White Paper

Rising to The Challenge:

Five key focus areas for Life Sciences during and after the COVID-19 pandemic

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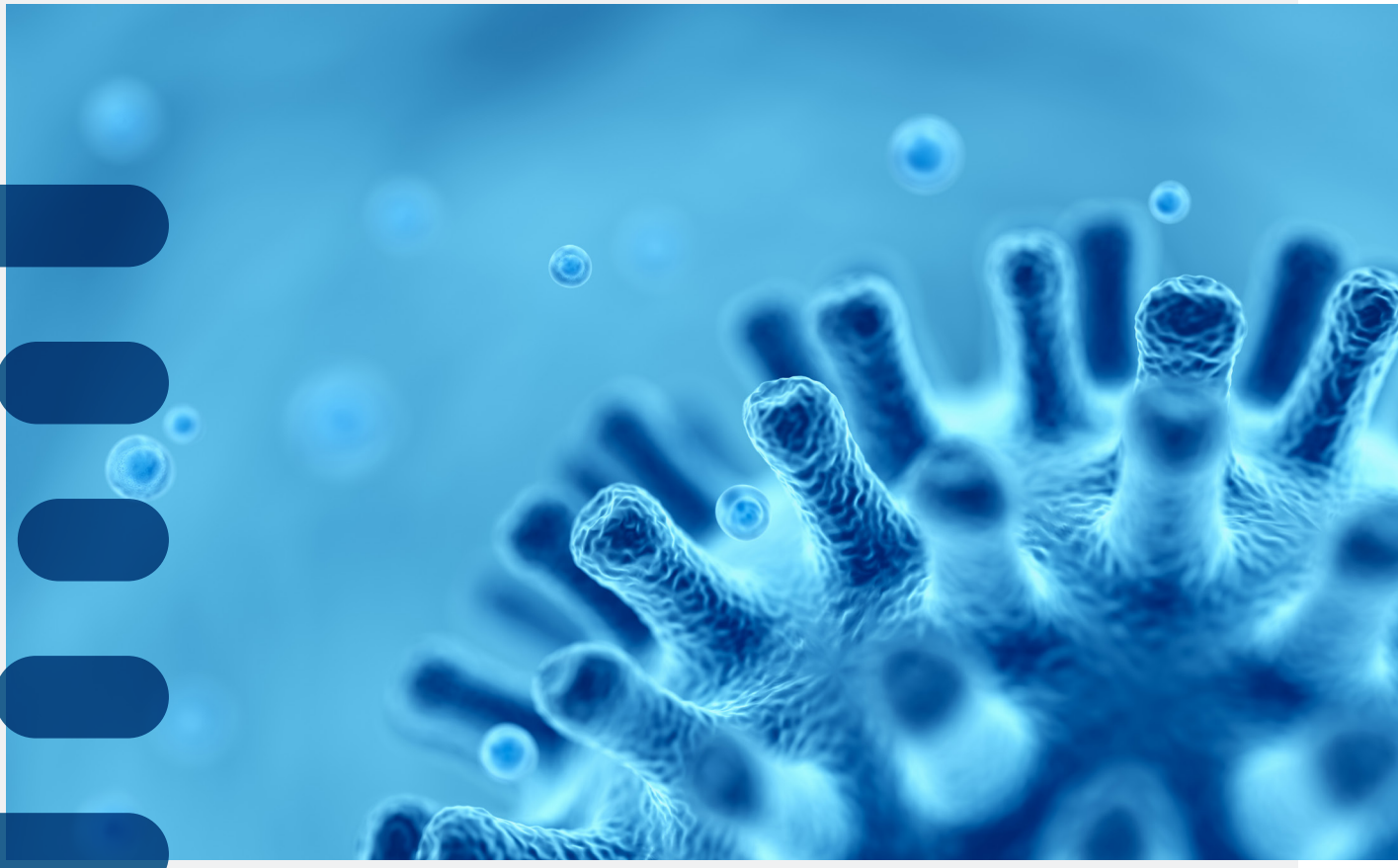

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Introduction

The spread of COVID-19 has created a global healthcare crisis, and has led to an unprecedented response from people, communities and systems. Healthcare workers on the front lines are giving it their all to contain, treat and reduce the impact of this pandemic. The pharmaceutical and life science industry has risen to the challenge by rapidly mobilising to join the fight against the virus. Their support extends beyond the development of treatments and vaccines for COVID-19; across countries we have seen offers of people, expertise, and financial support to the healthcare systems they partner with.

