EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Development and authorisation status of Covid-19 vaccines

Webinar: ENCePP in the Time of Covid

20 November 2020

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EMA pandemic task force

- Exploratory review of current investigational products for treatment or prevention of Emergent disease including TCs with developers.
- identify the most appropriate regulatory pathway to ensure that potential treatments and/or vaccines are approved/made available as swiftly as possible.
- Rapid scientific advice on questions from manufacturers on their development plans, endorsed by CHMP
- Interaction with academia or sponsors/investigators of clinical trials not funded by industry

Inventory of rapid procedures

Development support

- Rapid scientific advice
- Rapid agreement of a paediatric investigation plan and rapid compliance check

Evaluation (initial authorisation & post-authorisation)

- Rolling review
- accelerated assessment for Marketing authorisation, Extension of indication
- Compassionate Use/support to Emergency Use

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4 May 2020
EMA/213341/2020

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

The European Medicines Agency (EMA) together with the responsible scientific committees and their working parties, and in collaboration with the European Commission, operates rapid procedures to support the development and evaluation of treatments and vaccines for COVID-19. The EMA emerging health threats plan foresees that detailed procedures are set-up to adapt different types of review activities to the needs of the health threat/crisis situation. Whilst respecting the regulatory requirements and established review principles (e.g. independence of experts), these procedures aim, within timelines that are appropriate for the public health emergency situation, to provide most efficient management of product-review activities leading to scientifically sound and robust outcomes.

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines

Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

Scope (at least one):

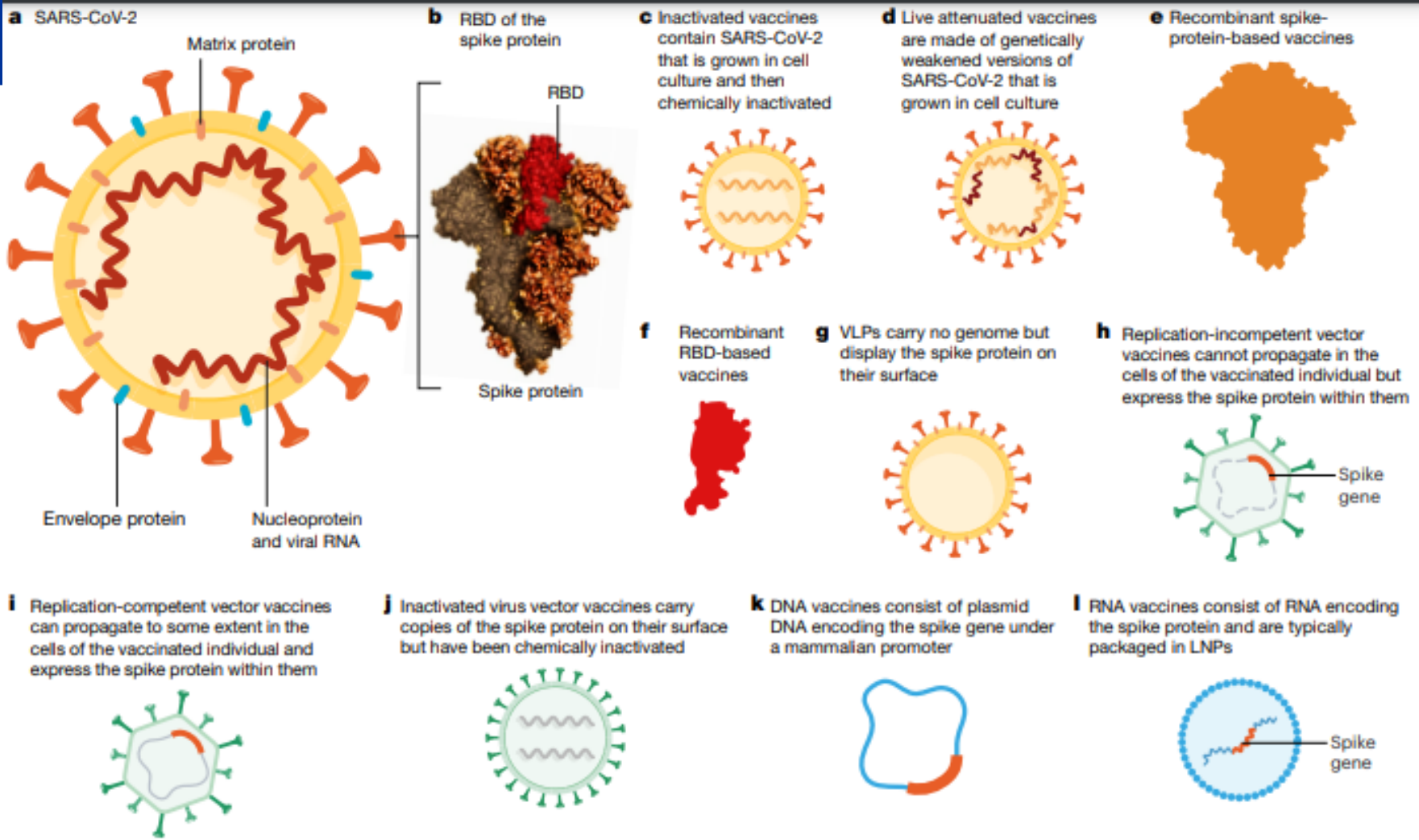
- for **seriously debilitating diseases or life-threatening diseases**;
- to be used **in emergency situations**;
- **orphan** medicinal products.

