mRNA vaccines: EMA and FDA regulations for gene therapy products

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Summary
The anti-Covid mRNA vaccines are not subject to biodistribution and excretion studies and this according to the regulations of the health agencies.
The European regulation is very vague.
The same product may or may not be classified as a gene product depending on whether or not it is qualified as a vaccine against an infectious disease.
In the latter case, it may be exempted from these studies.
This regulation is not justified from a scientific or ethical point of view.

Definition of pharmacokinetics: the action of the body on a drug, i.e., the fate of the drug from the time it enters the body to the time it leaves the body, the time course of its absorption, bioavailability, distribution, metabolism and excretion.

It may be useful to discuss the regulations concerning pharmacokinetic studies for mRNA vaccines:

European regulation
These are very vague and contradictory [1].
Indeed, according to the European Union (EU) legislation, RNA-based drugs can currently be classified in different regulatory statuses, depending, for vaccines, on their target (infectious disease or not) and, for other drugs, on the way they are obtained (chemically or biologically). This classification determines the controls and studies that must be carried out to obtain marketing authorizations. Thus, mRNA vaccines against infectious diseases are not classified as gene therapy products, whereas mRNA vaccines for the treatment of cancers are GTMPs (Gene therapy medicinal products which are part of ATMPs, advanced therapeutic medicinal products), in fact mRNAs are GTMPs according to the CAT (Committee for Advanced Therapies) and must therefore undergo complete pharmacokinetic studies [2].
Pharmacokinetic studies are not required for vaccines in general except when new excipients or formulation or antigens are used, which is the case here.
According to the TGA [3], no absorption studies have been performed for BNT162b2, which is acceptable according to WHO and EMA guidelines (WHO, 2005; EMA, 1998) [4].

It should also be noted that according to the EMA and without any scientific justification, vaccines against infectious diseases cannot in any case be considered as gene therapies [5].

However, according to the EMA, Covid vaccines also require biodistribution studies to know which organs and tissues are affected after the injection, for how long and if this causes toxicity [6].

According to the EMA repeated dose toxicity studies are required when biodistribution after a single dose suggests concentration in certain tissues or organs [7].

US regulations
According to FDA guidelines, gene therapy is defined in the United States as: *"a medical intervention based on modification of the genetic material of living cells. Cells may be modified ex vivo for subsequent administration to humans or may be altered in vivo by gene therapy given directly to the subject. When the genetic manipulation is performed ex vivo on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight"* [8].
The U.S. definition refers only to the possibility of using recombinant DNA, whereas the European

definition refers to the use of recombinant nucleic acid (which can therefore refer to both DNA and RNA). Thus, in the United States, mRNA technologies should not be considered as gene therapy.

Why are mRNA vaccines excluded from the regulation of gene products?
According to Guerriaud and Kohli [1], it is difficult to answer with certainty why vaccines against infectious diseases have been excluded. The definition [of vaccines] has not changed since 1975, a time when there was no "vaccine" against cancer [2].

However, the exclusion text in the more recent GTMPs definition specifies "vaccines against infectious diseases" and not just "vaccines." In the same spirit, the definition of vaccines given by the European pharmacopeia, provides that a vaccine produces active immunity in man against an infectious agent [9]. Two other explanations concerning public health could explain the special place of vaccines against infectious pathogens. The first relates to the target population: a very large healthy population, mostly including children. The second, which is a consequence of the first, is the specific regulation of vaccines, adapted to this mass use of a drug in a population. Let us mention the possibility, given by Article 114 of the consolidated Directive 2001/83/EC [2], for a Member State, in the interest of public health ("immunological medicinal products used in public health immunization programs"), to require the holder of an authorization for marketing to "submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory" (OMCL). The competent authorities issue a "Batch Release Certificate" when the results are satisfactory. This is known as "Official Control Authority Batch Release" (OCABR). In conclusion, it is clear that the specification "against infectious diseases" is especially important as vaccines that induce immunity to an infectious disease are excluded from GTMP scope, while mRNA-based "therapeutic vaccines" which are directly injected and induce immunity to a non-infectious disease will be considered as GTMPs."

One could object to these public health justifications that precisely a product intended for a majority of the world's healthy population should be subject to more stringent regulation than a gene therapy product intended for a few people suffering from a rare disease or cancer (this time concerning millions of people).

References

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[2] 28.11.2001 EN Official Journal of the European Communities L 311/67
DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use
ANNEX I
ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS FOR THE TESTING OF MEDICINAL PRODUCTS
Pharmacokinetics
The following pharmacokinetic characteristics should be described: absorption (rate and intensity), distribution, metabolism, excretion.
(13) Advanced therapy medicinal products should be subject to the same regulatory principles as other types of biotechnology medicinal products. However, the technical requirements, in particular the type and amount of qualitative, pre-clinical and clinical data needed to demonstrate the quality, safety and

efficacy of the product, may be very specific. While these requirements are already defined in Annex I of Directive 2001/83/EC for gene therapy medicinal products and somatic cell therapy medicinal products, they must be established for tissue engineered products.
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF
REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007
on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

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https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-preclinical-pharmacological-toxicological-testing-vaccines_en.pdf
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