Failure by US FDA to Require Environmental Assessments

Invalidates BLA approvals of Covid-19 modRNA products

Under Code of Federal Regulations Title 21 applicants for a Biologics License Application (BLA) are required to submit an Environmental Assessment (EA) pursuant to section 25.15:

> (a) All applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion. A claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that to the applicant's knowledge, no extraordinary circumstances exist. Failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in § 25.20, unless the agency can determine that the action qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, 25.34, or 25.35 is sufficient grounds for FDA to refuse to file or approve the application or petition. An EA adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment.

The BLAs of Pfizer and Moderna sought categorical exclusion from submitting EAs by invoking section 25.31.

The FDA's Summary Basis for Regulatory Action in respect of Pfizer, dated 8 November 2021, states at page 14:

> **f. Environmental Assessment**
>
> The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

The FDA's Summary Basis for Regulatory Action in respect of Moderna, dated 30 January 2022, states at page 13:

> **f. Environmental Assessment**
>
> The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

The only[1] parts of section 25.31 possibly available to Pfizer and Moderna to seek categorical exclusion read (emphasis added):

> The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:
>
> (a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, **if the action does not increase the use of the active moiety**.
>
> (c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, **for substances that occur naturally in the environment** when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

In respect of section 25.31(a) and increased use of the active moiety, FDA guidance[2] states (in part; emphasis added):

> Increased use of an active moiety may occur if the drug will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, **or if the drug is a new molecular entity**.
>
> Attachment A contains examples of actions that would not be considered to increase the use of a drug and Attachment B contains examples of actions that would be considered to increase the use of a drug or biologic.

Attachment B states (in part):

> The following are types of actions that are considered to result in increased use of an active moiety if approved by the Agency:
>
> - New molecular entities.

Pfizer and Moderna submitted Investigational New Drug Applications (INDs) for products containing patented and novel modRNAs as new molecular entities, as a consequence the categorical exclusion under section 25.31(a) was not available to either sponsor.

In respect of section 25.31(c), and it can be first noted the modified RNA contained within the Pfizer and Moderna Covid-19 products does not occur naturally in the environment.

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[1] FDA *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications*, page 3: 'BLAs should be evaluated for whether they are eligible for categorical exclusion using 21 CFR 25.31(a) or (c)'
[2] Ibid.

FDA guidance[3] in respect of gene therapies[4], vectored vaccines, and related recombinant viral or microbial products (GTVVs) goes into further detail:

> Specifically, a GTVV that includes functional protein-coding sequences from a genus that is different from the organism that is expressing the sequences is not considered to "occur naturally in the environment" under 21 CFR 25.31(c).

The functional protein-coding sequences (modRNA) contained in the Pfizer and Moderna products are wholly created and synthesised using recombinant technologies, consequently, the modRNA of Pfizer and Moderna has no genus and is distinctly different from the functional protein-coding sequences of the SARS-CoV-2 virus coding Spike protein.

The same FDA guidance details GTVVs deemed to occur naturally as:

> GTVVs that contain functional protein-coding sequences from one or more species within a single genus to "occur naturally in the environment" for purposes of 21 CFR 25.31(c).
>
> GTVVs that differ from a wild-type substance only in attenuating point mutations or deletions to be substances that "occur naturally in the environment" for purposes of 21 CFR 25.31(c) because such mutations can occur as natural variants during replication/propagation.
>
> GTVVs that have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate to be substances that "occur naturally in the environment" because they are not viable and are degraded into substances that occur naturally in the environment.
>
> GTVVs that consist of genetically-modified human cells to be substances that "occur naturally in the environment" for purposes of 21 CFR 25.31(c) because these cells have stringent nutritional requirements for survival and replication and are therefore not viable in the environment and are degraded into naturally occurring substances.

None of the above descriptions apply to the LNP-modRNA complexes contained in the Pfizer and Moderna Covid-19 products.

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[3] Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products: see pages 5, 6, and 7.

[4] Gene therapies are defined in the FDA guidance document entitled, "Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" dated November 2006 as "[p]roducts that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient.

In light of the above, the decisions by the FDA to grant the requests for categorical exclusion from having to submit an Environmental Assessment under 21 CFR 25.31 to each of Pfizer and Moderna had no basis at law.

As a consequence of this regulatory failure by the FDA, both Pfizer and Moderna continue to be in breach of section 25.15 for failing to submit EAs, nullifying the approvals by the FDA of each of the BLAs of Pfizer and Moderna (emphasis added):

> (a) All applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion. A claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that to the applicant's knowledge, no extraordinary circumstances exist. **Failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in § 25.20**, unless the agency can determine that the action qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, 25.34, or 25.35 **is sufficient grounds for FDA to refuse to file or approve the application or petition. An EA adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment.**

The failure by the FDA to reject the requests for categorical exclusion from an Environmental Assessment under 21 CFR 25.31, was a regulatory failure nullifying the effect of the subsequent approvals of the BLAs for Pfizer and Moderna. Section 25.15 is clear and unambiguous:

> **An EA adequate for approval is one that contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment.**

No EAs were submitted, so no information sufficient for approval formed part of the consideration processes of the FDA, therefore the purported BLA approvals were always *void ab initio*, or void from the beginning.

