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Corona debate

Approval of Covid vaccines: the battle over the concept of gene therapy

Critics say safety standards were neglected in the approval of mRNA vaccines - because they are gene therapeutics. A guest commentary.

Paul Cullen, Brigitte Röhrig, Jens Schwachtje, Henrieke Stahl, 23.3.2023 - 10:00 a.m.

Vaccine production of the Mainz-based company Biontech in Marburg, 2021

Under the headline "Was there an 'approval disaster' with vaccinations? Two perspectives", a controversy recently appeared in the Berliner Zeitung on the question of whether applicable law was broken in the approvals of the Corona vaccines. Actually, the mRNA vaccines are not vaccines in the conventional sense, but gene therapeutics and as such are subject to high testing standards, wrote a group of lawyers.

Under the influence of pharmaceutical companies, however, a legal redefinition had taken place in order to circumvent the intended strict safety requirements. This definition of vaccines as gene therapeutics was contradicted by the Berlin molecular biologist Emanuel Wyler in a rebuttal. This is now followed by another article by four authors to substantiate the thesis of the "approval disaster". This text is a guest contribution. It does not necessarily reflect the opinion of the editorial team. Feedback to: briefe@berliner-zeitung.de

"Not true: mRNA vaccines are a form of gene therapy", MDR repeats a mantra of the fact checkers that has accompanied the Covid vaccinations from the beginning. This mantra also finds its supporters in the scientific community.

For example, Emanuel Wyler recently objected in his rebuttal to the lawyers' article on the "approval disaster" that the legal exclusion of mRNA preparations that act preventively against infectious diseases from the class of gene therapeutics and their assignment to vaccines "does not contradict the definitions used in biomedicine".

"From the perspective of biological science", he writes, gene therapy "involves altering a person's genetic make-up". For this, Wyler refers to a text written by patent lawyers, but which merely proposes such a definition (literally: "alteration of the cellular genome"). However, Wyler does not provide any evidence for his statement that the mRNA vaccines are "not considered gene therapy by the *majority*" (our italics).

Business interests collide with safety standards

But Wyler has put his finger in an open wound with his statement - a battle is currently raging over the term gene therapy. And it is an important battle in which the business interests of the pharmaceutical companies collide with the safety standards of their products. Therefore, this battle concerns all of us. So, what does this battle consist of?

Let us first look at what the Paul Ehrlich Institute considers a gene therapy medicinal product to be. It is a "medicinal product whose active substance contains or consists of a nucleic acid [...]". It is "used to regulate, repair, replace, add or remove a nucleic acid sequence". Its "action is directly related to the recombinant nucleic acid sequence it contains" or to its "product".

On its website, the Paul Ehrlich Institute lists some gene therapeutics that introduce DNA (nucleic acid) into cells with a vector virus, but for which integration into the genome is explicitly excluded, e.g. Zolgensma from Novartis. Thus, the above-mentioned definition of the Paul Ehrlich Institute for gene therapeutics also includes therapeutics that do not change the genetic material.

Vaccines against cancer are legally classified as gene therapeutics

The definition of the American Society for Gene and Cell Therapy (ASGCT) does not indicate otherwise. It defines gene therapy as the "introduction, removal or alteration of genetic material from a human being" with the aim of "treating" or "preventing" disease.

In the FAQs, the ASGCT explicitly explains that the introduced "genetic material alters how a single protein or group of proteins is produced by the cell". This is a provision under which mRNA techniques also fall.

The fact is that mRNA vaccines that are not used against infectious diseases, such as those against cancer, are not only medically but also legally classified as gene therapeutics. This follows, for example, from the opinion of the Committee for Advanced Therapies (CAT) for BioNTech's mRNA cancer therapeutic.

Furthermore, other drugs are indisputably considered gene therapy drugs, even though they do not alter the genome. An example of this is the product Luxturna for the treatment of congenital blindness, which is described as a "gene therapy drug" by both the manufacturer and the US Food and Drug Administration (FDA). Luxturna consists of a cDNA construct that does not alter the patient's genome.

Term gene therapy initially assumes no alteration of the genome

In the course of the pandemic, the discussion about the status of the Covid vaccines as gene therapeutics also flared up in the scientific community. On 14 November 2022, the journal Human Gene Therapy published a letter to the editor arguing for finally establishing a "clear terminology" that would resolve the "ambiguity" of the term.

The ambiguity is that gene therapy includes both genome-modifying substances and those that do not. The criterion of introducing "genetic material into cells" is thus considered too broad; it is to be replaced by the criterion of changing the genome, thus making the definition unambiguous.

