Safeguards for accelerated market authorization of vaccines in Europe

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This article has been published by the Stanford Law School 'Center for Law and the Biosciences', Stanford University, 15 March 2021. *https://law.stanford.edu/2021/03/15/safeguards-for-accelerated-market-authorization-of-vaccines-in-europe/*

People around the globe are concerned about safety issues encircling the accelerated introduction of corona vaccines. In this article, we discuss the regulatory safeguards for fast-track market authorization of vaccines in Europe. In addition, we explain how the transmission of European Union law into national Member State legislation works. We then clarify what happens before a drug can be introduced into the European market. We conclude that governments should build bridges of mutual understanding between communities and increase trust in the safety of authorized vaccines across all population groups, using the right messengers.

The first COVID-19 vaccines have been approved. Pharmaceutical manufacturers have delivered vaccines in record time, and vaccination programmes have been started. With expected effectiveness margins of 55% to 95%, light is finally on the horizon.

This news caused a lot of extra upheaval in an already troubled public debate. Is it actually possible to develop a safe vaccine so quickly? Have steps been skipped in the research and development process? Has there been fiddling with the requirements for clinical research? Is there a clash with the pharmaceutical industry? And will vaccination become mandatory? Many wondered.

These questions are entirely understandable. The speed with which the new vaccines have been developed, is at sharp contrast with the slow and lengthy drug development procedures we are used to. The fact that the development and approval of the COVID-19 vaccines have taken place within just a few months seems worryingly short for the general public. How can the quality and integrity of the vaccine possibly be ensured? How does one prevent citizens from being harmed by vaccines and medicines that are effective and safe for the masses, but not for every individual? How does one deal with problems, such as adverse effects that have gone unnoticed? Is the drug manufacturer solely responsible for all this, or is the government responsible as well? Should we set up a collective damage fund for these questions of insurance and liability in the event of substandard quality? And should compulsory vaccination become part of any government's arsenal of measures?

The purpose of this article is to shed a little light upon the accelerated market authorization procedures on the European continent, with a focus on the situation in the Netherlands.

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Reception of European Union law in Member State legislation

In order to give you some essential background information, it is crucial to say a word or two about the reception of European Union Law in the various Member States. Often the European Union is thought of as one single state with a unified body of law. The reality is a bit more complex.

It all began in the early 1950's. In the aftermath of World War II, the Treaty establishing the European Coals and Steel Community ('ECSC' but also known as 'the Treaty of Paris) was signed in April 1951, entering into force in July 1952. It was followed up by the Treaty of Rome in 1957, creating the European Economic Community (or EEC). Back in the day, it was assumed that the traditional principles of international law would apply to the European Communities. This meant that the Member States would retain the right to jointly alter the jurisdiction of the European Communities. In addition, each Member State could individually determine the extent to which rules of European law could affect its national legal order. It was heartfelt that the European Communities had no business interfering with the sovereignty of the Member States.

In the early 1960's, the European Court of Justice broke with this idyll of sovereignty in two judgments that became famous. In *Van Gend & Loos* (1963) the Court declared the legal order of the Communities to be of an independent nature and declared that this legal order had a separate basis of authority, more or less beyond the reach of the Member States. A year later, The Court gave its famous ruling in *Costa/ENEL* in which it established that European law must, by virtue of its own legal order, take precedence over all the law of the Member States.

We are a good seventy years and many legislative reforms later. Since the Lisbon Treaty entered into force in 2009, the constitutional structure of the European Union has been reformed and amended by the Treaty on the European Union (TEU) and the Treaty on the Functioning of the European Union (TFEU); creating the European Union as we know it today.

It is essential to understand that the European Union has no absolute legislative power. It can only legislate in certain areas and only to the extent that the Treaties provide mandate. The European Union has four legislative procedures, which are set out in Article 289 TFEU.

Which legislative procedure the Union is to follow and the scope thereof, are determined by certain specific provisions in the TEU and the TFEU. As a rule, the Treaties also prescribe which legislative instrument is most appropriate in a given situation. Member States usually have a say as to the subject that is under legislative scrutiny.

The TFEU provides for the so called 'Secondary Union law' (as opposed to primary Union Law, establishing the institutional structure of the EU), as is clear from Article 288, which consists of "regulations, directives, decisions, recommendations and opinions" adopted by the institutions of the Union in order to exercise the powers of the Union. Regulations being the most commonly used. Regulations do not, in principle, address specific individual circumstances. On the contrary. They are a measure of general application within the meaning of Article 288 of the TFEU. Such a measure applies to objectively defined situations and has legal effect for general and abstractly defined categories of persons.