Had Pfizer and Moderna submitted EAs the content of those EAs would have relied upon the following FDA guidance:

> Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications (1998)
>
> Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products (2015)

In the paper *Hurdles of environmental risk assessment procedures for advanced therapy medicinal products: comparison between the European Union and the United States*, Iglesias-Lopez et al (2019) set out in Table 2 the matters Pfizer and Moderna should have addressed in EAs submitted with their BLAs:

Table 2. Environmental risk assessment step procedure in the EU and the US.

Region	ERA step process	Environmental analysis	Examples and/or Comments	Comparison
EU	1. Identification of characteristics which may cause adverse effects	• Characteristics of the GMOs linked to the genetic modification that may result in adverse effects on human health or the environment • Comparison of the characteristics of the GMO(s) with those of the non-modified organism under corresponding conditions of the release or use will assist in identifying the particular potential adverse effects arising from the genetic modification	• Location of the construction in the genome of the GMO where the transgenes were inserted • Potential interaction of the different transgenes • Phenotypic and genetic instability. • Spread of the GMO(s) in the environment (e.g. pathways of dispersal, biological fitness, etc.) • Interactions with other organisms	Equivalent to steps 1 and 2 of the ERA in US
	2. Evaluation of the potential consequences of each adverse effect, if it occurs	• For each adverse effect identified, the consequences for other organisms, populations, species or ecosystems exposed to the GMO have to be evaluated • In quantitative terms the magnitude should be expressed as "high", "moderate", "low" or "negligible"	• One single hazard could have more than one adverse effect, and the magnitudes of the individual adverse effects could be different	Equivalent to step 2 of the ERA in US
	3. Evaluation of the likelihood of the occurrence of each identified potential adverse effect	• Estimate how likely it is that adverse effects will actually occur. In some cases, both the likelihood and the frequency should be addressed. • The likelihood of the occurrence of an effect will depend on the specific risk management measures that may prevent that risk from occurring	• The relative likelihood of the consequence can probably not be assessed quantitatively, but it can be expressed in terms of "high", "moderate", "low" or "negligible"	Equivalent to step 2 of the ERA in US
	4. Estimation of the risk posed by each identified characteristic of the GMO(s)	• Estimation of the risk to human health or the environment posed by each identified adverse effects, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs • The overall uncertainty for each identified risk has to be described	• To include assumptions and extrapolations made at various levels in the ERA, different scientific assessments and viewpoints, uncertainties, the known limits of mitigation measures	Equivalent to step 2 of the ERA in US
	5. Application of management strategies for risks from the deliberate release or marketing of GMO	• The ERA may identify risks that require measures to manage them, and a risk management strategy should be defined	–	Equivalent to steps 3 and 4 of the ERA in US
	6. Determination of the overall risk of the GMO	• An evaluation of the overall risk of the GMO(s) should be made taking into account any risk management strategies which are proposed	–	Equivalent to step 3 of the ERA in US

Iglesias-Lopez et al further observe:

> The ERA in EU and the US is based on nonclinical and/or clinical data, which mainly includes: description of the biological properties of the product that may pose a hazard, pathogenicity, its genetic stability, replication competence, host range, tissue tropism, the ability of the virus vector to survive after being shed, or the clearance, persistence and latency, shedding and biodistribution (Anliker et al. 2010). Therefore, during the development of the product it is necessary to generate enough information to address all these issues and conduct a proper ERA.
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> One of the most important factors to analyze consists in the shedding assessment, which is the dissemination of the virus/vector through secretions and/or excreta of the patient, i.e. saliva, sweat, urine, feces, nasopharyngeal fluids, blood, exudates from skin lesions, breast milk and semen.

Independent of the required EAs, and to date neither Pfizer nor Moderna have released any studies on shedding, or the pathogenicity, genetic stability, replication competence, host range, tissue tropism, or the clearance, persistence or latency of their products. Pfizer did disclose a single and inadequate biodistribution study when requested by Japanese authorites.

The essential nature of biodistribution studies were reinforced by Iglesias-Lopez et al as follows:

> Biodistribution assessments are also another key point for the ERA [EA], as they provide information about the dissemination of the recombinant vector from the site of administration. This fact may influence the routes of shedding of the virus from the recipient, and therefore, the likelihood of transmission to third parties, including vertical transmission. Similarly to shedding assessments, biodistribution is usually part of the pivotal study and there is a minimum panel of tissues to be analyzed, apart from the ones considered necessary depending on the product and route of administration, i.e. blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen (FDA Center for Biologics Evaluation and Research (CBER) 2018). If vector is detected in gonads, germline transmission studies should be performed (EMEA/273974/20 2006).

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