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A Coming Tidal Wave

Predicting Impacts of the Pending COVID-19 Vaccination Campaign on Safety Reporting, Tracking, and Liability for the Entire Industry

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A Coming Tidal Wave

Given limited information at market authorization, combined with the speed at which vaccination will take place, upcoming mass vaccination programs for COVID-19 will be associated with a significant spike in adverse event reporting. The pharma industry must plan its response to gathering data on the safety of both vaccines and medicines used with them in response to this unprecedented global campaign. Pharmacovigilance teams across all companies must be prepared.

The mass vaccination campaigns bring together 3 factors that will have both a medical and a legal impact.

Firstly, development cycles have been shortened, so that the period from drug discovery to market authorization has been compressed into less than 1 year.

Secondly, the first vaccines are highly likely to be authorized under lower-than-normal standards for demonstration of safety and efficacy.

Thirdly, mass vaccination will follow an exponential curve with huge numbers of subjects being immunized simultaneously.

Adverse events will occur, whether causally related or incidental to a particular vaccine, and these events will be multiplied by the speed of vaccine roll out combined with the level of public interest through news outlets and social media. It is well recognized that issues with medicines or vaccines highlighted by media drive significant peaks in adverse event reporting.

Preparation for this scenario with timely evaluation and sharing of information with COVID-19 vaccination manufacturers will also be critical for public health.

COVID-19 vaccine classes include:

Virus
- Inactivated
- Weakened

Viral vector
- Replicating
- Non-replicating

Nucleic acid
- RNA
- DNA

Protein-based
- Protein subunit
- Virus-like particles

Impact of accelerated vaccine authorization

The US COVID-19 vaccination initiative, Operation Warp Speed, aims to deliver 300 million doses of a safe and effective vaccine by January 2021.[1] The commencement of mass vaccination is imminent with the necessary scale-up of manufacturing and distribution already being put in place.

Whilst the CEOs of the 9 companies with the most advanced vaccine development programs have signed 'a united commitment to uphold the integrity of the scientific process as they work towards potential global regulatory filings and approvals of the first COVID-19 vaccines'[2] initial release through Emergency Use Authorization (and equivalent in regions outside the USA) remains highly likely.

Emergency Use Authorization requires a reasonable belief that the product may be effective, and that the known and potential benefits outweigh the potential risks. Compared to the typical approval standard, this permits significantly more uncertainty and unknowns about the benefit-risk balance of a product.

In any event, including if authorization took the form of traditional approval, vaccination will quickly move from highly select groups in Phase III trials to a diverse population in terms of ethnicity, background disease or background medication. Even with trial participants in the region of 30,000 subjects the boundaries of understanding for adverse events will be narrow, and detection of additional adverse events should be expected once the mass vaccination campaigns begin.

The National Academies of Sciences, Engineering, and Medicine (NASEM) have released a draft plan for distributing a COVID-19 vaccine in the US[3] which prioritizes individuals based on their risk of infection. In the phased plan healthcare workers will be among the first to receive the vaccines, however other at-risk populations such as those in assisted-living facilities are also included in phase 1, and other people with comorbid and underlying conditions would be able to receive the vaccine in phase 2.

Key Fact

Summary of National Academies of Sciences, Engineering, and Medicine (NASEM) Framework

Phase 1a: High-risk health workers and first responders. People with significant comorbid conditions; older adults in congregate or overcrowded settings

Phase 2: Teachers, school staff and child care workers; critical workers in high-risk settings; people with moderate comorbid conditions; people in homeless shelters or group homes and staff; incarcerated/ detained people and staff; and all older adults

Phase 3: Young adults; children; workers in industries important to the functioning of society

Phase 4: All other individuals residing in the United States who are interested in receiving the vaccine for personal protection

Why does this matter for mass vaccination campaigns?

Figure 1 illustrates an anticipated scenario for mass vaccination in the US, assuming a target of vaccinating 70% of the US population (230 million people) within 12 months.