Criteria (all):

- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health **of the immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

'**unmet medical needs**' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

Regulation (EC) No 507/2006


a SARS-CoV-2
Matrix protein
Envelope protein
Nucleoprotein and viral RNA
b RBD of the spike protein
RBD
Spike protein
c Inactivated vaccines contain SARS-CoV-2 that is grown in cell culture and then chemically inactivated
d Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture
e Recombinant spike-protein-based vaccines
f Recombinant RBD-based vaccines
g VLPs carry no genome but display the spike protein on their surface
h Replication-incompetent vector vaccines cannot propagate in the cells of the vaccinated individual but express the spike protein within them
Spike gene
i Replication-competent vector vaccines can propagate to some extent in the cells of the vaccinated individual and express the spike protein within them
j Inactivated virus vector vaccines carry copies of the spike protein on their surface but have been chemically inactivated
k DNA vaccines consist of plasmid DNA encoding the spike gene under a mammalian promoter
l RNA vaccines consist of RNA encoding the spike protein and are typically packaged in LNPs
Spike gene

Compressed vaccine development plans

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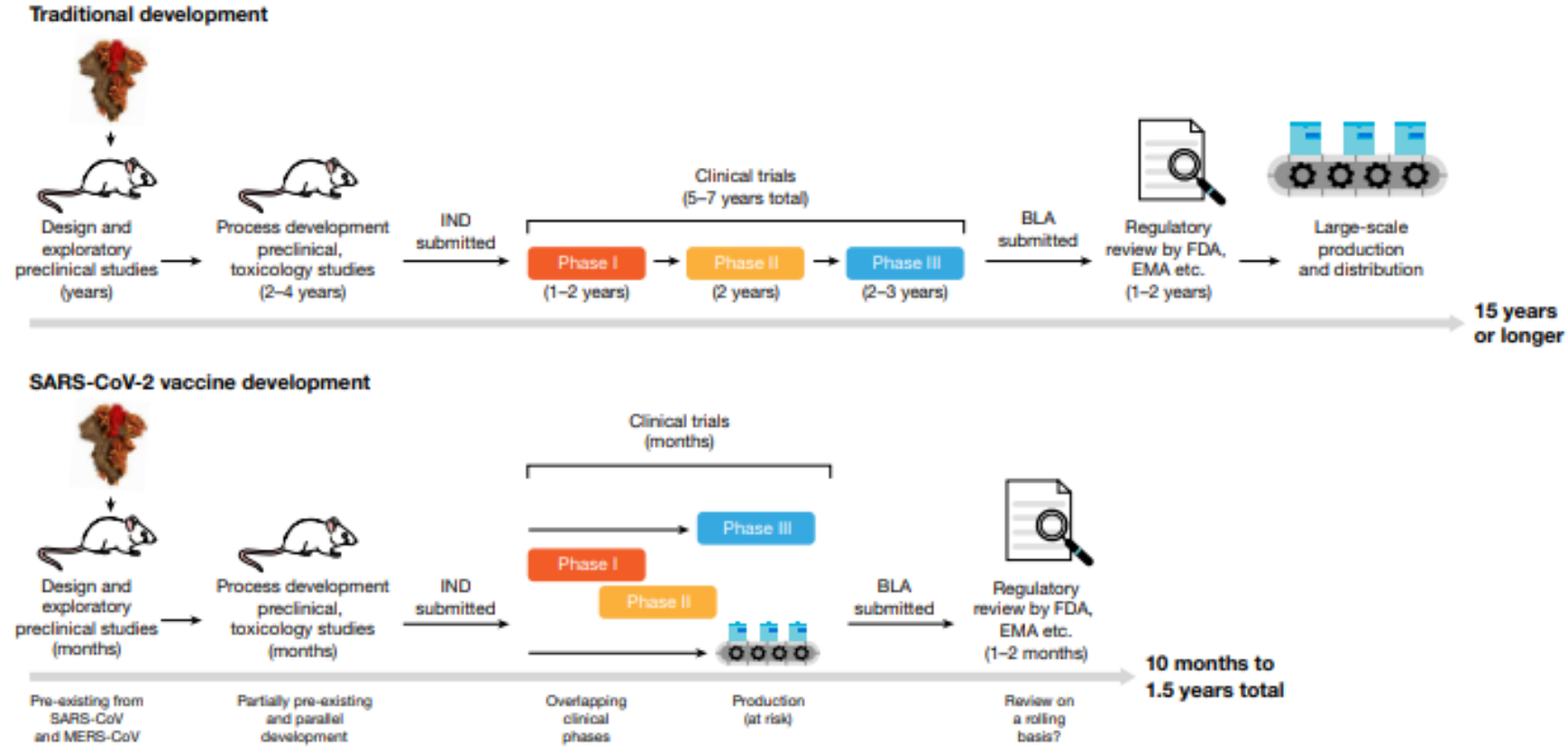