Another important feature of the regulation is that it is directly applicable in the national legal orders of the Member States, without the need for transposition or implementation. A regulation is therefore regarded as the legislative instrument of choice where there is a need for uniform regulation within the Union. Thus, regulations result in *unification* of legal rules.

Directives, unlike regulations, are binding only as to the result to be achieved. It is up to the Member States to choose the means to achieve this. Directives are generally used where there is a need for approximation of laws of the Member States in order to ensure the establishment or functioning of the internal market, and *may be mandatory in nature*. Because directives have to be transposed into national law, they take the form of national law. For the sake of completeness, we would like to point out that the European Parliament has already expressed its views on this issue in a number of opinions.

Usually, directives are the preferred legislative tool with regards to topics that are traditionally thought of as being a matter of national affairs. Health care and social security are good examples of such traditional national affairs. The European Union offers a harmonized legislative framework; everything else is left to the discretion of the individual Member States. In other words, directives result in *harmonisation* of legal rules.

We see a clear example of this when looking at pharmaceutical law. It is harmonized by directive 2001/83/EC establishing a Community code relating to medicinal products for human use. The implementation of this directive is left to the Member States, meaning that there are national varieties in the way pharmaceutical products are governed. The situation in the Netherlands may therefore differ from the situation in Belgium, France or Germany. These differences may seem small, but can in practice be significant.

That being said, fast forward to June 2020, The Hague, The Netherlands. Just a few months into the pandemic.

How a vaccine is introduced into the market

In June 2020, the Dutch government, in close cooperation with Germany, France and Italy, formed a Joint Negotiation Team which, under the watchful eye of the European Commission, has been negotiating with vaccine developers. Its objective: to conclude agreements with drug manufacturers at an early stage about the availability of vaccines for European countries. In case these manufacturers are to succeed in developing a successful vaccine for which the so-called Market Authorization (MA) is granted, this could lead to the availability of about 50 million vaccines (for the Netherlands alone).

From the above, it follows that obtaining an MA remains a condition for the market introduction of a medicine. This is an absolute obligation that is based on Article 40 of the Dutch Medicines Act. This rule also applies to other European countries. As stated, pharmaceutical law has been harmonized within the European Union by directive 2001/83/EC, which creates a legal code for medicines for human use. The obligation to obtain an MA, either on a Member State level or on EU level, is included in Article 6 of that directive. An application for an MA is submitted by a drug manufacturer and must meet all kinds of strict criteria.

Pharmaceutical Manufacturing License (M-License)

Who is allowed to produce these vaccines? The Dutch Medicines Act is very clear about this. Only "market authorization holders" are allowed to manufacture medicines, including vaccines. These are parties that have gone through an extensive application procedure, who demonstrably have a solid pharmaceutical quality management system in place and have obtained a pharmaceutical manufacturing license (the MIA, short for Manufacturing and Importation Authorisation). This license

is granted after assessment by Farmatec, an implementing body of the Ministry of Health, Welfare and Sport (VWS). The M-license is mandatory for parties who prepare, or import medicines. Once the license is obtained a drug manufacturer can start developing and producing medicines, but he must always take into account the scope of the license. A license - which is public and published in the EudraGMDP database - specifies exactly what kind of medicines may be produced. If a manufacturer wants to produce other types of pharmaceuticals, he must submit a new application (to extend the license) and a re-inspection will be carried out. Pharmaceutical manufacturers - as well as pharmaceutical wholesalers - are regularly re-inspected by the government which verifies in particular whether the manufacturer still complies with the authorization conditions.

Market Authorization (MA)

Note though that being the proud owner of an M-license does not allow the manufacturer to just make medicinal products available on the market. Market introduction is only allowed after a license holder has obtained the aforementioned MA for this purpose, and after the European Commission has approved the MA. It is fair to say that there is always a double compliance check: both at manufacturer level and at product level.

To obtain an MA, a manufacturer must submit a comprehensive product dossier to either the Dutch Medicines Evaluation Board (MEB) or the European Medicines Agency (EMA).

The submission process leading to an MA is the final stage before market introduction of the medicine. All the preliminary work has been done and the requesting market party must supply sufficient data. The MEB (on national level) or EMA (on EU level) assess the dossier. Please be informed that these bodies mainly check the *content* of the dossier against the state of science and technology. The law sets specific requirements for the content of the dossier. For example, the dossier for a COVID-19 vaccine should include a description of the preclinical *in vivo* animal studies performed and the different phases of the human clinical trials. It also looks at the results and findings during these research phases, including the evidence for the correct immune response.