However, rather than a flat rate of vaccinations, in reality the rate would ramp up over time, eventually reaching to between 1 to 2 Million immunizations daily (depending on whether it involves a single or 2 dose vaccine).

The phased approach of the NASEM framework proposes vulnerable populations with background disease/medication will be included in the initial stages of the program. Sub-groups with higher levels of morbidity are at higher risk for adverse events, whether purely coincidental and due to background disease or caused by concomitant medication or the COVID-19 vaccine itself. The real-world data early in the campaign is likely to contain adverse events at a higher rate than would be expected from the population as a whole.

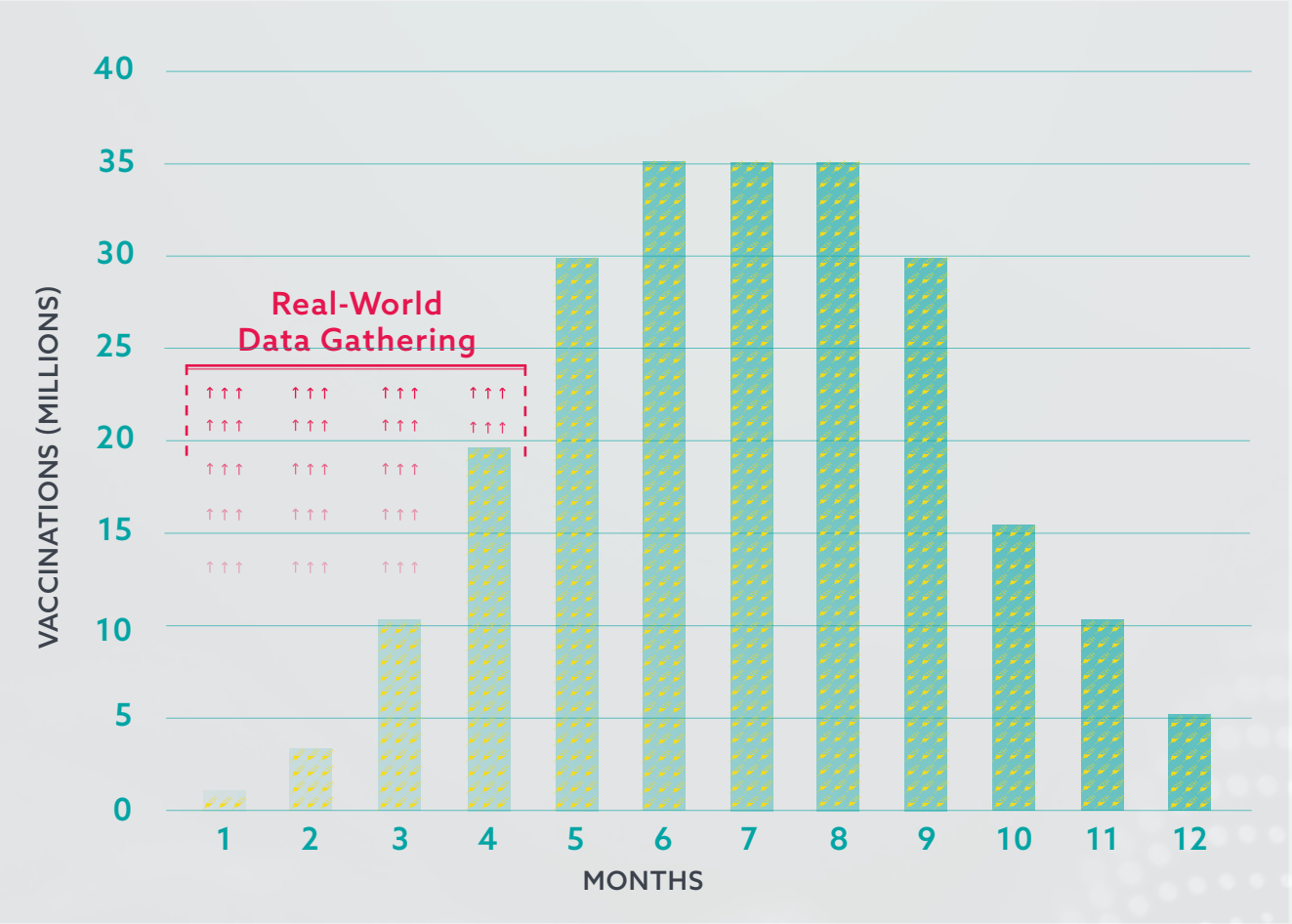

Figure 1 – Potential scenario for a mass vaccination campaign in the US

External influences on the rates of safety reporting

Levels of adverse event reporting across the COVID-19 vaccines post-authorization is still uncertain, but much can be inferred from the clinical trial data and previous vaccination campaigns where there are well-recognized influencers on adverse event reporting rates. Analysis of Australian passive surveillance data for adverse events following immunization (AEFI) showed significant increase in adverse event reporting (AER) during the H1N1 pandemic[4].

The report found a substantial increase in AEFI reported in 2009 associated with the introduction of the pH1N1 influenza vaccine, with a >3-fold increase in AER rates in 20-64 age group and >4-fold increase in >65 age group for the H1N1 vaccine.

The increase in reporting rates was driven primarily by direct reporting by the public in response to strategies to encourage reporting as part of the H1N1 vaccination program. Given the level of reporting, and, that majority of the AEFIs were non-serious, this provided valuable evidence of an acceptable safety profile for the H1N1 vaccine. During the H1N1 vaccination programs in 2009/10, social media was still in relative infancy, for example at the time there were <35 million Twitter users globally vs ~330 million in 2020[5, 6].

Surveillance of adverse events following immunisation in Australia, 2009[4]

The 2009 annual report summarising the Australian passive surveillance data for adverse events following immunisation (AEFI) found that, although the majority of AEFI reported were mild, transient and well recognised vaccine side-effects, there was a large increase (55%) in the number of AEFI reports received for 2009 compared with 2008.