In any fast moving, uncertain situation such as the COVID-19 pandemic, any article or white paper comes with a practical warning - as the situation changes, so too will insights and perspectives. This paper is therefore based on the evidence in hand as of the end of March 2020.

This feels like an immediate crisis only. It isn't.

The challenge of COVID-19 for pharmaceutical and life sciences industries is that nothing and no country can – nor should – be viewed in isolation. While it is true that there are acute scenarios at the country level that occupy our immediate attention, the long-term consequences are starting to become apparent. Fighting COVID-19 is the top priority, but adjusting to a new reality is a close second. In fact, it is entirely possible that in some ways, the pharmaceutical industry will never return to the pre-COVID-19 normal.

This is why, in thinking about COVID-19, we need to think both fast and slow: clearly there's a huge amount coming at us every day in terms of addressing the immediate crisis. But this "fog of war" must not prevent us from thinking about the longer term implications for healthcare systems and our industry.

This white paper will cover five key focus areas for pharmaceutical companies as they address COVID-19. For now, the focus is on illuminating the immediate levers of pharma market movement, though long term hypotheses are also raised.

1. Supply and demand
2. Pressure on regulators;
3. Change in interactions between pharma and Healthcare Professionals;
4. Global interconnectedness of active pharmaceutical ingredient (API) and generics manufacturing;
5. Launch schedules, and other longer term impacts.

Focus 1: Medicines demand and supply

The COVID-19 pandemic has actual and potential impacts on medicines manufacturing, supply and demand. Decisions pharmaceutical companies must make in these early days will be about the manufacturing and sourcing of medicines, addressing demand and managing supply. At the time of writing, European countries are generally not reporting significant or concerning shortages linked to COVID-19, and in the US the FDA has re-emphasised its requirement for manufacturers to communicate on any anticipated supply disruptions. In both administrations, of course, there were shortages reported for products prior and unrelated to COVID-19, but everyone is aware of the possibility caused by exceptional changes in both demand and supply, and all have initiated plans to monitor and address the situation, including for some countries, export bans, changes in regulations covering distribution, and auditing of the distribution system.

