# UK Science, Research and Technology Capability and Influence in Global Disease Outbreaks

## Consultation response from the Institution of Chemical Engineers (IChemE) and the International Society for Pharmaceutical Engineering UK Affiliate (ISPE UK)

## Executive summary


1 Pandemics such as COVID-19 can trigger spikes in demand for critical medicines and disrupt supplies[1,2]. This placed considerable stress on the UK's medicines supply chain.

2 The Government's flu pandemic preparedness report considers subsequent waves of infection are possible and this could exacerbate medicine supply issues[2].

3 Assuring patient safety is at the heart of the pharmaceutical industry, making it highly regulated. Furthermore, drug manufacturing processes are often complex and inherently hazardous, and thus the current medicines supply chain is not very resilient to sudden changes in demand.

4 The robustness of the supply chain could be improved by employing more flexible manufacturing techniques, and accelerating product transfers into new or upgraded manufacturing facilities. There are advancing process and information technologies to facilitate rapid transition.

5 Alongside stockpiling and strategic spare capacity, building a more resilient manufacturing base could help avoid shortfalls in medicinal supplies during future pandemics.

6 The entire supply chain is underpinned by a workforce skilled in a broad range of pharmaceutical manufacturing practices and the underpinning regulations. Specialised education and training programmes must be in place to support this.

7 Achieving a resilient supply chain will require organisation, resources, and financial support from the Government, as well as co-operation across industry bodies, suppliers, manufacturers, professional institutions, educators, and the medicines regulator.

## Background

8 The COVID-19 pandemic led to an upturn in demand for critical medicines. This was initially for existing adjunctive therapies such as muscle relaxants and medical gases for ventilators[3], but as the search for COVID-19 medicines intensified, new treatment indications were discovered (eg Dexamethasone). These are already produced at scale and the UK's medicines supply chain was able to meet demand, but not without increasing throughput, alternative sourcing and utilising stockpiles[3].

9 The development of novel treatments and COVID-19 vaccines are being accelerated and some are looking promising. Even if ultimately successful, their bulk production capacity will arrive too late for the first wave.

## Scope

10 This evidence concerns making the medicines supply chain more resilient to pandemics by examining the opportunities and barriers to manufacturing robustness. The focus is on the process engineering aspects of chemical and biological manufacturing routes.

11 This review considers critical treatments currently used by the UK's healthcare system that are available for the first wave (approximately 8–12 weeks)[1]. The Government's healthcare authorities will determine which medicines are critical.

12 New indications for small volume drugs are also in scope.

13 Building a new supply chain for a novel treatment or vaccine for future pandemics is considered. This is more difficult to plan for because of the initial delay (~12 months) for discovery and efficacy/toxicology testing, and success is not guaranteed until clinical trials are completed. Each potential treatment/vaccine will have different manufacturing and facilities requirements. Hence, the scope for novel medicines will target delivery for a possible second wave.

14 Quality assurance and regulatory affairs compliance is discussed because it has a significant impact on engineering design and manufacturing operations.

## Introduction

### Drug Quality Assurance and Registration

15 Patient safety underpins the manufacture of all medicinal products and forms the basis of a highly regulated industry. To reliably guarantee drug product quality, all aspects of the manufacturing processes must be fully qualified and auditable against industry standards.

