MHRA GUIDANCE

PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN REQUIREMENTS FOR COVID-19 VACCINES IN THE UK

BACKGROUND

1. The MHRA will have legal power to nationally authorise COVID-19 vaccines from 1 January 2021. In anticipation of this, and to ensure we are able to rapidly approve vaccines as soon as the evidences demonstrates acceptable safety, quality and efficacy, we encourage applicants to submit marketing authorisation applications (MAAs) in advance of 2021. MHRA now has in place a process for rolling review of MAA packages in order to expedite approval in 2021.

2. In support of industry preparations for MAAs to MHRA, this document outlines our requirements for pharmacovigilance and the Risk Management Plan for COVID-19 vaccines.

REQUIREMENTS OF A PHARMACOVIGILANCE SYSTEM AND CORE RISK MANAGEMENT PLAN FOR COVID-19 VACCINES

3. The MHRA will require full compliance of any MA applicant with the legal obligations outlined in Part 11 of HMR 2012, and the requirement of a Risk Management Plan (RMP).

4. However, there are aspects and specific challenges of the pandemic scenario, and potential mass deployment of a COVID-19 vaccine over a relatively short timescale, that will require more rigorous and *ad hoc* approaches to pharmacovigilance.

5. In developing these principles, we have drawn from experience from the 2009/10 influenza pandemic, in which MHRA played an active role in EU pharmacovigilance activities. We have also drawn from the EMA Good Vigilance Practice (GVP) module on vaccines[1], which applicants should use as a basis for RMP planning.

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-i-vaccines_en.pdf

6. We therefore request the following for pharmacovigilance and RMP content for any national authorisation for a COVID-19 vaccine:

Required routine activities

6.a Part 11 of HMR 2012 lays out the expected minimum requirements of an effective pharmacovigilance system, and **all applicants must comply with this legislation**.

Required *ad hoc* approaches to routine activities

6.b. We anticipate that any COVID-19 vaccine will be deployed on a mass scale, with several million vaccines administered over a relatively short time period. Therefore, with a likely large volume of suspected ADRs, very frequent signal detection activity is an essential additional standard. **We require this to be undertaken in as close to real-time as possible, and no less than at a weekly interval**.

6.c. With reference to section P.I.B.4.5 of the EU GVP vaccines guidance, **we require 'observed vs expected' analysis of suspected ADRs and adverse events of special interest (AESIs - see below) to be undertaken as part of routine signal detection**. For this purpose, data will be needed on vaccine exposure and the expected number of cases. Applicants should actively liaise with public health and regulatory authorities in countries where its vaccine(s) will be used in order to explore the availability of exposure data, appropriately stratified (e.g. age, gender, risk group). Use of electronic databases should be used where available to derive exposure and background incidence data. If data are not available, they should be appropriately extrapolated based on vaccine distribution data in each country. Background incidence rates should be provided with any specific signal evaluation.

Given uncertainties around the 'observed' number of cases, levels of diagnostic certainty, the level of vaccine exposure and the background incidence rates, sensitivity analyses should be applied in statistical analyses around assumed levels of under-reporting, numbers of 'confirmed' and 'non-confirmed' cases (using several categories of diagnostic certainty as appropriate), numbers of vaccinated individuals or vaccine doses administered and confidence intervals of incidence rates.

6.d. The routine requirement of 6 monthly periodic safety update reports (PSUR) reporting for the first 2 years of marketing of a new product (then annually for 2 years) should be complied with. However, we also require a form of PSUR that is more frequent during the first 6 to 12 months of vaccine deployment, but with a different format, that allows a more frequent, focused and efficient review of risk-benefit. During the 2009/10 pandemic, the EMA adopted a 'simplified PSUR' (sPSUR) which allowed a more efficient and more timely approach.

The EU GVP vaccines guidance also states that "*In exceptional circumstances (for example in a pandemic with mass vaccination), competent authorities and marketing authorisation holders may agree on an additional system to rapidly exchange information on emerging safety data whose submission timelines would depend on the extent of vaccine exposure, epidemiological situation and emerging risk. For example, a structured worksheet could present the observed and expected numbers of cases and integrate simple signal detection methods discussed in P.I.B.4., such as observed-to-expected analyses. Where such an additional system has been agreed, its inclusion as an additional pharmacovigilance activity in the RMP, along with information on its rationale, format and periodicity, should be discussed between the marketing authorisation holder and the competent authority*".

In accordance with this guidance, **we therefore request a supplementary PSUR approach in the form of a monthly sPSUR** which will capture the most relevant periodic data to evaluate risk-benefit in an efficient way – the precise format of the sPSUR is under consideration by MHRA, but we envisage a broadly similar approach to the sPSUR as adopted by EMA in 2009[2].

These *ad hoc* approaches should be described in the RMP.

Required additional activities

6.e. We request that all applicants give consideration to additional activities described in the EU GVP module on vaccines when developing their PhV system and RMPs. **Any deviation from the additional requirements as laid out in section P.I.B.1.3.2 of that guidance should be justified**.

