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Reflection paper on lessons learned from the COVID-19 pandemic: Scientific considerations on non-clinical aspects

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List of Abbreviations

ERA	Environmental risk assessment
ERD	Enhanced respiratory disease
ETF	EMA Emergency Task Force
FIH	First-in-human
GLP	Good laboratory practice
GMOs	Genetically modified organisms
GMP	Good manufacturing practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
ICSRs	Individual case safety reports
LNP	Lipid nanoparticles
MAA	Marketing authorisation application
mAbs	Monoclonal antibodies
MERS	Middle East Respiratory Syndrome-virus
NCAs	National competent authorities
NcWP	Non-clinical working party
NHPs	Non-human primates
RDT	Repeat dose toxicity
RSV	Respiratory Syncytial Virus
SARS-CoV-2	Severe acute respiratory virus, coronavirus 2
TRS	WHO Technical Report Series
WHO	World Health Organisation

1. Introduction

The global COVID-19 pandemic resulted in a rapid, highly focused shift of resources to develop effective and safe vaccines or treatments against infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for both adult and special populations such as elderly and paediatric subjects. From an organisational perspective, this required prioritisation of procedures at National Competent Authorities (NCAs). The pandemic also influenced how non-clinical data sets were used to support clinical trials and marketing authorisations. While the strategies outlined in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for evaluating non-clinical safety and efficacy remained applicable, the expedited evaluation (rolling review) and authorisation of novel products, or existing products with new coronavirus disease 2019 (COVID-19) related indications, posed a unique challenge. When scientifically justified, and without compromising patient safety, deviations from non-clinical guidelines were accepted.

This reflection paper does not contain explicit guidance on which non-clinical targeted approaches are most suitable in a pandemic situation. Rather, it aims to reflect on lessons learned that could be used to improve the efficiency of non-clinical development and regulatory interaction, particularly in potential future pandemic or emergency settings. For general considerations on lessons learned for clinical trials in public health emergencies the 'Report of the EMA/ETF workshop on Lessons Learned on Clinical Trials in Public Health Emergencies' (EMA/340269/2023) of the EMA Emergency Task Force (ETF) can be referred to. Regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 (including quality requirements) were also published (EMA/117973/2021).

2. Scope

This reflection paper covers SARS-CoV-2 vaccines and medicinal products intended to prevent or treat COVID-19 and its complications. It focuses on the experiences gained during the pandemic and the resulting non-clinical scientific considerations for pivotal, non-clinical data used to support clinical development and marketing authorisation without jeopardising patient safety. Procedural regulatory aspects are not in scope of this document.

3. Non-clinical requirements to develop medicinal products including vaccines in current practice

Non-clinical requirements for the development of therapeutic molecules are based on generating efficacy and safety data to support their administration to human volunteers or patients. These requirements are globally harmonised through ICH guidances. The core non-clinical ICH guideline, M3(R2), outlines the non-clinical data recommendations for each clinical trial phase. In addition, other ICH guidances on the evaluation of specific non-clinical safety endpoints should be considered (e.g. ICH S6(R1)). In general, deferring the evaluation of safety endpoints until a later phase clinical development is not accepted.

For the development of vaccines, in addition to ICH and product-specific regional guidance, the World Health Organisation (WHO) provides general guidance in Technical Report Series (TRS) No 927, Annex 1 (2005), TRS No 987, Annex 2 (2014) and TRS No1039, Annex 3 (2022). Here, the same principle applies i.e. that specific safety data are generally required before progressing to a next phase of (clinical) vaccine development.

4. Non-clinical safety in the COVID-19 pandemic setting

While at the end of the pandemic novel molecules started to be developed, the acceleration of drug and vaccine development during the pandemic was based around two principal concepts:

- Leveraging pre-existing technologies in order to rapidly progress from early development into late clinical development (e.g., use of (mRNA) platform technology to develop vaccines, or to generate monoclonal antibodies against SARS-CoV-2 spike proteins).
- Repurposing existing small molecule therapies based on the potential to treat COVID-19, including prophylactic treatment to prevent SARS-CoV-2 infection.

In line with the WHO TRS No. 1039, Annex 3 (2022), platform technologies are defined as those cases where: (a) the manufacturing methods of a drug are essentially unchanged (but may be optimised for each specific candidate); (b) the test methods (except for identity, potency and stability) and quality acceptance criteria of the molecule are unchanged; (c) the immunomodulatory compounds or elements of the molecule are unchanged; and (d) compliance with good manufacturing practice (GMP) is unchanged.

Several of the SARS-CoV-2 vaccines (especially the mRNA and viral vector vaccines) were based on such established platform technologies, with multiple platform-based repeat dose toxicity (RDT) studies already available.

For example, RDT studies with products belonging to the same mRNA platform (i.e. similar mRNA, only differing in coding sequence for the target antigen, packed in similar lipid nano particles (LNP)) resulted in comparable risk profiles. Adverse findings were anticipated immune-related effects primarily induced by the lipid carrier, rather than the mRNA (Schilder 2023).