These were mainly related to the commencement of the pH1N1 immunisation program in September 2009, which contributed 54% of the total AEFI reports for 2009. This included a large increase in reports from members of the public direct to the Therapeutic Goods Administration (TGA), from 3% of the total in 2008 to 28% in 2009, 94% of which were for pH1N1 influenza vaccine.

Influence of 'news' through social media

Adverse event reporting rates are also influenced directly by media activity and in particular the massive amplification of 'news' through social media. Over the course of the development of COVID-19 vaccine candidates there has been significant media interest in any positive or negative trends observed during the course of the clinical trial programs.

Indeed, a study into the influence of news coverage and Google searches on adverse event reporting found that media coverage and internet searches may have prompted increased awareness and therefore motivation to report common adverse events such as headache, fever and nausea[7].

Given that COVID-19 vaccines will be administered to the majority of the population, non-vaccine manufacturers are also likely to experience spikes in adverse event reports associated with the use of their medicines. Therefore, all pharmacovigilance teams should also be prepared not just for a smooth increase in reporting but for large spikes as news stories break.

Additionally, it is noteworthy that several classes of vaccine are likely to be authorized and each will carry different levels of effectiveness and risk. This, combined with the speed of development and authorization followed by the projected mass vaccination campaigns, will necessitate rigorous surveillance through proactive programs from the outset.

VACCINE RELATED	POPULATION RELATED	PUBLIC INTEREST
Novel vaccines	Ethnicity	Speed of vaccine programs
Cold storage (logistics)	Concomitant medication	Media interest
	Background disease	Impact of social media

Table 1 – Factors influencing adverse event rates following vaccination

Pharmacovigilance teams should also be prepared not just for a smooth increase in reporting but for large spikes as news stories break.

Systems must be capable of capturing the appropriate data, no matter which reporting route a patient selects.