Before the MA for the vaccine can be granted, the EMA Committee on Medicinal Products for Human Use (CHMP) studies and assesses the dossier provided by the manufacturer containing the scientific data on the effectiveness and side effects of the COVID-19 vaccine. Member State level institutions such as the Dutch MEB are also represented in the CHMP.

Directive 2001/83/EC contains an exception (Article 5.2) stating that Member States can temporarily green-light a vaccine for distribution and use in the event of an emergency, before EMA has given clearance. In Hungary, temporary market authorization has been granted on a national level to Oxford's AstraZeneca and Russian Sputnik vaccines, before EMA approved these medicines. Although this unilateral act will raise eyebrows in Brussels, the exception is in line with the room and flexibility that EU directives provide to Member States to choose how they reach their intended legislative targets.

Fast-track procedures

We currently see that the pandemic has accelerated the admission trajectories significantly. The EMA has a rolling review for urgent dossiers. We also see this happening elsewhere in the world. Across the pond, the US Food & Drug Administration (FDA) introduced -on top of the already existing Emergency Use Authorization (EUA) - the Coronavirus Treatment Acceleration Program. The purpose

of these fast-track procedures is authorization and market introduction as fast as possible. In the eyes of policymakers, having access to a vaccine at warp speed is good for both the patient and the economy. But does this mean that we have to make a sacrifice to due care, documentation obligations, medicinal safety and public health?

It should be pointed out that neither policy makers nor the industry intend to make any concessions to the safety, integrity and effectiveness of a vaccine. But given that, how is it possible that the various COVID-19 vaccines from Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, and Janssen/Johnson & Johnson could be brought to market so much more quickly?

The current virus -SARS-CoV-2- is part of a strain of coronaviruses. This virus strain has several variants, which show similarities at the molecular level. In recent years we have seen outbreaks of coronaviruses such as MERS (Middle East Respiratory Syndrome), SARS-CoV-1 (Severe Acute Respiratory Syndrome) and HCoV-NL63. Research has already been conducted on these viruses in recent years. Besides that, key R&D trajectories have been carried out synchronously instead of consecutively, which saves time. With the acquired prior knowledge, together with extraordinary advances in the science of vaccine platform technology, the research and development process has been significantly sped up. Coupled with the fact that COVID-19 is a global problem, there is an increased willingness to cooperate and a sense of urgency to develop an effective vaccine.

Mind you, foreknowledge is definitely not sanctifying. The predicted herd immunity, for example, is very disappointing. Moreover, we do not know how long protection against the virus, including its variants and mutations, would last after vaccination (durability). Antigenic drift may make it necessary to update the strain used in vaccines on a regular basis. There is also no conclusive insight into possible reactions of the human immune system to contamination with COVID-19, and to the chance of reinfection.

In theory, a person vaccinated can still infect other people, by transmitting virus particles present in his or her nose. It is expected that vaccines reduce transmissibility, but do not completely eliminate the virus' spread. Rapid antigenic testing kits to be used to test contagiousness at home are not yet available. Such antigen self-test kits require a CE-marking before they can be admitted to the EU market, indicating they have met safety, health and environmental protection standards for the region. This EU conformity marking applies to serology tests, LAMP, PCR and breath tests as well.

Please note that contagiousness and infection are not the same thing. Significant advances in reducing viral transmissions have recently been made by using a nasal spray in ferrets. Intranasal infusion of lipopeptides effectively blocked SARS-CoV-2 infection in animal models, including variants. The researchers strive to rapidly progress this preventative method into human trials.

Currently, hundreds of second-generation vaccines are in the pipeline worldwide, utilizing self-amplifying RNA, Protein Subunit, and Designed Protein Nanoparticle techniques. Scientists are exploring various strategies that could help slow down the pandemic. Such as mucosal immunity, which requires intranasal vaccination instead of, or in combination with intramuscular vaccine administration. Similar to the annual flu shot, the holy grail of COVID-19 vaccines might be a multivalent vaccine that can immunize against multiple strains of the same disease.

No concessions will be made to testing the efficacy and safety of the vaccines under development. All vaccines must be produced in accordance with Good Manufacturing Practices (GMP), a system of quality assurance that is used within the pharmaceutical industry. In addition, dossiers must comply with Good Documentation Practices and the pharmaceutical supply chain must be completely

transparent. The mandatory three phases of clinical research must have been successfully completed.