Platform data or well-characterised precursor safety data could be leveraged to speed up clinical trial development, although differences have been observed in the amount of pre-existing data available for products developed for the prevention or treatment of COVID-19. Non-clinical toxicology data and clinical data of these platform products were used to support the first in human (FIH) clinical trial application in the absence of product-specific data. This was possible provided that comparability between the novel product and the pre-existing product was sufficiently demonstrated. Similarly, for products other than vaccines with a high level of non-clinical characterisation, such as existing products redeveloped for a novel indication or products based on previously developed platforms, new non-clinical safety data to support later clinical development as specified in ICH M3(R2) were not required if adequately justified. In these cases, non-clinical studies could be waived if previous study data and the weight of evidence sufficiently addressed specific risks. Genotoxicity and reproductive toxicity, as well as safety testing in a second species, could be deferred to a later stage. These studies were expected before submitting a marketing authorisation application (MAA).

4.1. Vaccines and platform data

Early discussions at a global level led to a clear and shared regulatory view on the minimum non-clinical data needed to establish efficacy and safety to support the initiation of FIH studies and further clinical development with SARS-CoV-2 vaccines.

Regarding the minimum non-clinical proof-of-concept data to support a FIH trial, there was global agreement (First International Coalition of Medicines Regulatory Authorities (ICMRA) meeting, March 2020) that immunogenicity data in an appropriate animal model should be available. Information on particular features related to the virus family was carefully reviewed. Vaccine associated enhanced respiratory disease (ERD) had previously been identified in Respiratory Syncytial Virus (RSV)vaccine

development and was also acknowledged during SARS/MERS (Middle East Respiratory Syndrome-virus) vaccine development. Therefore, demonstration of a functional humoral immune response (neutralising antibody titer) and Th1-biased T-cell immune response was required before initiating FIH trials with SARS-CoV-2 vaccines. Later in development, and preferably before initiating phase III studies, *in vivo* data from the vaccine candidate in an animal challenge model were expected to further demonstrate the lack of ERD (Second ICMRA meeting, June 2020). This strategy to stagger data requirements on potential ERD risk ensured an optimal balance between speedy access and risk mitigation.

Both biodistribution and repeat-dose toxicity platform studies were received for mRNA and viral vector-based vaccine clinical trial applications. However, a general European statement on the regulatory acceptance of such data for marketing authorisation was never issued. This may have created uncertainty about whether product-specific RDT and local toxicity data would be needed for MAA if sufficient platform data were available, or if such studies could be deferred or even waived. Ultimately, for each of the authorised vaccines, product-specific RDT studies of the SARS-CoV-2 vaccine candidates were completed in parallel to the clinical development during the COVID-19 pandemic. None of these studies revealed novel findings compared to the existing platform safety data. In addition, product-specific good laboratory practice (GLP)-compliant studies on reproduction and development were provided. Similar to the RDT studies, the developmental and reproductive toxicity studies did not reveal toxicities of concern (Schilder 2023).

With respect to environmental risk assessment (ERA), a temporary deferral from the mandatory ERA was issued in the EU for vaccines containing genetically modified organisms (GMOs) to accelerate clinical trial application. However, an ERA was required for all SARS-CoV-2 vaccines containing GMOs prior to marketing approval.

4.2. Therapeutic monoclonal antibodies

Several monoclonal antibodies (mAbs) were developed to prevent or treat COVID-19 in patients. For therapies targeting regions of the SARS-CoV-2 spike protein, proof-of-concept *in vivo* studies showed highly effective and dose proportional neutralisation of SARS-CoV-2 virus. Pharmacokinetic profiles were typical of IgG antibodies, with long half-lives. Safety data for mAbs against viral, i.e. exogenous targets, were generally generated in a single RDT study. Our review of scientific advices for mAbs against exogenous targets, evidenced that the use of non-human primates (NHPs) was not recommended unless adequately justified. In other cases, it was agreed to use rodents for a single RDT. However, for mAbs directed against the spike protein that received marketing authorisation, NHPs were used in the GLP-compliant RDT studies. The justification of the applicant for selecting this species was often not clear and may have been to satisfy regulatory requirements outside the EU in view of a global clinical development. No direct test-article related adverse effects were observed for any antibody at any dose level in these studies.

In addition, existing mAbs directed against pro-inflammatory cytokines were also being repurposed to be used in COVID-19. Non-clinical data for these products were therefore already available.

4.3. Small molecule therapeutics

A review of applications for medicinal products to treat COVID-19 and its complications revealed that, in most instances, the molecules had already been developed or marketed for indications other than COVID-19 treatment.