Krammer, F. SARS-CoV-2 vaccines in development. *Nature* **586,** 516–527 (2020). https://doi.org/10.1038/s41586-020-2798-3

Table 2 | Overview of phase I/II results

Company (reference)	Vaccine (type)	Dose range (route)	Neut. titre after prime	Neut. titre after boost	T cell response	Trial registration number
Sinovac[35]	CoronaVac (inactivated SARS-CoV-2 + aluminium hydroxide)	3–6 μg (i.m.) 2× (day 0 and 14 (0/14) or 0/28)	ND	1:30–1:60 range[a]	ND	NCT04352608
Sinopharm[40]	Inactivated whole virus COVID-19 vaccine (inactivated SARS-CoV-2 + aluminium hydroxide)	2.5, 5 or 10 μg (i.m.) 3× (0/28/56) 5 μg (i.m.) 2× (0/14 or 0/21)	Not reported in detail	1:316 (2.5 μg, 0/28/58)[b], 1:206 (5 μg, 0/28/58)[b], 1:297 (10 μg, 0/28/58)[b], 1:121 (5 μg, 0/14)[b], 1:247 (5 μg, 0/21)[b]	ND	ChiCTR2000031809
CanSino[36]	Ad5 nCoV (non-replicating AdV5 expressing spike protein)	5×10^{10}, 10^{11} VP (i.m.)	1:18.3–1:19.5 range[c]	NA	Yes	NCT04341389
AstraZeneca[47]	ChAdOx1 nCoV-19 (non-replicating chimpanzee AdV expressing spike protein)	5×10^{10} VP 1× or 2× (i.m.)	Median 1:218[b] Median 1:51[d] Range 1:4–1:16[e]	Median 1:136[d] Median 1:29[d]	Yes	NCT04324606
Moderna[59]	mRNA-1273 (mRNA expressing spike protein)	2× 25, 100, 250 μg (i.m.)	Low	1:112.3 (25 μg)[f], 1:343.8 (100 μg)[f], 1:332.2 (250 μg)[f], 1:339.7 (25 μg)[g], 1:654.3 (100 μg)[g]	Good $CD4^+$ and low $CD8^+$ response	NCT04283461
Pfizer[60]	BNT162b1 (mRNA expressing a trimeric RBD)	2× 10, 30, 100 μg (i.m.)	Low	1:180 (10 μg)[h], 1:437 (30 μg)[h]	ND	NCT04368728
Pfizer[61]	BNT162b1 (mRNA expressing a trimeric RBD) and BNT162b2 (mRNA expressing spike protein)	2× 10, 20, 30 μg	Low	Day 28[h] BNT126b1 (18–55 years): 1:168 (10 μg), 1:267 (30 μg) BNT126b1 (65–85 years): 1:37 (10 μg), 1:179 (20 μg), 1:101 (30 μg) BNT126b2 (18–55 years): 1:157 (10 μg), 1:363 (20 μg), 1:361 (30 μg) BNT126b2 (65–85 years): 1:84 (20 μg), 1:147 (30 μg)	ND	NCT04368728
Novavax[62]	NVX CoV2373 (Matrix-M) spike protein 'rosettes'	2× 2.5–25 μg (i.m. ± Matrix-M) 1× 25 μg (i.m. + Matrix-M)	1:128 (25 μg + Matrix-M)[i]	1:3,906 (5 μg + Matrix-M)[i], 1:3,305 (25 μg + Matrix-M)[i], 1:41 (25 μg unadjuvanted)[i]	$CD4^+$	NCT04368988