Speed to analysis and insights

Current adverse event processes are still largely based around healthcare professional (HCP), call center, and email processes that are not scalable, are error-prone and may fail to link the details of the vaccine to the subject. It is likely that AEFI may be reported to the Vaccine Marketing Authorization Holders (MAHs), but also may be reported to other MAHs where patients are taking medicines for other chronic background conditions. Therefore systems must be capable of capturing the appropriate data, no matter which reporting route a patient selects, as well as integrating the data from the 2 sources to ensure all both parties have access to the information (Figure 2).

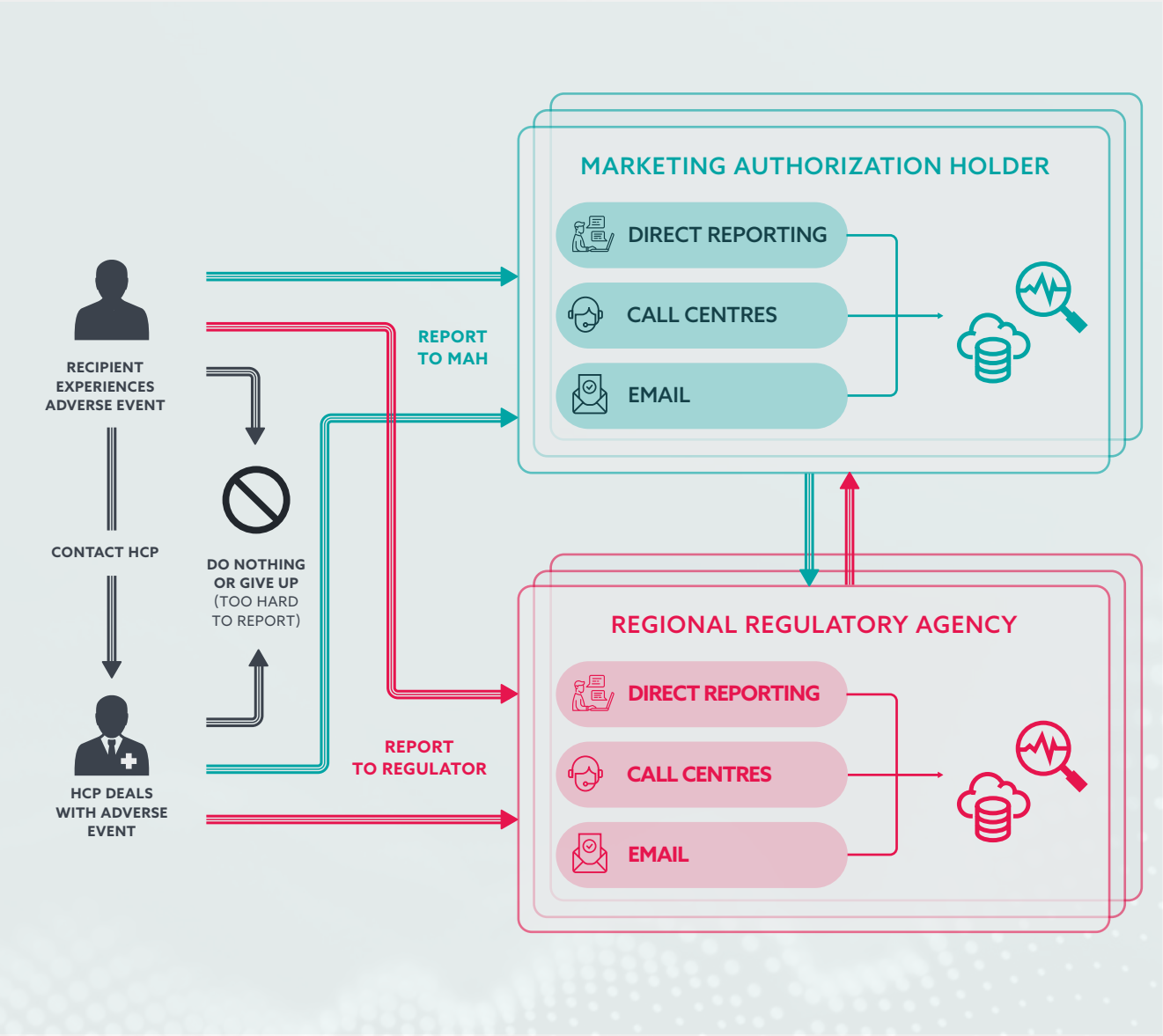

Figure 2 – Where will adverse events be reported?