No specific deviations from ICH M3(R2) for small molecules (i.e. not falling under ICH S6) were identified in this review. Since the vast majority of products were developed for other indications, a

non-clinical data package was already available, either to support clinical trials or marketing authorisation. Some non-clinical data gaps were related to pharmacodynamics and pharmacokinetics, considering the newly added COVID-19 indication or the (new) route of administration. While the provision of missing *in vivo* genotoxicity data and the conduct of DART studies were considered mandatory, it was accepted that these could be deferred to a later stage of clinical development for the COVID-19 treatment. However, it should be noted that most of the applications were withdrawn after scientific advice or during the clinical trial phases, due to lack of efficacy against COVID-19, or end of the pandemic situation. No safety concerns were identified based on pre-existing non-clinical data nor by deferring missing data to a later time.

While several drugs or drug candidates were repurposed to treat COVID-19, no new small molecules were developed specifically for a COVID-19 exclusive target and reached a marketing authorisation. During the pandemic, only two antiviral products, originally in early development for other indications, but later repurposed for COVID-19, demonstrated a positive benefit-risk profile and were granted marketing authorisation in the EU, namely nirmatrelvir and remdesivir.

5. Identification of novel safety issues based on non-clinical data in clinical trials and after MAA

Data from *in vitro* studies as well as animal studies supported progression to clinical development and were adequate to support a MAA. The non-clinical studies generally suggested a favourable safety profile with few, if any, adverse findings.

The EU report on pharmacovigilance tasks shows that during 2021 and 2022 the EU database of suspected adverse drug reactions, EudraVigilance, received 2.8 million individual case safety reports (ICSRs) related to SARS-CoV-2 vaccines (EMA, 2023).

The vast majority of the side effects of SARS-CoV-2 vaccines were mild or moderate, appeared soon after vaccination, and were short-lived. These were all likely the result of the anticipated induction of an immune response and thus not considered adverse. Rare or very rare side effects that had not emerged during the clinical development were quickly detected, assessed and acted upon. Pharmacovigilance activities around monoclonal antibodies and small molecules have also not suggested unanticipated or serious adverse drug reactions requiring label changes. None of the novel, rare adverse reactions reported for SARS-CoV-2 vaccines were observed in, nor could have been anticipated based on, animal data. In addition, animal studies are generally not powered or designed to identify such rare adverse reactions. Thus, neither a change in the nature (e.g. platform data), or timing of submission of non-clinical data negatively affected clinical safety or the benefit/risk profile of a SARS-CoV-2 related vaccine.

6. Lessons learned that can be extrapolated to future pandemic settings

The global pandemic resulted in a drastic but temporary shift in regulatory processes and requirements with respect to generating non-clinical efficacy and safety data to accelerate the support of clinical trial applications and marketing authorisation applications. The rolling review procedure and the possibility to defer certain non-clinical studies to a later stage in drug development, coupled with the availability of pre-existing platform technologies and associated platform data, allowed for the rapid deployment of safe and effective prevention and treatment options for SARS-CoV-2 infection and related COVID-19. The following lessons can be drawn to facilitate efficient and rapid non-clinical development and safety assessment in the future:

1. The use of platform data to establish the safety profile of an emergency therapy is accepted from a regulatory perspective and allows for deferred submission of product-specific data (if considered necessary; see point 2 below) before MAA.

2. An aligned, global view on the need for, and timing of, product-specific data to supplement platform data is required. It should be noted that product-specific safety studies thus far did not reveal novel findings of clinical concern, other than those already known. In the future, applicants are encouraged to submit a weight-of-evidence assessment to justify whether further animal studies (such as general toxicity or developmental toxicity) are needed. This will be evaluated on a case-by-case basis by regulatory authorities.

3. For vaccines with well characterised platform data, repeat dose toxicity studies are not needed to support FIH studies.

4. Existing globally harmonised guidance should be followed and can be leveraged to optimise non-clinical drug development. When a new molecule is developed in an emergency setting, a non-clinical package in accordance with ICH M3(R2) or ICH S6(R1) would typically be expected before the FIH study. All deviations from ICH M3(R2) or ICH S6(R1) would then be assessed on a case-by-case basis.

5. The scientific basis to select a non-rodent test species to evaluate the safety of a biological molecule binding to an exogenous target is limited and should only be accepted if adequately justified. Furthermore, the pharmacokinetic profile of IgG antibodies is well known, particularly when dosed at levels that do not undergo target-mediated drug disposition. Therefore, if possible and if RDT assessment is necessary, it is preferred to use a rodent species. In line with ICH S6(R1), the duration of such a RDT study does not have to extend beyond 2 weeks, thus limiting the confounding effects of immunogenicity.

7. Future Perspectives

Parallels could be drawn from the experiences outlined above between products developed during the pandemic and products being developed for other emergency settings with regard to the non-clinical testing strategy. Streamlined non-clinical data packages, where pre-existing data is leveraged, or additional data is deferred to later timepoints could be considered as long as safety for the target patient population is not threatened. Regulatory acceptability of such an approach should further be explored dependent on the respective indication.

8. References

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