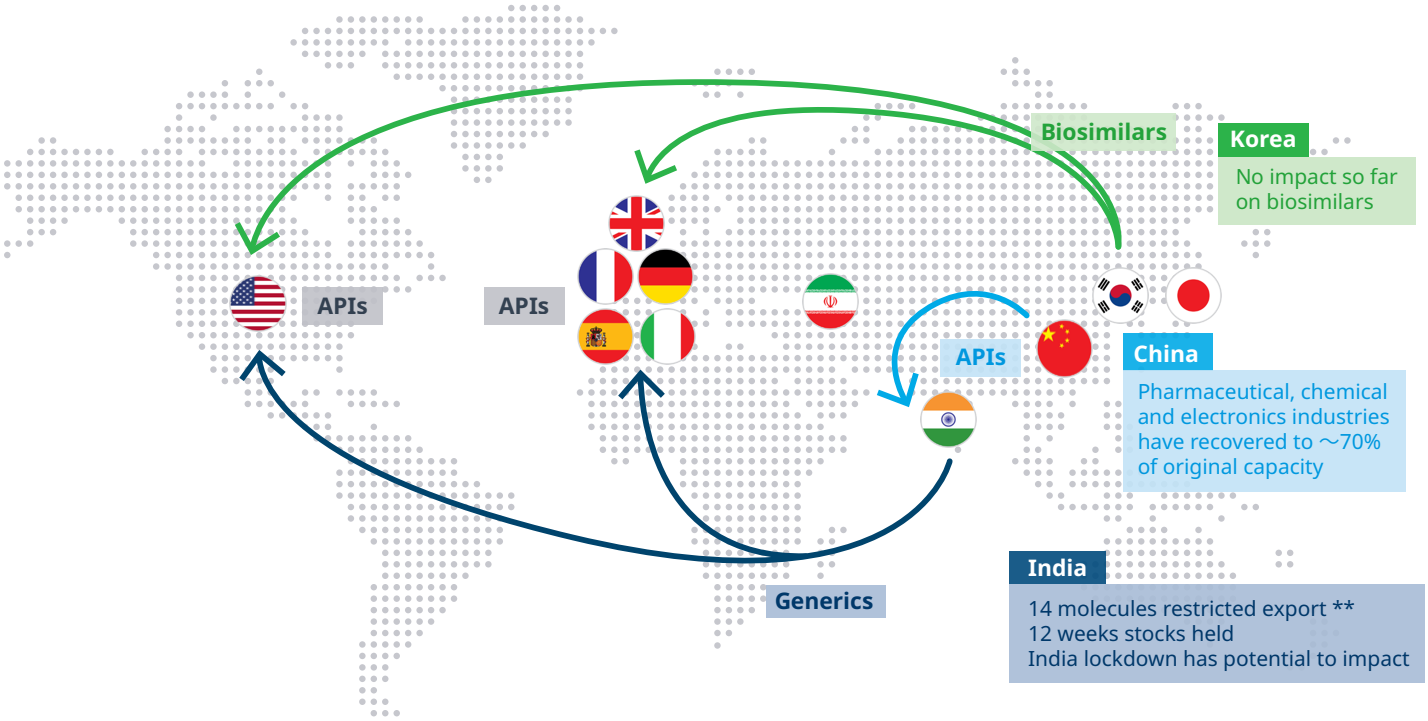
MEDICINES AND ACTIVE PHARMACEUTICAL INGREDIENT SUPPLY

The global pharmaceutical industry has become far more integrated in terms of Active Pharmaceutical Ingredients (APIs) and finished medicines manufacturing, and supply for the high volume medicines which treat the majority of patients over the past decade. The COVID-19 pandemic has therefore unsurprisingly raised concerns about the resilience (and vulnerability) of such a highly interdependent network as waves of countries are affected by the virus. China is a significant and growing API supplier, and those APIs make their way into generics which supply the European and US markets, among others.

In China, pharma is fortunate that API manufacturers tend to be located on the coast, away from the epicentre of the COVID-19 infections, and manufacturing is expected to be resilient. Equally, Indian generics manufacturers, often dependent on

Chinese APIs, do have substantial stockpiles, although India did restrict the export of certain molecules on the 3rd March, a restriction the authorities emphasised was intended to be temporary[1]. South Korea, a major centre for biosimilar manufacturing and a country that was affected early by the pandemic, has not, according to our research, seen factory closures.

Figure 1: Generic/API supply chain across countries
Global interdependency has grown significantly; and this increases fragility in COVID-19 crisis



List of India restricted export 26 products (14 molecules), now includes Hydroxychloroquine prohibition as of 25/03 https://dgft.gov.in/sites/default/files/Noti%2050_0.pdf

The potential for impact exists, but could be mitigated

- Biosimilars not flagged as being impacted. Major Korean producers operating at full capacity
- Chinese API manufacturers based in less affected provinces
- Reportedly 70% of Chinese API for Indian manufacturers sourced from China
- Asia most exposed to Chinese products
- EU sees “limited immediate risk” due to stockpiling**
- US manufactures some APIs in the US. In August 2019 13% of API facilities supplying the US were based in China

MEDICINES DEMAND

The refocus of healthcare systems to managing the immediate COVID-19 crisis, combined with lockdowns and social distancing, fundamentally means a reduction in routine healthcare system contacts. In the US, this has already resulted in longer prescriptions in retail pharmacies, according to IQVIA daily prescription data, in terms of number of days of prescription so renewals need to be more infrequent and this trend is also seen in other countries.

However, in the medium term of the next 3 months, treatments for chronic illness, especially chronic asymptomatic illnesses, could see falls in treatment initiation and switch because these require healthcare professional intervention, which most commonly would have happened face to face. Ironically, this may be concurrent with a rise in repeat prescriptions as patients stock up in anticipation of isolation. In either scenario, changes in how medicines are prescribed and dispensed may need to be taken. In the US we already see a switch to longer term repeat Rxs, for example. The result will be a drop in the share of major chronic medication markets that is dynamic (i.e. new or switched prescriptions). Pharmaceutical companies will need to monitor if this happens and find ways to re-ignite the dynamic market should it contract.