	T (DAYS 1-10)	T +30	T +60	T +120
NUMBER OF VACCINATIONS	1,000,000	5,000,000	10,000,000	100,000,000
1/1000 SUBJECTS REPORT AN AE	1,000	5,000	10,000	100,000
X1.5 FOR DOUBLE DOSE VACCINE	1,500	7,500	15,000	150,000

Table 2 – Adverse Event Time: Exposure

Figure 3 – Impact of delayed analysis

Pharmacovigilance teams must be prepared to manage the volume of reports, but more importantly, analyze those reports in real time.

Using the vaccination rate estimates from Figure 1 and a plausible AEFI reporting rate of 1/1000, the volume of additional adverse events pharmacovigilance teams should prepare for are between 100,000 -150,000 over the first 120 days (Table 2).

Extrapolating further, if a serious adverse event occurs at a rate of 1/10,000 the impact of prolonged signal evaluation cycles can be seen in Figure 3. When just 1 million vaccinations are administered daily that translates to 100 people at risk of that SAE. Therefore, pharmacovigilance teams must be prepared to manage the volume of reports, but more importantly, analyze those reports in real time to generate insights that can be communicated to the public and healthcare community rapidly. Without such a system in place future vaccinees are not protected and public trust will be eroded.

Mapping individual benefit-risk

Benefit and risk of medicines or vaccines at the level of an individual is governed by genetics, lifestyle, the presence of chronic diseases and concomitant medications. Given the speed of development, inherent limitations of trials and number of subjects being immunized on a daily basis, the speed of analysis to understand the benefit-risk(B-R) for different populations will be critical and post market surveillance must be particularly diligent.

Clinical trial populations by design are highly selective, carefully managed and tracked. The objective is to generate data without confounding variables that obscure the true product profile. Ideally trial subjects who received active COVID-19 vaccine will experience higher levels of efficacy with few risks versus placebo groups (Top left-hand quadrant; Figure 4A). However, in the 'real world' the distribution of vaccine response in an individual subject will be impacted by co-morbidities, ethnicity, lifestyle, concomitant medications may be completely different.

Similarly, the COVID-19 vaccines may trigger new disease, or alter benefit profiles of existing medications in unexpected ways (Figure 4B).

The population groups in the various phases of mass vaccination campaigns will carry very different sets of risk factors. Therefore, consistent data collection and rolling analyses must be in place to ensure that the full picture of COVID-19 vaccines effectiveness and risk is understood as rapidly as possible given the numbers of people being exposed over a short period of time.