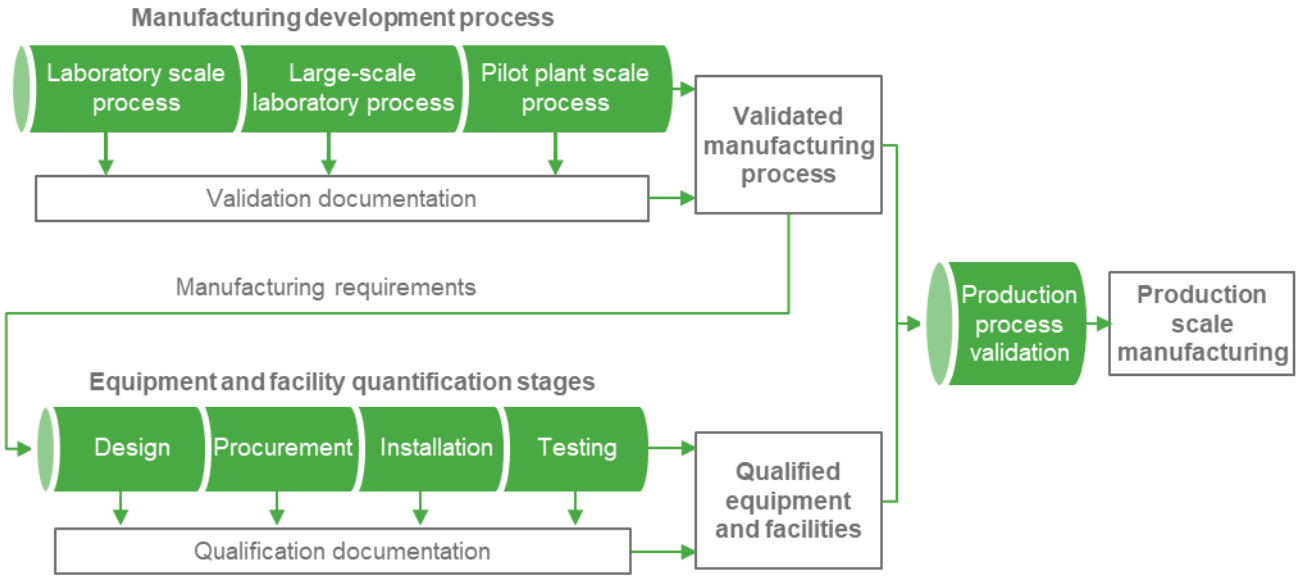


*Figure 1. Stages in the validation and qualification of pharmaceutical production processes and equipment*

16 Qualification ensures that the equipment and facilities deliver the process manufacturing requirements.

17 Process validation assures the quality of the material produced.

18 The technical transfer process to create a seat of manufacture is fundamentally the same for manufacturing processes coming through R&D or from an established production facility.

19 The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) registers the supply of drugs and ensures that manufacturers adhere to the strict quality assurance standards.

## Achieving Resilience

20 Resilience is ability the recover quickly from difficulties, and this can be addressed by a supply chain in several ways.

21 One strategy is to stockpiles drugs to tide over any surges in demand. The SPI-M Modelling Summary[1] covers scenarios for stockpiling prophylaxis and reactive antivirals, antibiotics, and pre-pandemic vaccine, although some critical medicines are outside of these categories.

22 A second strategy might be to have spare manufacturing capacity that could be brought online at short notice. Due to regulations and complexities surrounding pharmaceutical manufacture, maintaining a fallow plant in a state of short-term readiness is not straightforward.

23 An engineered solution could be to increase, re-purpose or extend capacity that in normal times is commercially sustainable. For extra capacity to be available in time though, the plant would have to be readily adaptable, and the qualification and technical transfer processes either be completed beforehand or extremely efficient.

## Drug Manufacturing Lifecycle

24 Developing medicines and bringing them to market takes 10-15 years (although this is decreasing). The manufacturing license will normally be held by a single operating company until the patent expires.

25 Off-patent drugs are available to generic manufacturers, and frequently remain as front-line treatments for many more years.

## An Overview of Medicines Manufacturing Processes

26 A typical medicine supply chain involves the synthesis of an active pharmaceutical ingredient, (API), that is then manufactured into a dosage form that a patient or medical practitioner would administer.

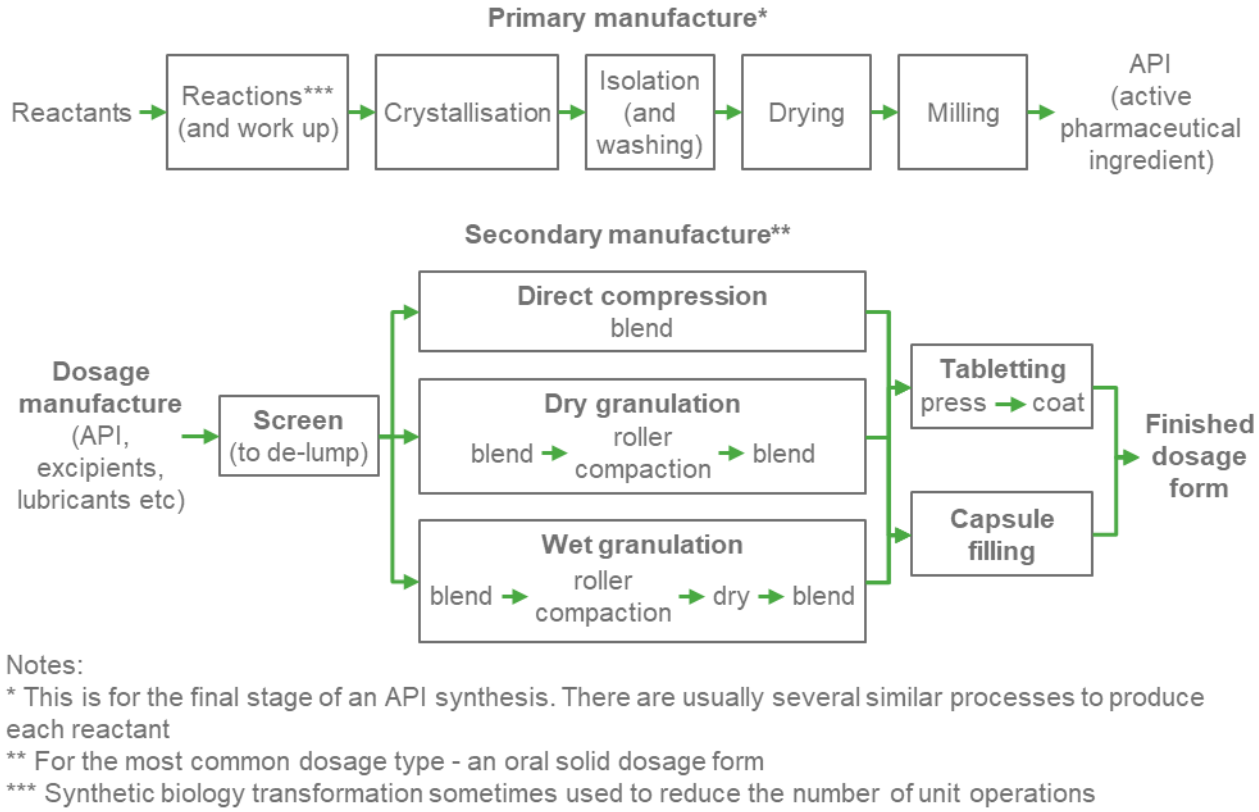


*Figure 2. Overview of primary and secondary manufacturing processes for a chemically synthesised (small molecule) medicine*

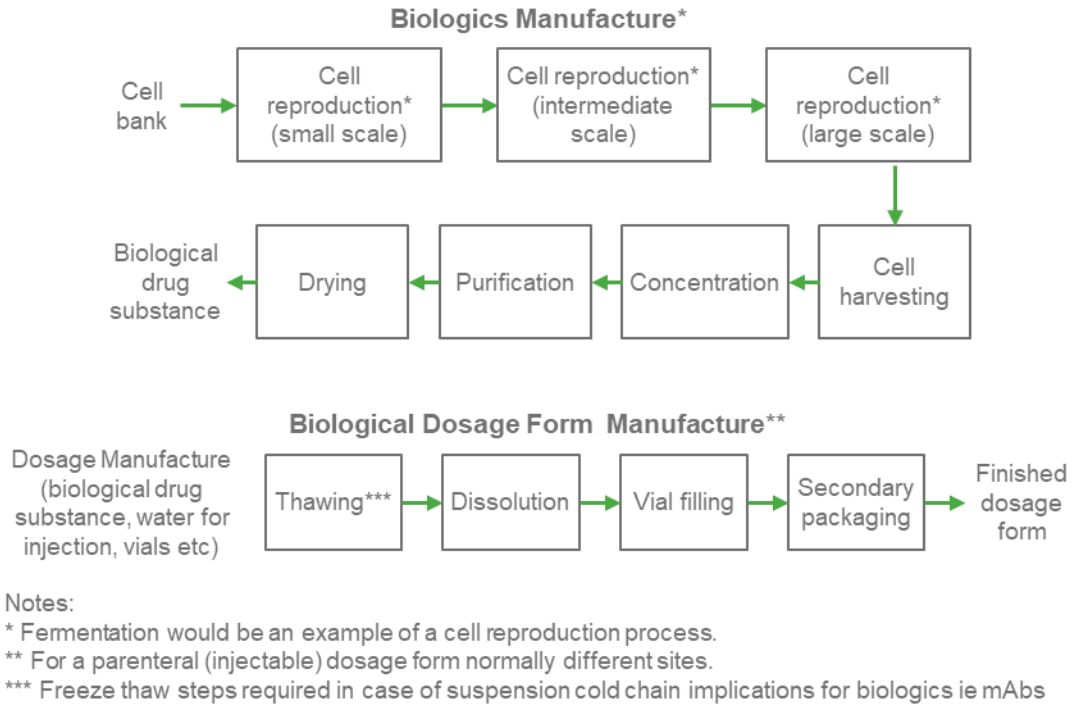


*Figure 3. Overview of the manufacturing processes for a biologics (large molecule) medicine*

27 Primary manufacturing is the often-complex sequence of process operations to form and purify the final API. Chemical synthesis routes create ‘small molecule’ APIs, but increasingly, the APIs are ‘large molecule’ manufactured via biological processes.

28 Secondary manufacturing is where the API(s) is transformed into a dose form. There are many types of dose form, depending on (amongst other factors) the route for a drug to reach its target, the rate of drug release into the body, and the stability of the drug substance. Examples of dosage forms includes tablets, capsules, topical creams and vials for injection.

29 Every dose form type has typical manufacturing techniques, and these will be followed by an appropriate product packaging operation.

30 Quality assurance encompasses all aspects of facility design and operation, this means:

- The quality of raw materials and intermediates consumed by drug production is controlled throughout their manufacture, transport, and storage.
- The manufacturing equipment is specialist to pharmaceutical manufacture, requiring comprehensive and detailed specification.
- Manufacturing processes restrict the operating parameters within set quality control ranges.
- Process cleaning prevents product contamination from batch-to-batch carry over and (for multi-product plants) between products.
- The building facilities have stringent design and operating requirements to ensure the drug products are not adversely affected by the manufacturing environment.

- Biologicals and injectable medicines are manufactured under sterile conditions, necessitating rigorous attention to hygienic compliance.
- Manufacturing facilities are designed and operated by people with skills across many disciplines, reinforced with a framework of mandatory industry-specific training.

31 Over a product lifecycle, there will be many changes to materials, process equipment, manufacturing site and scale. After each change, the end-product is assessed and compared to the originally approved product registration to ensure there is no undesired change to product's safety efficacy and quality.

32 The original drug manufacturing processes can potentially be improved by application of new techniques, but any updates will need to be re-qualified.

## Opportunities for Improving Manufacturing Resilience

33 Advanced process technologies that are finding their way into manufacturing includes:

- Process intensification to simplify and shorten production processes. For example, moving from batch to continuous processing reduces the size and complexity of equipment. Importantly, continuous processes are more responsive to changing product demands. Smaller equipment is also easier to clean, and transfer or replicate in another location.
- Process analytical technologies[6] (PAT), measure the critical process parameters on plant instead of by remote analysis, bringing improvements in cycle time, process robustness and operational efficiency.
- Telescoping is running two sequential process steps as one end-to-end step, ideally eliminating an isolation operation. The simplified step is quicker overall, and removes the ancillary operations of packing, storing, and re-loading an intermediate product.
- Single-use process equipment is employed by some (mainly biological) pharmaceutical processes, and although operationally expensive compared to fixed installations, reduces the requirement for re-sterilising equipment and is more flexible. Mobile equipment is another alternative that is found in both small-scale biological and synthetic processes.
- Modular and system-based techniques allow the facility design and construction to be partially or fully carried out remotely from the manufacturing site, cutting down the installation and qualification durations.

34 Information technologies (eg data science, machine learning, artificial intelligence) are rapidly evolving areas that potentially offer huge manufacturing benefits ie:

- Digital twins deliver quicker design, installation, and qualification of new equipment. Digital twins can also assist with process optimisation and setting up virtual factories.
- Robotics are being introduced to make routine operating tasks safer and more compliant.

- Statistical techniques, like chemometrics and statistical process control, characterise production processes and improve understanding of the critical process parameters. This in turn yields greater predictability and less process variability, resulting in more efficient and robust processes.
- Digitalisation can link manufacturing information into the supply chain, enabling real-time optimisation and end-to-end product traceability.
- Virtual and augmented reality is being used to train people to operate specialised pharmaceutical machinery.

## Constraints on Modifying Drug Manufacturing Processes

35 The highly regulated nature of pharmaceutical manufacturing makes it difficult to add capacity at short notice. Examples of these constraints are:

- pervasive and stringent change control procedures to assess any proposed modification and maintain compliance.
- plant cleaning can require a substantial amount of time and effort. The cleaning issues are exacerbated in multi-purpose process facilities where cleaning is mandated between products.
- complicated technical transfer processes for introducing new/different products into a new/multipurpose production plant. Even an intentionally designed multipurpose plant may require extensive plant re-configuration when switching products.
- a reliance on a limited number of machinery suppliers, offering equipment delivery times of more than six months.
- specialised equipment must go through a lengthy qualification exercise before beneficial use, as must the facility's buildings and services.

36 Process safety, environmental protection and occupational health compliance is equally important to regulatory compliance. Pharmaceutical production materials can be (bio)toxic and/or flammable (*ie* difficult to handle safely), adding another layer of complexity and inflexibility to the process and facility design.

37 The Association of the British Pharmaceutical Industry, (ABPI)[4,10] has highlighted some skills shortages in the UK's workforce. Implementing education and training programmes is a long-term undertaking.

## Discussion

38 A stable and versatile medicines supply chain would consist of a distributed network of independent production facilities[5]. Ideally the facilities would be multi-product, which would provide additional agility and reserve capacity.

39 Developing a distributed network runs counter to the economic arguments for having a small number of large-scale production facilities. High throughput production facilities provide more efficient administration of regulatory, quality and safety compliance. Dedicated (or limited) product facilities need less oversight than the equivalent small-scale multi-product facilities. Ultimately these factors

lower the unit cost of goods, and because the price of medicines is an important consideration[7,8,9], this is the current situation.

40 Balancing the opposing forces of production resilience and cost is difficult to achieve, but the direction of travel should be towards flexible multi-product facilities. The latest processing and information technologies must be fully exploited to reduce the cost of goods to competitive levels.

41 Considering strategies to cope with an 8-12 week first wave, the most plausible solution is a combination of stockpiling, increasing the output from existing facilities, and re-purposing an existing facility. Unless peak demand can be foreseen several months in advance, the re-purposing option would be limited to facilities with pre-qualified manufacturing equipment and processes. Having fallow facilities available should not be ruled out, but these too will have a re-qualification lead time, and would need trained staff available to operate them.

42 Assuming a second wave does not occur for several months later, the coping strategy could extend to re-purposing facilities for first time production, expansion projects and new builds. The project execution periods cannot be underestimated, although modern design and fabrication techniques should be used to reduce this.

43 In both first and second wave scenarios, the precise mix of solutions will be different for each critical drug, because it depends on individual factors like their cost, shelf-life, end-to-end production capacity and dosage.

44 The responsibility for updating and operating the manufacturing processes logically sits with the current or relocated producers. A support structure would need to be in place to assist operating companies with the cost of carrying extra stock, holding strategic production capacity, plus all the ancillary costs for transferring and qualifying processes, maintaining trained staff and introducing new technologies. To this end, the ABPI have put forward a *Life Sciences Recovery Roadmap*[12], and the US has implemented a state funded programme with the Phlow-Barda contract[13].

## Conclusion

45 The onset of a pandemic is difficult to predict, and is likely to cause a short, sharp peak in demand for critical medicines. Even after the initial spread of infection is controlled, the population is vulnerable to the disease re-appearing in a second wave some months or years later.

46 The pharmaceutical industry has a moral and legal responsibility[11] to assure patient safety, which has led to a high degree of statutory regulation. Combined with complex and hazardous (bio)chemical manufacturing routes, handling toxic materials and utilising specialist equipment, this results in lead times of months/years for a facility expansion or new product introduction projects.

47 The first wave peak would probably be accommodated by stockpiling and increasing existing or pre-qualified production capacity.

48 A second wave comes with more certainty and preparation time, and this makes introducing fallow capacity, re-purposing facilities and/or expansion projects more feasible.

49 New technologies can improve the flexibility and robustness of the manufacturing facilities, which would help in all scenarios.

## Recommendations

50 The key recommendations are:

- The supply chains for each critical medicine should be mapped out, and all opportunities to increase manufacturing resilience investigated. This could include installing spare common manufacturing platforms (at risk).
- Develop rapid implementation plans to bring existing/spare/new capacity on-line.
- Identify where emerging technologies, *eg* continuous processing and PAT, could be most appropriately and effectively utilised, and propose strategies to incorporate them into the supply chain.
- Ensure that the existing training and education framework provides the correct breadth and depth of skills required by the pharmaceutical industry and address any gaps.

51 Executing these recommendations will involve close collaboration between industry bodies, vendors, operating companies, academia, and professional institutions alike. The medicines regulators would have to be consulted over any changes to current working practices.

52 IChemE is already working in areas directly relevant to the recommendations[14], and together with our partners in ISPE UK, can provide non-partisan assistance.

## The Institution of Chemical Engineers

The Institution of Chemical Engineers (IChemE) advances chemical engineering's contribution worldwide for the benefit of society. We support the development of chemical engineering professionals and provide connections to a powerful network of around 35,000 members in 100 countries.

We support our members in applying their expertise and experience to make an influential contribution to solving major global challenges, and are the only organisation to award Chartered Chemical Engineer status and Professional Process Safety Engineer registration.

Chemical, biochemical and process engineering is the application of science, maths and economics in the process of turning raw materials into every day, and more specialist products. Professional chemical engineers design, construct and manage process operations all over the world. Oil and gas, pharmaceuticals, food and drink, synthetic fibres and clean drinking water are just some of the products where chemical engineering plays a central role.

IChemE members use their professional competence to produce evidence-based contributions to policy inquiries.

## The International Society for Pharmaceutical Engineering

The International Society for Pharmaceutical Engineering (ISPE), is the world's largest not-for-profit association serving its Members through leading scientific, technical, and regulatory advancement throughout the entire pharmaceutical lifecycle. The 18,000 Members of ISPE are building solutions in the development and manufacture of safe and effective pharmaceutical and biologic medicines and medical delivery devices in more than 90 countries around the world. Founded in 1980, ISPE has its worldwide headquarters in Bethesda, Maryland, US and the Operations and Training Center in Tampa, Florida, US.

The UK Affiliate was initiated in 1988/89 and held its first annual general meeting in October 1990. ISPE UK acted as the springboard to launch ISPE throughout Europe. UK membership is around 900 members with active regional representation in four areas of the UK organising evening seminars, conferences and networking events.

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