Demand challenges fall into three main groups:

- Primary demand: products managing infection control (e.g. face masks, hand hygiene, disinfectant, and other disposable paper items and surgical devices). These items have already seen hundred fold increases in demand over the previous period in 2019, for example, in Italy in February. There is also primary demand for treatments for fever such as paracetamol and other anti-pyretics. In the UK, paracetamol has seen volume changes in the week commencing 9th March of +91% versus the 2020 average.
- Adjacent to primary demand: treatments associated with respiratory infections such as antibiotics (even though the main culprit is a virus), and asthma and other respiratory medications. Beclometasone and salbutamol, both asthma treatments, each saw UK increases in volume in the week commencing the 9th March of 27% and 23% respectively. These movements could well be driven by asthmatics, aware they are more at risk from getting very sick from COVID-19, stocking up on vital medicines so they do not have to visit health facilities.
- Other stocking up effects are possible, where patients are on chronic medications for long term conditions, such as diabetes or cardiovascular patients anticipating isolation or reluctant to visit healthcare facilities.

So far, global supply chains seem to be resilient, but the threat remains, and close attention must be paid to supply and demand in the coming weeks and throughout 2020, as knock-on downstream effects are possible.

Potential treatments (separate from vaccines), all currently unlicensed for use in the treatment of COVID-19, could also see movement.

There are multiple molecules, all currently unlicensed for this indication, which have been discussed as possible treatments for COVID-19. Some of these are on the market across multiple countries, some only in a few and some are developmental and have not been authorised for any purpose. Potential candidates for treatment will undoubtedly change, and rapidly, with some under consideration already failing in trials, and new ones being considered. The WHO publishes a regularly updated landscape of pharmacotherapies under consideration[2]. These include generics; corticosteroids (which were also used to treat SARS and MERS); chloroquine, indicated for malaria; antivirals, mostly currently used for HIV but also broad spectrum antivirals; immunological treatments, including MAbs for RA; JAK kinase inhibitors and Avastin; interferons alpha and beta; and others, including Gilenya, a multiple sclerosis medication. Some of the immunological and interferon treatments are also available in biosimilar form.

Figure 2: Which therapeutic areas might be directly or indirectly impacted?

PREVENTION & EARLY SYMPTOMS	ASSOCIATED WITH/TREAT SYMPTOMS RELATED TO THE VIRUS MIGHT INCLUDE:
Over-the-counter	Analgesics, NSAIDs and anti-pyretics such as aspirin, paracetamol and ibuprofen**
Hand Sanitizers	Antiviral and antibiotic hospital solutions
Masks	Antibiotics for lower respiratory tract infections (even though COVID is a virus)
Cough & cold	Respiratory agents- especially asthma treatments
Hygiene	ICU medications
Analgesics, NSAIDs and anti-pyretics*	Flu and other vaccines (people getting the vaccine to avoid another source of infection)

THE FOLLOWING PRODUCTS DISCUSSED AS POSSIBLE TREATMENTS FOR COVID-19 (ALL CURRENTLY UNLICENSED, AND WILL BE INCOMPLETE LIST)***

- **Actemra** (tocilizumab)
  Roche
- **Kevzara** (sarilumab)
  Sanofi
- favipiravir
  In development
- **BDB-001**
  Staidson
- **JAK kinase inhibitors Jakavi and Olumiant**
- Interferons:
  IFN-α, IFN-α-2a, IFN-α-2b, IFN-β
- **Gilenya** (fingolimod)
  Novartis
- methylprednisolone
  Generic
- chloroquine
  Generic
- **Avastin** (bevacizumab)
  Roche
- ribavirin
  Generic (in combination)
- GS-5734 (remdesivir)
  Gilead ****

*such as aspirin, paracetamol and ibuprofen
**NSAIDs such as ibuprofen have called out by French Health Minister as a potential aggravator of COVID-19 infection, although data is lacking.
*** Not all will be available in Europe, in fact not all are even approved
**** not on market yet but being actively trialled for COVID-19
Kaletra(lopinavir/ritanovir) has been trialled and early results not positive https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
Other agents have been includes in the WHO Landscape analysis of therapeutics but are not necessarily endorsed as potential treatments for COVID-19- for example, darunavir (Prezista) is listed by WHO but as of 17th March, J&J played down its potential for COVID-19 https://www.fiercepharma.com/pharma/j-j-repurposed-hiv-med-prezista-s-chances-as-covid-19-treatment-unsubstantiated
Jakavi is in trials, Olumiant identified by machine learning as having potential https://www.nature.com/articles/d41587-020-00003-1

Remdesivir, a broad spectrum investigational antiviral from Gilead, is now undergoing clinical trials in China and in the US for COVID-19 treatment[3]. Actemra, a biologic for arthritis from Roche, has now been written into China's National Health Commission treatment guidelines for COVID-19 from 4th March, and is already in Phase III trials for COVID-19 treatment[4]. Roche made a substantial donation of the product to China.