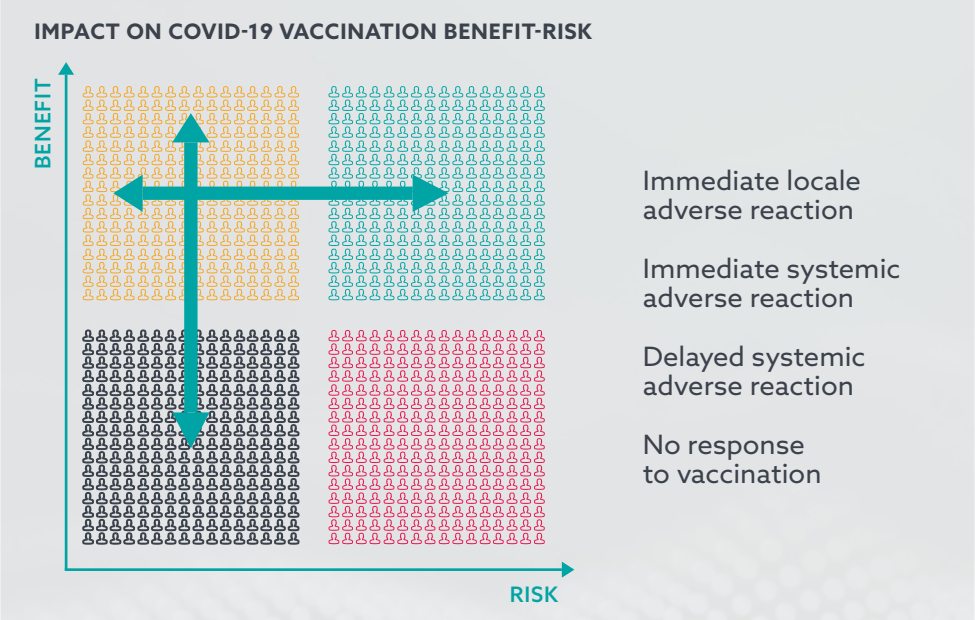

Figure 4A – Impact on individual benefit-risk profiles: COVID-19 vaccination

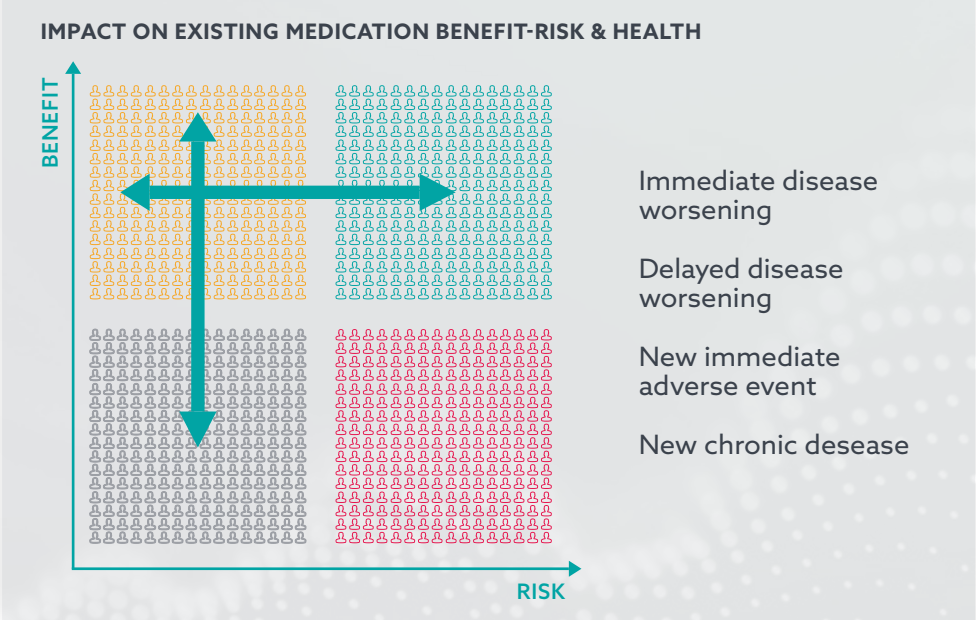

Figure 4B – Impact on individual benefit-risk profiles: Existing medication

Considerations for liability and potential litigation

The speed at which COVID-19 treatments and vaccinations are being developed amplifies product liability concerns. Critically, potential interaction with other medications and expected influx of adverse events reported to all manufacturers mean these concerns are not just for COVID-19 vaccine manufacturers, but impact all of pharma.

