Editorial
Reconstruction of Regulatory Science in the Age of Genetic Technologies: Restoring Biologically Grounded Safety Assessment and Ethics

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1. Introduction: Historical turning point and regulatory void

During the coronavirus disease 2019 (COVID-19) pandemic, modified mRNA (modRNA) products and related genetic therapeutics encapsulated in lipid nanoparticles (LNPs) were rapidly and widely administered to billions of healthy individuals worldwide. This is an extremely critical historical turning point in the medical application of synthetic biology and genetic technology. The ethical foundation established by the 1975 Asilomar Conference, stating that "when scientific progress overtakes safety management, scientists must lead the precautionary principle prior to deployment" [1], is currently in a grave crisis.

The collection of papers included in this issue, "Regulatory Science on Gene Vaccines for the Prevention of Infectious Diseases," serves as an *ex post facto* academic systematization of the detailed scientific and jurisprudential bases underlying the demands for correction (Part 2, Materials 1-3 of this collection) previously submitted to administrative agencies (such as the Ministry of Health, Labour and Welfare). Specifically, we placed at the beginning, as the latest proposal papers of Part 1, the "Proposal for the Amendment of the Cartagena Act" [2], which urges the correction of the legal system from the perspective of environmental and ecosystem conservation, and the "Proposal for the Amendment of Non-clinical Study Guidelines for Infectious Disease Preventive Vaccines" [3], which corrects the contradictions of examinations that diverted the framework of conventional vaccines. Following this, Japanese translations of English paper from an international perspective and their commentaries (Part 2) are included [4, 5]. The restoration of medical ethics and the presentation of a new regulatory framework based on facts are the purposes of this issue.

2. Institutional category error and the "paradox of classification"

The core structural defect in vaccine review, pointed out throughout this collection of papers, lies in the paradox of classification that "the purpose (intent) of preventing infectious diseases is treated as a legitimate reason to exempt strict safety evaluation based on biological mechanisms."

modRNA-LNP products and self-amplifying mRNA (saRNA)-LNP products are “gene transfer products” that introduce exogenous nucleic acids into cells and utilize the host’s cellular machinery to translate non-self proteins. Despite having a risk profile equivalent to that of gene therapy products from the perspective of the mechanism of action, they were defined as “infectious disease preventive vaccines” in administrative classification. Driven by the fact that this “administrative label” overwrote the “biological mechanism,” strict non-clinical studies regarding pharmacokinetics, biodistribution, long-term persistence, genotoxicity, and carcinogenicity, which are mandatory for gene therapy products, were institutionally exempted. Safety must be defined not by bureaucratic procedures (Bureaucracy), but by strict biological functions (Biology).

3. Facts demonstrated by real-world data and the inevitability of market withdrawal

As a result of this category error, extremely serious public health damage has become a reality. As detailed by the translated papers in this collection, uncertainties inherent to the platform, such as immune tolerance associated with IgG4 class switching, persistent expression of spike proteins in various organs, and furthermore, residual plasmid DNA originating from the manufacturing process, have manifested.

In addition, real-world data objectively demonstrate a lack of efficacy and an increase in risks, such as the loss of infection prevention effects due to multiple inoculations and an increase in excess mortality. Despite the fact that numerous safety signals have been confirmed, the current situation in which revocation of approval and market withdrawal based on the Pharmaceuticals and Medical Devices Act (Article 74-2, etc.) [6] have not been implemented is an administrative inaction, and a serious deviation from the principle of evidence-based policymaking.

4. Humans as hosts and prevention of diffusion into the environment (Limits of the Cartagena Act)

Furthermore, the deployment of genetic technology is expanding beyond individual health damage to the dimension of biosafety. After synthetic nucleic acids with persistent expression mechanisms, including saRNA, are administered to the human body, a risk exists that they are discharged (shedding) into the environment via extracellular vesicles such as exosomes.

However, under the current Cartagena Act [7] and related ministerial ordinances, artificially synthesized nucleic acids with self-replicating ability are not clearly positioned as “living modified organisms, etc.,” and genetic information that requires strict containment (BSL3, etc.) at the research stage has become institutionally unregulated at the clinical stage. In order to close this institutional void, it is necessary to clearly stipulate synthetic nucleic acids as subjects of regulation, incorporate humans into the definition of “host,” and legally obligate public health measures to prevent diffusion, including the ensuring of traceability.

5. Toward the construction of a new governance system

We propose a fundamental shift in the paradigm of regulatory science from the current reactive system of "Permission after harm" to "Precaution before deployment." This philosophy is completely aligned with the "Asilomar 2027" initiative (establishment of a global summit and a new security system to govern the era of genetic technology) advocated by an international team of scientists and legal scholars, including ourselves [8]. In order to govern the coming era of genetic technology, it is essential to establish the following principles and amendments to guidelines as an international framework.

i. **Classification based on biological mechanisms**: Regulate all platforms utilizing exogenous nucleic acids as substantial gene transfer products, regardless of their preventive intent.

ii. **Amendment of non-clinical study guidelines (Mandating of prior verification)**: Even for infectious disease preventive vaccines, the implementation of the following non-clinical studies shall be mandated in principle for gene transfer products:

1. Pharmacokinetics and biodistribution studies
2. Long-term persistence studies
3. Reproductive and developmental toxicity studies
4. Genotoxicity and carcinogenicity studies

iii. **Abolition of evaluation exemptions based on platform commonality**: Even if the platform technology (LNP, etc.) is common, if the expressed antigen is different, the omission of non-clinical studies on the grounds of equivalence shall not be permitted, and strict evaluation for each individual product shall be required.

iv. **Stepwise and strict prior verification**: Institutionalize independent and mandatory prior non-clinical evaluation panels according to the persistence of genes and the possibility of interactions.

v. **Evaluation by independent monitoring institutions**: A third-party institution, completely independent from conflicts of interest and possessing the right of direct access to raw data, shall lead the approval review and long-term post-marketing surveys.

6. Conclusion

The current crisis in public health and regulatory science is fundamentally rooted in the fact that the "administrative label" has overwritten the "biological mechanism." Each paper included in this collection is the result of analyzing phenomena based solely on pure facts, jurisprudence, and logical structure, while thoroughly eliminating existing authority and majority biases. Scientific trust is maintained not by administratively concealing uncertainties, but only by

continuously producing verifiable evidence. Toward the restoration of medical ethics and the securing of true safety for the public, we are confident that this collection of papers will serve as a firm foundation for structural reform within regulatory authorities, the scientific community, and society as a whole.

References

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