Focus 2: Clinical trials and regulatory engagement

Regulators will be under increasing pressure to rapidly approve treatments whilst ensuring effective evaluations of efficacy and safety. This latter demand will include close monitoring and up to the minute, accurate information on other COVID pharmacotherapy issues (e.g. the possible issues with ibuprofen which surfaced as a social media discussion, with accompanying fake news[5]).

Regulators are also moving swiftly to find ways to facilitate non-COVID related clinical trials which have been impacted by the crisis. The FDA, for example, announced in late Marchthat there would be more leeway in the marketing of remote monitoring devices which could help trials under way keep going by supporting patients who cannot (or do not wish to) visit health facilities[6]. This relaxation is limited to the duration of the COVID-19 crisis, and shows how the FDA does not intend to create barriers for companies that make certain changes to product indications, claims or functionality, or request limited hardware and software modifications. In fact, the FDA has already recommended the increased virtualisation of clinical trials wherever possible, including telehealth, phone interviews and self-administration. This could, of course, be a catalyst for a bigger shift to increased virtualisation of clinical trials in the longer term.

Focus 3: Engagement with healthcare professionals

Face to face interactions of all types have, of course, been minimised unless absolutely necessary and supportive. Fortunately, many pharmaceutical and life sciences companies recognised early on in the pandemic that their employees' role in moving between health facilities and health professions was a possible danger and proactively reduced these interactions. However, HCPs' need for information and support remains, and data shows an increase in remote interactions compensate. In fact, in all countries covered, face to face interactions is sharply down compared to the same period in 2019, likewise, in the majority of major countries remote engagement is up (see figure 3). The question now, of course, is what remote engagement is appropriate, and when.