According to the common definition and usage, the term gene therapy does not initially presuppose a change in the genome. Rather, gene therapy is always already present when stable expression of a gene product (RNA or protein) occurs due to a nucleic acid sequence present outside the cellular genome. With the exception of Valneva and Nuvaxovid, all Corona vaccines available in Germany fulfil exactly this condition; they can therefore without doubt be described as gene therapeutics, even if they do not normally alter the chromosomal genome.

Desire for acceptance of the vaccines

The outlined trend to exclude the gene-based Corona vaccines from the class of gene therapeutics, not only legally but also in the scientific discourse, or to narrow the definition of gene therapeutics with the help of the criterion of genome modification, has a surprising reason: the rejection of a classification of gene-based vaccines as gene therapeutics can be explained by the desire for their acceptance; the designation of the Covid vaccines as gene therapeutics was and still is considered an "anti-vaxxer" argument today.

The English Wikipedia, on the other hand, contradicts itself when it excludes "genetic vaccines against infectious diseases" not only from the point of view of "drug law", but also from the point of view of "gene therapy", since "the genome is not changed".

Behind the striving to narrow the definition of gene therapy medicinal products on the basis of the criterion of genome modification, however, is also the tangible business interest of the pharmaceutical industry. This is because the testing conditions for gene therapy drugs are considerably stricter and more expensive than for conventional drugs.

In 2009, following a corresponding statement by the pharmaceutical industry, the legal redefinition was made according to which "vaccines against infectious diseases are not gene therapeutics". The proposal of the Paul Ehrlich Institute of 2008 to the contrary, according to which gene-based vaccines should be subject to the regulations for both conventional vaccines and gene therapeutics and would therefore have had to be tested twice, was dropped.

Return to the previous definition would be detrimental to companies' businesses

Information provided by the pharmaceutical companies to the US Securities and Exchange Commission demonstrates their economic interest in gene-based vaccines being exempted from the regulations for gene therapy drugs. On the one hand, it says that "mRNA therapies have been classified as gene therapy medical devices", but on the other hand that "our Covid 19 vaccine is not *currently* classified as a gene therapy" (our italics).

The pharmaceutical companies see it as a danger that the broad scientific definition of gene therapeutics could undermine the legal exception again in the case of gene-based vaccines against infectious diseases. Because in this case, testing according to the standards for gene therapy would become necessary, which would bring a sharp increase in the time and cost factor until approval. The return to the previous definition would be detrimental to business.

The companies express fears that such a readjustment of the legal definition to the broad medical definition could occur under the pressure of negative public opinion, for example if reservations that exist about "other gene therapeutics" were transferred to the new vaccines. What is meant are undesirable side effects, such as those observed with therapeutically applied actual alteration of the genome, which, however, are not supposed to apply to the mRNA substances.

Pfizer documents confirm inconsistencies in approval study

In addition, as explicitly stated in Moderna's report, a public perception of side effects of the mRNA preparations could necessitate a revision of the drug law classification with a return to the high safety standards applicable to gene therapeutics. A suppression of side effects and vaccine damage from public perception thus corresponds to the wish of the pharmaceutical industry.

In recent months, more and more reports have reached the public that, as Elke Bodderas recently wrote in *Die Welt*, there were "inconsistencies in the Pfizer approval study". Inconsistencies also concern the handling of serious negative side effects - which were reduced by questionable changes in the patient groups. This approach is confirmed by the latest evaluation of Pfizer documents.

The information provided by the pharmaceutical companies to the US Securities and Exchange Commission shows that initially there were no approval regulations for the new preparations and that they first had to be developed. The interest in business-friendly approval rules played a role here. Could the approval of the mRNA-Covid vaccines, which is now officially described as "regular", also be a fast track for future gene-based vaccines?

And if the definition of gene therapeutics is narrowed to genome modification, for many other drugs that "introduce genetic material into cells"? This should not happen under any circumstances - we see an urgent need for action here.

Covid vaccine approval process must be independently audited

Let us summarise: According to a broad scientific classification, genetic vaccines against infectious diseases initially fall into the category of gene therapeutics by virtue of their mode of operation. They are only exempt from it according to the current legal situation. The necessity of such a "legal fiction" at this point already proves that these substances are gene therapeutics in substance.

However, the pharmaceutical industry has an interest in these vaccines not being perceived as gene therapeutics and fears that the legal redefinition could possibly be reversed.

There is currently a tendency in science to accommodate this wish of the pharmaceutical industry and to narrow the definition of gene therapy via the criterion of genome modification. In this case, not only the genetic Covid vaccines, but also many other genetic medicines would no longer have to be subject to the high safety standards of gene therapeutics in their approval.

We see it as an urgent imperative of this hour that, also in view of the growing doubts about the promised safety of the mRNA vaccines, the approval process of the genetic Covid vaccines and the role of the corporations as well as the competent authorities in these procedures be independently examined.

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