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Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints

- *Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group*
- *Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%*
- *Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved*
- *Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%*

moderna

Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study

November 16, 2020

First interim analysis included 95 participants with confirmed cases of COVID-19

Phase 3 study met statistical criteria with a vaccine efficacy of 94.5% (p <0.0001)

Moderna intends to submit for an Emergency Use Authorization (EUA) with U.S. FDA in the coming weeks and expects the EUA to be based on the final analysis of 151 cases and a median follow-up of more than 2 months

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 16, 2020-- Moderna, Inc. (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that the independent, NIH-appointed Data Safety Monitoring Board (DSMB) for the Phase 3 study of mRNA-1273, its vaccine candidate against COVID-19, has informed Moderna that the trial has met the statistical criteria pre-specified in the study protocol for efficacy, with a vaccine efficacy of 94.5%. This study, known as the COVE study, enrolled more than 30,000 participants in the U.S. and is being conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services.

The primary endpoint of the Phase 3 COVE study is based on the analysis of COVID-19 cases confirmed and adjudicated starting two weeks following the second dose of vaccine. This first interim analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% (p <0.0001).

A secondary endpoint analyzed severe cases of COVID-19 and included 11 severe cases (as defined in the study protocol) in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group.

Vaccines development summary (from US Warp Speed)

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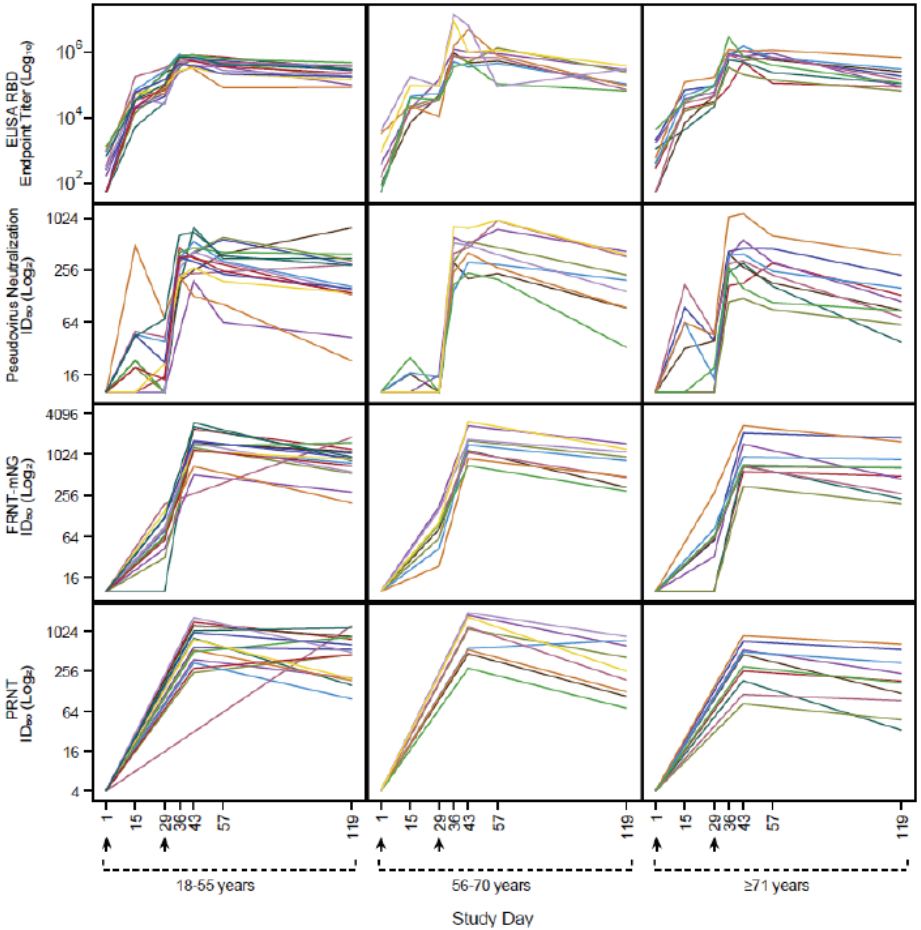
Status