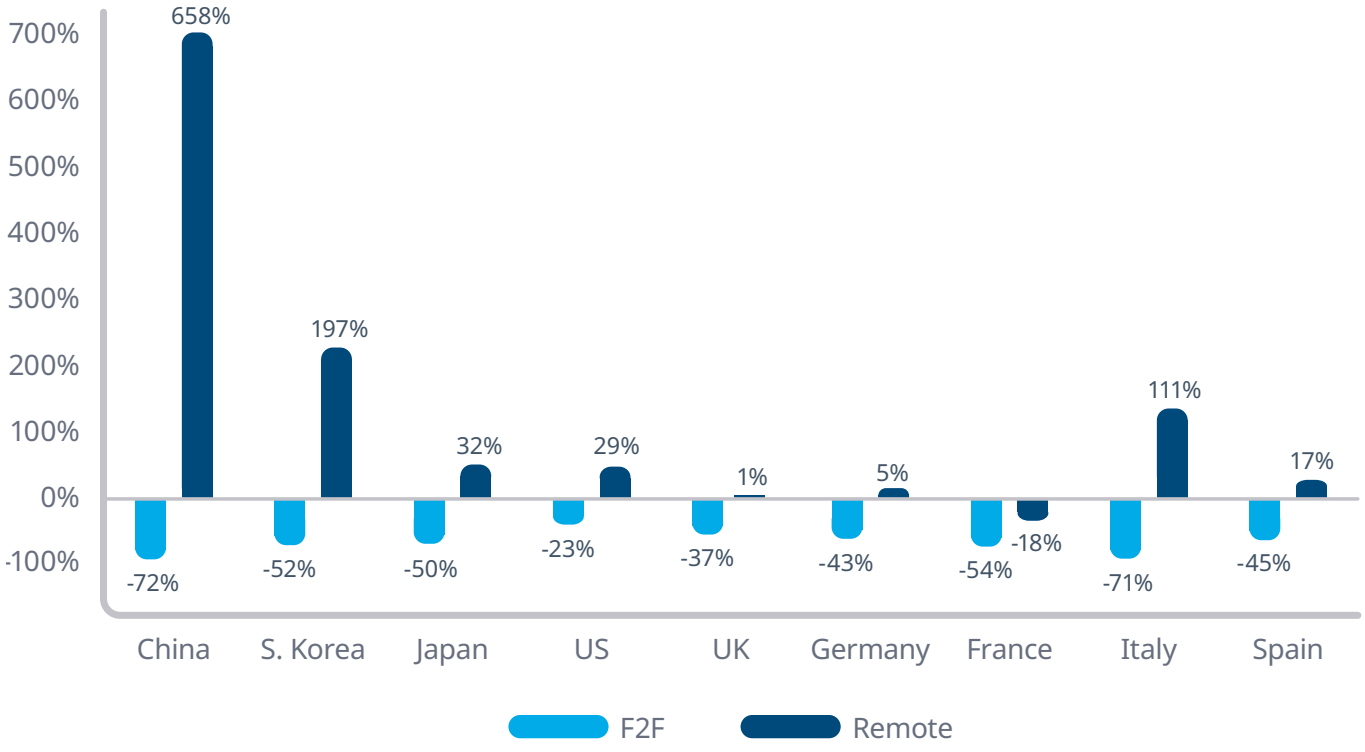
Focus 4: Innovation and Launch

The impact of COVID-19 on innovation is a longer-term challenge, but real nonetheless. Right now, with healthcare systems focused on crisis management, and restrictions on healthcare facilities, clinical development in non-COVID related areas faces some very real challenges.

The approval of innovative medicines relies on pharmaceutical companies having regular interactions with, and guidance from, regulators (the FDA and EMA in particular). In response to the current crisis, these regulators have announced they have shifted committee and working parties to virtual working. However, staff time and attention is almost inevitably going to be diverted to approve trials for potential COVID-19 treatments and vaccines, and of course to accommodate any vital staff who test positive for COVID-19. It is therefore likely that both approvals and commercial launches of products will see a slowdown in the months of immediate crisis around the world. On the 24th March, for

Figure 3: Significant decline in face-to-face promotional activity in countries affected earliest by COVID-19 to date
Substantial increase in remote interactions in S. Korea, Japan, US and Italy, although overall contacts decline

Mar 2019 vs Mar 2020
% Change in absolute recorded promotional volume*



*30 day period to 29/03
Source: IQVIA European Thought Leadership; ChannelDynamics 29/03/2020; F2F includes detailing and meetings, Remote includes phone detailing, e-detailing (live+automated), postal & e-mailings, e-meetings (live+automated)

example, Poland's drug agency, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), recommended no new clinical trials be started and stated they would suspend the inspection of clinical trials. As Poland is a major international centre for clinical trials, this has implications well beyond Poland. As of the 24th March, both BMS and Eli Lilly had announced they were pausing the start of new trials.

IQVIA undertook research on the public announcements of the top 20 pharmaceutical companies by IQVIA-measured prescription medicine sales, and other, smaller companies, between 28 March to 2 April. At that point, we found that less than half of the top 20 Pharmaceutical companies had publicly announced clinical trials as negatively affected by COVID-19, (the rest were either announced as unaffected or no announcement had been made) with marginally more announcing that the start of new trials would be delayed rather than existing trials interrupted. However, for smaller companies (where we did not limit the universe, but simply searched for public announcements) more announcements were about ongoing trials being impacted. There were far fewer announcements of launches being paused- BMS's delay of the commercialisation of their approved medicine Zeposia being only one of six launch delays announcements captured from public information so far[7].

The decision to pause the start of new trials is relatively straightforward - it is more complex to suspend existing trials and doing so may have complex ethical implications. Virtual clinical trial approaches, which have been developed for a number of years, now start to see their moment to demonstrate their value. The FDA issued a guidance on the 18th of March for the pharmaceutical industry, investigators, and review boards on conducting clinical trials during the COVID-19 pandemic, acknowledging the challenges of conducting clinical trials and making strong recommendations for considering remote and virtual approaches to keeping clinical trials running where possible.

Over 80% of doctors still wanted engagement and interaction with pharmaceutical companies during the COVID-19 crisis

In addition to decisions about clinical development, pharmaceutical companies face tough decisions about launches that were planned in the immediate months, balancing the value of the launch to patients with the potential impact on the healthcare system, not to mention commercial and competitive impacts. Products for for life threatening and severely life-impacting conditions which were scheduled to be launched during the crisis should be available to patients, but the nature of the launch will undoubtedly be modified.