HERA Incubator: European bio-defence against COVID-19 variants

On 17 February 2021, the European Commission announced the European Health Emergency Preparedness and Response Authority (HERA, not to be confused with spacecraft Hera, ESA's planetary defence mission's asteroid probe that was named after the Greek goddess of marriage and fertility). This novel bio-defence preparedness plan against COVID-19 variants is Europe's response to the increased spread of the recent United Kingdom, South Africa and Brazil mutations. The HERA Incubator is a public-private collaboration that combines the knowledge and resources of industry including the health sector, academia, and government. Part of the plan is the launch of VACCELERATE, the COVID-19 Clinical Trials Network. VACCELERATE aims to speed up the collection and exchange of high quality clinical trials data; in particular that the gathered data is passed on quickly to the EMA. Further, the European Commission intends to introduce a fast-track procedure (faster than the *rolling review*) for the authorization of updated vaccines that are effective to mutations.

The HERA Incubator will focus on five main priorities:

1. Developing specialised tests to help identify variants, monitor their spread in populations, screen their impact on transmissibility, and support genomic sequencing in Member States;

2. Adapt the existing vaccines through scientific research and development;

3. Facilitate clinical trials to diligently obtain evidence-proofed data needed for the product dossier, and get this information into the hands of EMA more quickly, via the VACCELERATE initiative;

4. Enable EMA to fast-track approval of adapted vaccines and certification of manufacturing sites. This includes adjusting the regulatory procedure to enable Market Authorization of the updated version of a previously authorized vaccine with a smaller set of additional data submitted to EMA on a rolling basis;

5. Upscale mass production of new vaccines but also of existing COVID-19 vaccines. This includes concluding additional Advance Purchase Agreements to support the development of new and adapted vaccines through EU funding, whereby liability for side effects would be borne by Member States, addressing production bottlenecks and developing a voluntary dedicated licensing mechanism to facilitate technology transfer.

Quality control is a "never-ending story"

After the Pharmaceutical Manufacturing (M-) License has been approved by Farmatec and Market Authorization (MA) has been granted by EMA or CBG, the quality of a medicine is continuously monitored. An integral part of the process of bringing a medicine to the market is extensive quality control at batch level by a specialized laboratory (in-house or external), so that a medicine can be released (referred to in the sector as 'batch release') for sale or distribution. A pharmaceutical manufacturer has a QAQC (Quality Assurance Quality Control) department that deals exclusively with this quality control.

Even after a vaccine has been released, continuous monitoring takes place in the context of pharmacovigilance. Detailed rules apply here too.

It is expected that in the course of 2021, we will have access to a number of vaccines from different manufacturers, all of which are acceptably similar in effect and effectiveness. Efficacy and side effects will be monitored ('phase four') at both European and Member State level. Quality control is an ongoing process.

Compulsory vaccination regimes?

The topic of mandatory vaccination has been discussed regularly in recent months. Not only in parliamentary debates, but also in talk shows where experts made all kinds of statements about the desirability of compulsory vaccination. What is the likelihood of this scenario? Will there be a compulsory vaccination regime?

Currently, there is little to no support within the administrations of most Member States for such measures. But in essence: these kind of measures are within the discretion of an individual Member State. The same is true for the introduction of vaccine passports or an obligatory recent negative CIVID-19 test. It is very likely that COVID-19 vaccination requirements will vary across EU Member States.

Doctrinally, it appears to be easier for private parties -such as employers and employees- to put in place contractual testing or vaccination obligations, than it is for public institutions -such as the government- to force citizens by law to be vaccinated. Nevertheless, employers must at all times carefully respect their employees' fundamental rights and freedoms, including privacy and data protection requirements as prescribed by the General Data Protection Regulation (GDPR).

Building trust in the safety of authorized vaccines

Citizens in a democratic society, have the inviolable fundamental right not to be subjected to involuntary medical treatment, including vaccination. In authoritarian, totalitarian regimes there may be less choice and a refusal may have more impact, such as social disadvantages and prosecution. From a normative perspective, we feel that saying that citizens who have been vaccinated have more rights or more access to society in the form of entrance and privileges, is not congruent with a democracy like the Dutch or European. Not even in times of a global health crisis.

What governments -both national and supranational- should do instead, is building trust in science, build bridges of mutual understanding between communities and increase faith in the safety of authorized vaccines across all population groups, using the right messengers.

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