mRNA	Non Replicating Vectors	Protein Adjuvanted	Live Attenuated
Moderna	AstraZeneca/Oxford U	Novavax	TBD
Pfizer/BioNtech	Janssen	Sanofi/GSK	
+ / −	+ / −	+ / −	+ / −
Speed	Speed	Speed	Speed
Efficacy	Efficacy	Efficacy	Efficacy
Cost/Capacity	Cost/Capacity	Significant human experience	Cost/Capacity
Cold chain	One dose potential	Cold Chain	One dose potential
Safety (lack of experience)	Cold chain	Safety in pediatrics	Oral
	Safety (lack of experience)		Safety

Moderna mRNA vaccine - immune response after 3 months



Evidence from Phase III Clinical trials

- Prevention against symptomatic COVID 19 disease of any severity is an acceptable primary endpoint – other secondary endpoints related to prevention of severe disease and infection

- Studies don't have to be powered for subgroups such as age, but inclusion of elderly, encouraged if posology adequate. Co-morbidities and minorities to be considered. Primary analysis should be in the seronegative at baseline

- Not possible to define precise criteria for vaccine success but recognizing value of adequately powered studies, e.g. assuming LB of 95% CI above 20-30% for VE of 50-60%

- Successful Interim Analysis above 20-30% and with point estimate of e.g. 70% could support regulatory decisions such as CMA

Clinical safety and efficacy

- For a CMA a clinical safety database in the order of thousands of subjects followed up for at least 6 weeks would be sufficient
- Longer term follow-up is relevant for both safety and efficacy and studies should continue after reaching primary endpoint, e.g. occurrence of ADE once antibodies decay
- Rare adverse reactions occurring with a frequency of less than 1/1000 cannot likely be defined in the context of the pre-approval clinical trials and will require post-approval surveillance studies
- Long term protection and immunogenicity data post-approval will inform the need and timing of booster doses

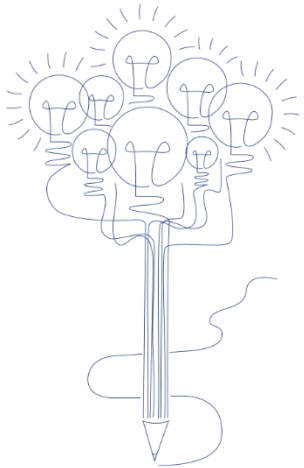
ICMRA COVID-related activities

ICMRA, the hub of international collaboration on COVID-19

- COVID-19 Statements
- Technical meetings (18 March, 2, 6 April, 19 May, 22 June)
  - Vaccines (First in Human regulatory requirements, design of Phase III studies)
  - Trials and treatments
  - Observational Studies and RWE
  - Working group(s) being set up for international agreement on vaccines, priority trials, etc.
- bi-weekly Policy meetings

- EMA holds cluster TCs with FDA, HC, MHRA, SwMed and WHO

Summary



39 vaccines identified for interaction with EMA

Rapid scientific advice proceeding for advanced vaccines and therapeutics (30 completed – more than 21 in the pipeline)

Rolling Review started for 3 vaccines and at least other 3 possibly coming soon

Results from large vaccines trials are coming – Biontech/Pfizerand Moderna results look promising but we need careful assessment

Reflection paper drafted by ETF on COVID-19 vaccines

Importance of continuation of trials long term and surveillance post-approval

Thank you for your attention

Further information

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