In all countries, companies must recognise that if they suspend launch plans today, the post COVID-crisis launch environment will not be the same; all aspects of launch plans will need to be reviewed and potentially modified. It is likely to take a long time, even into 2021, for healthcare systems to recover, and some dimensions may be permanently changed.

CASE STUDY: In Italy, equipment first; information second.

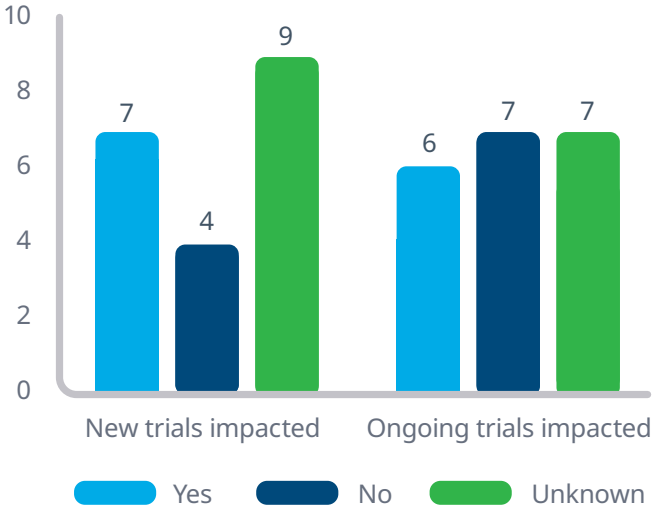
Between the 14th and the 16th of March 2020, IQVIA Italy was privileged to be able to interview over 1,000 Italian physicians, both specialists and general practitioners, to ask them whether they still wanted engagement and support from pharmaceutical companies during the COVID-19 crisis and if so, what type of support and information they required.

The results were clear over 80% of doctors still wanted engagement and interaction with pharmaceutical companies during the COVID-19 crisis, stating that maintaining an online/remote interaction was “important”. The nature of the remote engagement healthcare professionals are seeking, and the content and support they require, is important. Healthcare professionals are requesting practical support that will help them to do their job safely and effectively in the immediate crisis: first, protective equipment, second, information (scientific updates and information in real time, on symptoms, diagnosis and drugs, centers for treatment, management of complex cases, and communications on the healthcare situation). They want information in a rapid, time efficient format: email and WhatsApp messaging is preferred.

What was striking about HCP response was the expression of appreciation for pharmaceutical companies who were engaged and present for them during the crisis. In the medium-long term, healthcare professionals are looking for pharmaceutical company support in remote patient management, something which could be a feature of the post COVID-19 healthcare environment for some time. This includes exploring medicines delivery, and tele- and e-health solutions.

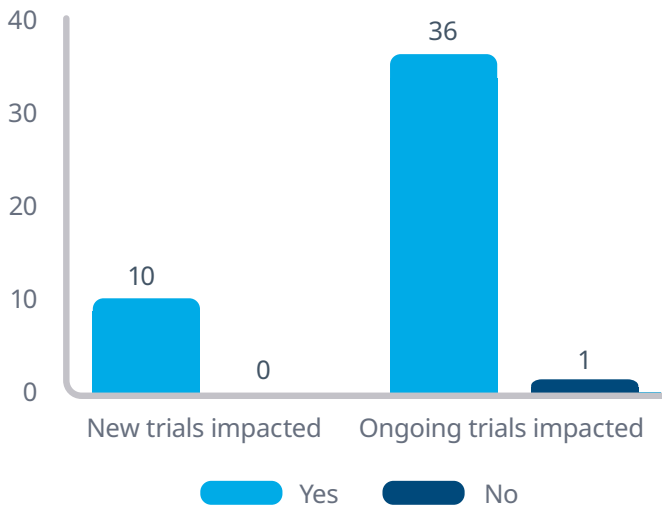
Figure 4: COVID-19 is impacting the ongoing and planned clinical trials of both major and smaller pharma companies

Number of top 20 pharma companies



- Top 20 pharma companies are focusing on delaying the start of new trials rather than interrupting ongoing trials.
- Companies are often citing the welfare of trial participants and future patients as a reason to continue with ongoing trials.

