidence I will give under oath, subject to any correction or qualification I may make before swearing to its veracity.

I believe the facts I have stated in this report are true and that the opinions I have expressed are correct.

Signed: ……. Date: 17th December 2021

Hedley Rees

---

[i] Heparin: A Wake-Up Call on Risks to the U.S. Drug Supply, PEW Trust (now PEW Health), May 16, 2012: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2012/05/16/heparin-a-wakeup-call-on-risks-to-the-us-drug-supply

[ii] Implementing the Falsified Medicines Directive: Safety Features; https://www.gov.uk/guidance/implementing-the-falsified-medicines-directive-safety-features

[iii] NEW DRUG DEVELOPMENT: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts https://www.gao.gov/assets/gao-07-49.pdf

[iv] Support for advanced-therapy developers: https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/support-advanced-therapy-developers#gmp-requirements-section

[v] KYMRIAH: https://www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/

[vi] Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017 (The Orange Guide): https://www.pharmpress.com/product/9780857112859/orangeguide?utm_source=mhra_email&utm_campaign=orange17&utm_medium=email

[vii] Medicines & Healthcare products Regulatory Agency: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

[viii] Clinical trials for medicines: apply for authorisation in the UK: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk#trial-sponsor-and-legal-representative

[ix] About Investigational Medicinal Product Dossiers: https://www.imp-dossier.eu/

[x] Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice, Medicines and Healthcare products Regulatory Agency, Published 31 December 2020: https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice