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With 2020 Vision: lessons for health, care and well-being: COVID – 19 and the impact on the supply of NHS prescription medicines

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HOW DOES THE UK MEDICINES SUPPLY CHAIN WORK?

Making medicines

Humans potentially suffer from an almost infinite number of diseases, conditions and syndromes. Medicines constantly evolve to meet these challenges: varying in the treatment targets, indication, dosage, formulation, mode of administration and increasingly by individual personalisation. Each country often requires their own unique supply with accompanying packaging.

To illustrate this product diversity, take two medicines – one made through a simple *chemical* process producing a tablet that can be simply packaged, stored and self-administered orally with a standard dose. Compare this to a highly complex *biological* medicine, made or derived from living organisms over a period of months typically using DNA technology. They will often need a cold chain distribution and storage system, be individually dosed to the patient and perhaps administered through infusion in a specialised setting. The pharmaceutical supply chain ensures that all these medicines, critical for patient care, get from the laboratory into the doctors' hands when they need them.

The supply chain

Within the UK itself there are several routes for prescription medicines to reach patients. The most important by volume is via a GP prescription and then dispensed through the practice itself or more commonly through a community pharmacy. The most important by value is secondary care where most new, highly specialised and often costly medicines are used. Other routes include direct to the patient's home and an increasing volume is dispensed through on line pharmacy. A further variation is where there are national contracts for say a vaccination programme, where the purchasing is central, but then the distribution is managed through thousands of local outlets most notably General Practice and NHS clinics. Consequently, the medicine supply chain is famously complex. The manufacturer has to plan to respond to all these variations along with shifting and unpredictable demand. They have to bring together the different components of the medicine along with its different layers of packaging and security features from many different global sources. And then deliver the medicine to over 100 markets often through intermediary stages at a cost that health services can afford and will pay for all in a "just in time" fashion. Thus, efficiency is vital.

It is important to understand the difference between the medicine "haves" and "have nots". The "haves" are branded medicines; they are protected from direct competition by a patent, are sold as a brand, with a marketing budget and full scientific support. In 9 cases out of 10 their supply is controlled in-house by the manufacturer who usually produces the all-important Active Pharmaceutical Ingredient (API) and controls the whole process from synthesis to final distribution. Pricing is agreed with the government. The "have nots" on the other hand are

generic medicines; those that are unbranded, have no marketing budget, are subject to fierce competition amongst multiple suppliers and have very small profit margins allowing very competitive pricing but little flexibility in a turbulent market place. Pricing is largely dictated by the market. About 90% of medicines used by the NHS are generic and cost about 10% of the original branded product once patent protection ends.

Another key aspect of the supply chain is how branded medicines are traded within the European Union. The EU is based on the premise of free movement of goods and no exception is made for human medicines. This means medicines can be bought in bulk from the manufacturer (or even individual packs from pharmacies which are aggregated and re-packaged) by a wholesaler in any country and traded across EU countries at a profit. This is known as parallel trade and happens with both exports and imports. This sort of trade effects about 3% of the UK market, but can be as much as 25% for an individual medicine at any one time and can have a dramatic effect on its availability to the NHS. The impact of EU transition and the potential for tariffs affecting trade is not known at this point.

A final aspect is how the above mechanisms are operationalised in the UK. The most complex is how government incentivises and pays community pharmacy to deliver primary care medicines. Typically, the biggest source of income to community pharmacy is from dispensing medicines to NHS patients. Increasingly, they are also paid for providing health services such as medicines reviews. Other sources of income include over the counter (OTC) non-prescription medicines and other retail. However, in this context, a key aspect is the income they make by buying and dispensing generics at a lower cost than they are reimbursed by the NHS. And joining in with parallel trade through buying more medicine than they need for their patients and selling the surplus to a trader at a profit.

QUESTIONS ARISING FROM THE COVID-19 PANDEMIC

1. How has the supply chain held up?

Almost fortuitously, the UK was already preparing for stresses on the medicines supply chain before COVID struck. As part of planning for transition out of the EU, pharmaceutical manufacturers and suppliers had been asked to build up a blanket six-month stockpile for use in the event of a no-deal Brexit causing supply chain interruption. This was something the industry did, at risk, and with no small amount of effort. The result was, as demand for specific medicines rose, (sometimes 5 or 10-fold for those related to ICU care) and some pharmacies did some precautionary stockpiling, very few supplies failed. At the time of writing only 5 out of about 12,000 medicine lines have a supply warning on them. This stockpile however, is now largely exhausted and will be extremely difficult to build back up due to global demands, but the increase in collaboration and understanding with the UK Department of Health and Social Care (DHSC) means that the industry is now having fruitful conversations about where demand may rise and how this might be more carefully planned for in future. A positive development and one that will hopefully continue and perhaps spread to other important actors such as the NHS who were not so understanding of how global supply works and the necessity for joint working. There relationships remain largely transactional.

This stockpiling was not the only action which has helped supply chain robustness. The main industry regulator (the Medicines and Healthcare products Regulatory Agency) and the DHSC have also shown flexibility in how some regulations are applied, such as the necessity for over-labelling some imported medicines. Another action taken as part of Brexit planning, restrictions on parallel exporting, has helped protect supply for UK patients. The original Brexit list of restricted medicines has expanded since COVID, from a handful to over 100. This is a strategy that other

countries have adopted, but the UK has been slow to follow, perhaps mindful of EU law on free trade and also the potential backlash from community pharmacy.

The parallel traders themselves have made herculean efforts to maintain supply, particularly as their usual mode of operation, highly intensive physically dextrous work of repackaging and labelling small batches has been significantly affected by the necessity for social distancing in the workplace. Again, it will be interesting to see if these beneficial regulatory flexibilities and government export constraints will continue post COVID and Brexit given the downsides identified for some sectors.

2. *What impact is national protectionism having on the supply chain?*

As mentioned above, free trade in medicines is a fundamental principle of the EU, but export controls as a form of protectionism have become commonplace. Whilst it may be human nature to stockpile under threat of shortages, this can have the effect of throwing the supply chain completely out of balance causing unexpected and unintended shortages elsewhere. Toilet rolls anyone? The industry would argue that some limited restrictions are helpful as that allows sensible conversations about how limited stock can be fairly distributed amongst all markets. In contrast, wholesale export bans are not, for by severely constraining the flow of medicines around the EU it becomes very difficult to move medicines to where they may be in greater need.
At a time when EU transition is now coming back on the agenda it might not seem as relevant to question the fundamental principle of free movement of goods, but it certainly might be a factor in exit negotiations when the UK can point at the way that some countries are bending the rules with export lists and some completely ignoring them with blanket bans.

The government in Wales might consider, in the midst of this global battle for stock, how they might protect themselves from the risk of shortages. The answer would seem to lie in the approach that the DHSC has now started to implement – that of collaborative conversations about future demand. They have realised that supply is not a suppliers' problem, just a part of a complicated supply/demand equation that all must work on together to solve. Dialogue that encompasses early warning of treatment changes and future plans to develop/implement new ways of working should take place alongside the logistics of meeting that new demand.

3. *Has fear for the security of the supply chain made on-shoring of manufacturing more likely?*

The rhetoric around the campaign to leave the EU left the impression that the UK would thrive after exit and part of that success would be an ability to attract more investment in industry in the UK. But there was also a negative aspect – that of protecting the UK from vexatious controls on our supply by other countries. This was characterised by some as a 'spiteful' EU punishing us for leaving the club, but recent geopolitical storms have thrust the issue of the pharmaceutical supply chain even more to the fore. It is sobering to know that 90% of the global supply of APIs originate in India and China.

There is an obvious reason for this situation – cost. Health services around the world demand cheaper medicines and the industry's response has been increasingly global outsourcing to reduce costs. The industry devolved manufacturing and packaging and as more efficiencies were demanded it out sourced the more fundamental aspects such as the API. The more modern complicated (to manufacture) medicines are still largely kept in-house, only 8% produced in China and India, but as they lose patent and cost becomes the most important characteristic to payers, they move to low cost economies.

The UK NHS only represents about 3% of the global market for pharmaceuticals and much of that is cheap generic prescribing – exactly the market that is suited to manufacture in low cost economies. As explained above, the key to successfully supplying health services demand is

efficiency. This efficiency is just not possible, even with government grant aid, in a high cost economy. The only incentive for global manufacturers to move to the UK must lie in the partnerships that are necessary in the development of new technologies with our academic and charitable sectors. It might be that academic research into highly specialised expensive new medicines can be linked with pharmaceutical development and then manufacture in associated facilities. In any other circumstances, the political idea of on-shoring is likely to fall at the hurdle of economic reality.

4. *Why has the pharmaceutical industry stepped up to the plate so readily?*

The speed and range of response by the pharmaceutical sector to the pandemic has been little short of astonishing. Not to in any way play down the achievements of academic centres such as Oxford nor the charitable work done by, for example, the Gates Foundation, it is a fact that over 70% of the activity on developing new vaccines, new treatments and creating manufacturing capacity has come from the global pharmaceutical industry.

There are obvious advantages to being the first to invent a new treatment. Not just the commercial benefit of the sales if you are first to market, but also the reputational benefit for your scientists and your shareholders. However, it is obvious that there is more to it than that. The industry is always striving to create new partnerships and new ways of cooperating as they understand (often better than health service leaders) that this is what brings optimal results. What better opportunity is there to find new ways of collaborating than with this global threat hanging over all of us? They have shown this with competitors and increasingly with government agencies – see the DHSC and MHRA examples above.

5. *What will be the impact on future medicines development of this refocussing of pharma attention?*

Large scale clinical trials have been put on hold because the logistics under lockdown are insurmountable, but also because industry and NHS resources have been diverted to COVID care and research. Some will undoubtedly be cancelled or moved overseas. Some patients, having had their treatment stopped, will never receive it. Some in oncology trials have now moved to palliative treatment only. The damage to the development of new technologies is incalculable. Not just because no one knows what or if trials will re-start, but more fundamentally the development of new medicine is a high-risk business with very few medicines getting to market and even fewer turning out to be commercially successful. It is not possible, normally, let alone in these circumstances, to predict future benefit and therefore what has potentially been lost.

There have been some upsides. Companies, academic centres, charities and government have made remarkable progress in cooperating and problem solving. Regulatory processes have been streamlined to allow faster access to novel or re-purposed treatments and to accelerate clinical trial approvals. Anecdotally, for one trial, ethics approval was reduced from months to over one weekend to allow an early start.

In other cases, treatment pathways involving new technologies that have been previously resisted for upfront cost reasons, have now been implemented allowing less patient time in NHS premises, reducing patient/clinician face to face contact and in the long-term saving costs. An all-around win. What is not known is how many of these benefits can be sustained when normal levels of activity and regulatory scrutiny return.

CONCLUSIONS

As you would expect, in a crisis, a crisis that has a very human face, government, the NHS, regulators and the industry have stepped up to the plate to do what they could to help maintain the pharmaceutical supply chain for patients. It was fortuitous that much thinking and work on

ensuring the continuity of the supply chain commissioned in case of a no-deal Brexit had already been done. But the reaction went far beyond that.

It is too soon to know whether things could have been done much better, but it is not too soon to identify that many things have been done differently and that there is real merit in asking whether some of those changes can be maintained when some sort of normality returns. The one thing that would be an enormous regret would be if the new-found ways of collaborating between all actors in the supply chain for the greater benefit of patients and the NHS were to be lost.

In conclusion and in light of the temporary and necessary changes implemented, there are a number of questions which it would be sensible for the Welsh Government and the NHS in Wales to consider:

- Which of the regulatory and administrative flexibilities for primary care can be maintained post COVID?
- How can Wales become the most efficient place in Europe to run clinical trials?
- Which treatments that were previously seen as not best value may now be considered best practice?
- What new opportunities are there to accelerate the trend to more pharmacy clinical care?
- Where can dialogue between all the supply chain actors be improved to ensure a swift resumption of NHS care and a robust future supply?

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26.6.2020