[2] http://repositorio.h1n1.influenza.bvsalud.org/fileserver.php?fileid=2007

6.f. Attention should be paid to the aspects of the EU GVP guidance that refer to AESIs. The MHRA, as well as several other international organisations, are developing a list of AESIs for COVID-19 vaccines, and (aside from the expected signal detection of *any* ADRs to detect potential new risks) **we request adoption of a list of AESIs[3] for targeted pharmacovigilance**. The following list should be adopted, but you should also consider international work in this area, including standardised case definitions. This is in additional to any potential risks identified in the safety specification. As well the conduct of 'observed vs expected' analyses (see below), **we require targeted follow up of such events**:

COVID disease enhancement
Sudden death (all ages, inc. SIDS)
Guillain-Barré syndrome, and other peripheral and polyneuropathies
Multiple sclerosis, transverse myelitis and other demyelinating disorders
Optic neuritis
Encephalitis (inc. ADEM)
Myasthenia gravis
Bell's palsy
Seizure disorders (inc. febrile)
Myocardial infarction

Myo/pericarditis

Stroke and other cerebrovascular events
Venous thromboembolism
Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia
Rheumatoid arthritis, polyarthritis
Autoimmune thyroiditis
Chronic Fatigue Syndrome/ME/PVFS
Fibromyalgia
Post Orthostatic Tachycardia Syndrome
Narcolepsy
Paediatric inflammatory multisystem syndrome (or otherwise a recent definition condition associated with COVID in children and adolescents)
Kawasaki syndrome

Pregnant women – pre-term labour, stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or neonatal

[3] AESIs should not necessarily be considered as l kely, potential or anticipated side effects of any candidate COVID-19 vaccines – the proposed endpoints are for planning purpose to guide study design and are based on past associations, whether causal or not, with unrelated vaccines (and therefore with no plausible reason to suspect any association with COVID-19 vaccines) or are conditions that we expect to occur naturally in the absence of vaccination

renal failure, chorioamnionitis, major structural congenital malformations, all serious events that can occur naturally in pregnancy

6.f. **We request that batch-specific surveillance** should be undertaken in accordance with the principles outlined in section P.I.B.5 of the EU GVP vaccines guidance.

6.g. **We request a regular (e.g. two-weekly) video/telecon with the MA holder** to discuss the sPSUR content, ongoing observed vs expected (O/E) analysis of adverse events of special interest (AESIs), and any other emerging safety data and signals.

These additional activities should be described in the RMP.

Post-Authorisation Safety Studies (PASS) And Post-Authorisation Efficacy Studies (PAES)

7. We may require other additional pharmacovigilance activities depending on the 'safety specification' and product-specific characteristics. These should be considered in the context of the pandemic scenario, available data sources and the practicality of implementing such measures.

8. The requirement for a post-authorisation safety studies (PASS) study requires proactive consideration, and potential applicants encouraged to engage in early discussions with the MHRA. However, we anticipate that several 'generic' AESIs (such the potential for COVID disease enhancement, potential for multi-system inflammatory syndrome, and potential for neuroinflammatory and demyelinating disorders), and any potential product-specific risks, will require more than routine pharmacovigilance or 'observed vs expected' analysis.

9. PASS may involve a formal epidemiology study, but may also include proposals for active surveillance of AESIs based on use of electronic healthcare record data.

10. Standard forms of active surveillance may also be considered (i.e. recruitment and active follow up of vaccinees), but if the probable size of any such cohort is unlikely to be of value in identifying or characterising rare events (over and above the power of the pre-authorisation trials to characterise such risks), then such approaches may be of less value than approaches based on large electronic healthcare datasets.

11. The requirement for a PAES study will also require active consideration, and manufacturers should be encouraged to engage in early discussions with the MHRA. If not already part of the product development plan, applicants should consider proposals for evaluation of long-term immunogenicity and efficacy (inc. breakthrough COVID), and ability to prevent acquisition, carriage and transmission of virus.

12. If a well-designed and feasible PASS or PAES study in a non-UK territory is proposed, we may consider accepting that in fulfilment of a UK RMP.

Risk Minimisation Measures

13. In relation to risk minimisation measures, the Summary of Product Characteristics and the Patient Information Leaflet may be the most useful channels of communication from the manufacturers to healthcare professionals and vaccinees for COVID-19 vaccines. **To facilitate the traceability of individual products in the reporting of adverse events, the manufacturers should ensure that information on the batch (such as sticky labels), are made available to health professionals in a form that can be shared with vaccinees**.

14. However, given that the relevant national public health authorities will be actively co-ordinating all NHS and public-facing communications relating to a COVID-19 vaccine programme, we will not, by default, require additional risk minimisation material particularly is this can be achieved via communications from the MHRA or other relevant national public health authorities. Any additional risk minimisation material will be considered on a case by case basis.

CONCLUSIONS

This guidance provides the 'core' requirements which all applicants should adhere to. However, there may be additional requirements for individual applicants based on the safety specification and characteristics of individual products, particularly in relation to the need for evaluation of specific AESIs, and the requirements for post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES).

We encourage early and active engagement with MHRA on product-specific requirements for the RMP [redacted] Vigilance and Risk Management of Medicines, MHRA, [redacted]