Number of other pharma companies (n=54)



- Non-top-20 companies are mainly reporting impacts on their ongoing trials in juxtaposition to more highly ranked companies.
- However, the reporting companies are often smaller with a single asset, and therefore unlikely to have a wide pipeline of planned trials to be impacted.

Source: IQVIA European Thought Leadership, pharma company press releases and public statements, analysis updated 02/04/2020

The most obvious change is likely to be the continuation of remote engagement with healthcare professionals in both promotional and non promotional situations. For promotions, including launch promotions, the importance of remote engagement was already established and growing. Already in 2018, the most commercially successful launches in the seven major country markets (which account for almost 90% of the first five years of launch sales) were also the most digital, as defined by the makeup of the first year's promotional activity[8]. Post COVID-19 launch planning should anticipate further changes in engagement with healthcare professionals, likely with not only more use of digital channels, but also changed expectations of which channels and types of content. Asking healthcare professionals about their changed engagement preference and responding to their feedback with adjustments will be important. Planning for non promotional medical affairs engagement, which in a highly specialised world is increasingly important, will also need to be a priority.

Outside of promotions, other launch activities will certainly see shifts. Market access discussions for post-COVID launches will be conducted in the new context of healthcare systems which have seen huge calls on resource and budget. Even with substantial emergency funding specific to COVID-19, other areas of funding may be weakened. The value healthcare systems place on the benefits of new launches may change; for example, greater value will likely be placed on products with the potential to keep patients away from visiting hospitals (i.e. sub-cut as opposed to iv, or applications that reduce the number of face to face interactions, such as smart delivery devices).

More broadly, the whole complex business of coordination behind launch - the internal and external meetings, kick offs, updates, reviews, training and educational sessions and advisory boards - must be reviewed with a more virtual approach considered and, in many cases adopted. Companies find alignment and coordination behind launches a challenge in normal situations. In today's extraordinary situation, they should recognise it could be more challenging still, and make extra efforts to compensate.

Focus 5: Mapping out the strategic implications for medium and longer term continuity

In the thick of the immediate crisis, it's still crucial for pharmaceutical companies to plan for the post crisis period. Healthcare systems and pharmaceutical markets will not see a rapid return to situation normal. In fact, it is possible that for some fundamental aspects of healthcare systems and pharmaceutical businesses, COVID-19 will be a catalyst for substantial and lasting change. Pharmaceutical companies must keep a watchful, if not proactive, eye on their environment, which may revert to "normal" only slowly – or perhaps not at all.

It's possible that remote communication, and remote interaction on clinical trials, will become even more routine than it is now. As we noted, there is a specific challenge for launches which were planned in this time period- not only will postponed launches (if companies postpone) be entering a very different healthcare environment to that which the launch was planned for, there are also likely to be more launched in a shorter space of time. Both issues necessitate a launch planning rethink. Healthcare delivery itself may see an accelerated shift to digital. The rise of remote engagement is a strong driver to technology companies who were already very active in putting into place telemedicine and remote engagement technologies. And finally, the progress towards an increasingly interdependent manufacturing and supply chain globally could see a slowdown, or even a reverse. In late February 2020, Sanofi announced it would invest in launching a new European drug manufacturing firm[9].

The COVID-19 pandemic is a transformative event in world history, and also for the Life Sciences industry which is at the heart of the fightback. As well as rising to the challenge of keeping medicines flowing, identifying treatments and developing vaccines, the pharmaceutical industry has opportunities to transform and evolve more rapidly than it would otherwise have done. Whilst there are huge challenges ahead, the fact is that the crisis is sparking more innovation in an already highly innovative industry.

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Sarah Rickwood has 28 years' experience as a consultant to the pharmaceutical industry, having worked in Accenture's pharmaceutical strategy practice prior to joining IQVIA. She has an extremely wide experience of international pharmaceutical industry issues, having worked most of the world's leading pharmaceutical companies on issues in the US, Europe, Japan, and leading emerging markets, and is now Vice President, European Marketing and Thought Leadership in IQVIA, a team she has run for 10 years.

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For further information on IQVIA's perspective and response to the COVID-19 pandemic please visit https://www.iqvia.com/about-us/commitment-to-public-health/covid-19-resources

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