In light of the significant time constraints, combined with significant public and political pressure, it is inevitable that some liability issues are likely to arise despite the intentions of manufacturers and regulators to develop COVID-19 products to the usual standards. To address this, the US invoked the PREP Act in March 2020 to provide immunity for activities related to COVID-19 countermeasures. Whilst this provides a level of immunity for COVID-19 products it is limited to the US and does not cover the rest of the world, meaning the risk will be different in other countries and will be dependent on national laws and compensation methods. Additionally, the PREP Act only covers COVID-19 countermeasures, therefore if the product is not deemed a COVID-19 product it will be outside the scope of that immunity.

Therefore, given the variation and limitations on immunity from prosecution, it is essential that pharma companies implement risk management plans for their COVID-19 portfolios or those products likely to be impacted by COVID-19 vaccinations or medicines. MAHs have to analyze data fast and communicate even potential risks quickly. Full and early disclosure builds trust and reduces the probability of downstream litigation.

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Developing risk management strategies

As discussed throughout this whitepaper, it is essential that pharma companies rapidly develop an understanding of the potential risk of COVID-19 vaccines as well as any interplay between the vaccines and any other medications that patients may be taking, especially as at-risk populations are likely to receive the vaccine early on in the mass vaccination programs.

In addition, the relatively limited amount of safety information available at the time of authorization, the level of public scrutiny, and broader trends all highlight the need for robust post-market surveillance. These trends include generally increased expectations for openness and transparency with respect to drug safety, and use of advanced technology (e.g., data mining) to quickly identify new safety signals.

Whilst the principles of risk management remain the same as in all circumstances – proactively collect data, analyze it in real time and act on it quickly – arguably the consequences of delay and lack of transparency are amplified. Any delays in signal management and communication to patients and HCPs could result in other patients being exposed to those same risks, which is not only harmful to public health, but creates liability for the manufacturer.

Actions taken now will be scrutinized in litigation regarding the attention, transparency, and disclosure of adverse events, even if there is no known link to the vaccine at that time. Therefore, pharmacovigilance departments for every company – whether or not they are a COVID-19 manufacturer – must be prepared to manage the expected influx of adverse events.

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Conclusion

Pharmacovigilance departments for every regulatory authority and for every MAH, regardless of whether they are a COVID-19 manufacturer, must be prepared for the anticipated surge in adverse event reporting.

The anticipated mass vaccination campaigns for COVID-19 bring several key challenges for Pharmacovigilance teams:

- The mass influx of adverse events reported within a short period of time
- The need for rapid signal evaluation and impact assessments
- Increased liability risks given the prominence and scale of the vaccination programs

To address these challenges Pharma must adapt their operations and implement processes to capture data at source, make it available immediately for analysis and enable prompt communication of insights back to patients, HCPs and regulators in an open and transparent fashion.

With a such an open and scientifically rigorous system in place not only will patient health be protected, but the whole industry will build public trust – and confidence – in a safe and effective vaccine.

About The Author

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Andrew has deep expertise in Pharmacovigilance and is a trained physician who has held senior roles spanning Drug Discovery and Development within GSK working across USA, Europe and Asia-Pacific. He was previously Head of Safety at GSK and EU QPPV where he drove significant innovation and streamlining into the organisation.

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About MyMeds&Me®

MyMeds&Me® was founded by Senior Pharma executives to transform safety data capture, processing and reporting through a digital platform. Their prior involvement in the H1N1 pandemic vaccination program provided key insights into the current challenges faced during COVID-19. The company has deployed its Reportum solution to many global organisations, including 5 of the top 20 Pharma.

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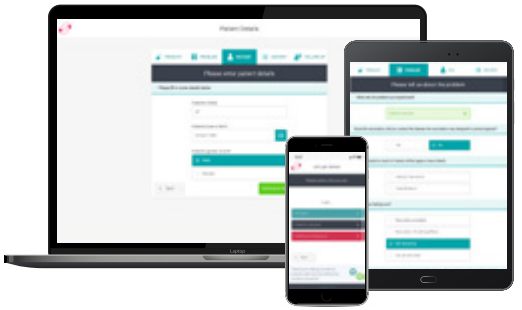

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