# COVID-19 Mini-series
# Episode #5 – Therapies against Covid-19: Fast-tracks and regulatory pathways

**Gabriel Avigdor**, CIPP/E**, Dr Ludovic Tirelli,** Swiss Certified in Criminal Law, / Attorneys-at-law
**Francesca Belli**, Life Sciences lawyer

**Covid-19 Mini Legal Series**

This mini-series aims at providing legal guidance and recommendations to Swiss organizations during the uncertainty relating to the spread of the coronavirus and the recent decisions from the Swiss authorities. While this public health threat impacts and disrupts numerous businesses and organizations, we provide regular practical advices on selected topics on this page and on our social media channel. You may click on any underlined term to access further information.

In only a few months, scientists around the world have become the new heroes together with key citizens performing jobs that are crucial for our society under confinement measures.

Thousands of scientific papers have been published on Covid-19. To date, the World Health Organization (WHO) database shows more than 15,253 results on the new coronavirus disease. Also, many other "github" and similar platforms have arisen for sharing scientific knowledge, models, data and publications. While scientists are running against the clock to understand all what the virus means for our society, citizens are waiting for a potential cure in order to eradicate it. Despite the need of finding fast solutions, developing a vaccine or a medicine is never easy from a regulatory point of view.

**But why does it take so long?** This (longer) episode aims at providing an overview of the special measures that have been implemented to date by the authorities, both in Switzerland and in the EU, to ensure that therapies with the potential of preventing or treating the new coronavirus can enjoy easier and faster pathways and approval mechanisms compared to the standard ones.

## Q.1 Which are the standard regulatory pathways and timelines to get a medicinal product approved by the authorities and ready to be placed on the market in EU and in Switzerland?

A.1: Placing a new vaccine or medicinal product on the market and getting it available to the general public with all the necessary authorisations takes a long time. Even when brilliant and hard-working scientists discover active principles and mechanisms of action, which prove to be effective to prevent or treat a disease in the laboratory, several more years are usually needed for the larger population to take advantage of a new medication. This also applies to vaccines and medicines against viruses that create diseases with unknown effects on the human body, such as SARS-COV-2 (also known as "**Covid-19**").

**Europe**

According to the **EU pharmaceutical legislation**, the evaluation of a medicine by the competent authority (European Medicines Agency, "**EMA**") can take up to **210 active days** under a standard procedure. During this time, a developer can request guidance and direction from EMA on the best methods and study designs to generate robust information on how well a medicine works and how safe it is (so called "**scientific advice**"). This sub-procedure (request and granting of the scientific

advice) is a parenthesis that takes normally **40-70 days** to close.

Then, when applying for a marketing authorisation, the developer submits all the data generated on the medicine to EMA. The Agency assesses this information and determines whether or not the medicine is safe and beneficial to patients. Once the EMA expresses a positive evaluation, the European Commission will take an additional couple of months to make a final legally binding decision on whether the medicine can be marketed in the EU. The actual market "access", and hence the availability of the drug to the patients in each of the EU (and EEA) member States, can then usually happen only after decisions about pricing and reimbursement have taken place at national and regional levels (which may even require additional years, depending on the regulatory framework applicable in the specific country).

**Switzerland**

The timeline for evaluating a drug under development, although not specifically defined by the legislator, does not differ substantially from the one applicable in the EU and is set at an average of **200 days**. As an advantage compared to the EU procedure, though, the competent authority that evaluates the marketing authorization application concerning a medicine (**Swissmedic**) is the same that will eventually grant the authorization itself and there is no need to wait to reach any further agreements at a cantonal level.

Under art. 13 of the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, "**TPA**"), where a medicine is already authorised to be placed on the market in a country having equivalent controls, the results of tests carried out for this purpose can be taken into account. Swissmedic published its revised guidance on Authorisation of human medicinal products under art. 13 TPA and maintains a list of countries with "comparable control of human medicinal products".

## Q.2 Are there alternative pathways (fast-tracks) in the EU to get a vaccine or a medication approved for use in humans faster for the ongoing pandemic?

A.2: The **European Union** already implemented procedures to speed up the availability of vaccines that we can use to protect the population against pandemic influenza. These procedures (in particular the so called "emergency procedure") are managed by the EMA and enable authorisation of influenza vaccines in around **70 active days**, as opposed to the **18 to 24 months** usually required for the authorisation of a medicine in the EU.

More specifically in the current Covid-19 situation, the EMA has recently put in place **special mechanisms to accelerate both the support during the research and development and the evaluation in authorisation and post-authorisation procedures for Covid-19 related medicines**. As far as clinical trials on humans are concerned, while the EMA has urged the research community to prioritise large randomised controlled clinical studies of potential anti-Covid-19 therapies including all EU countries in such trials, most of the European countries have put in place accelerated ("**fast-track**") procedures for the evaluation and authorization of such clinical trials.

Among the mechanisms that the EMA has introduced (defined in an inventory document published on 4 May 2020) to accelerate the support during the R&D phase, we find the following:

- **Rapid scientific advice**: fees for scientific advice are waived and the procedure is reduced to a maximum of **20 days** (compared to the standard 40-70 days mentioned above);
- **Rapid agreement of paediatric investigation plans (PIPs) and rapid compliance check**: reduction of the total review time for a PIP to **20 days** (instead of standard 120). The check to ensure compliance with the agreed measures of the PIP, in case it is required, will be also be reduced to **4 days**.

With regard to the acceleration in the evaluation of authorisation and post-authorisation procedures, we can list the following fast-tracks:

- **Rolling review**: with this procedure, the EMA may assess data for a promising medicine as it becomes available on a "rolling basis" instead of waiting for the applicant's formal submission containing all data at the start of the evaluation procedure. Several rolling review cycles can be carried out as data continues to emerge, each cycle requiring around two weeks, depending on the amount of data available. Once the data package is considered

complete, the applicant may submit the formal marketing authorisation to the EMA. It will therefore require a shorter timetable for the EMA to process the submission. Currently, rolling reviews of data have already started on the use of "remdesivir", an antiviral medicine for the treatment of Covid-19.

- **Accelerated assessment**: this procedure allows to reduce the review time of products from 210 days to less than **150 days**.

Recently, the EMA declared that it will be ready to apply further flexibility where shortening any other procedural steps could have an important public health impact in dealing with the Covid-19 pandemic. The various rapid procedures that we mention in this article are also available and can apply in the context of extensions of indications in the context of medicines that are already approved if they target the Covid-19 disease.

There are also other options available to receive enhanced support during medicine or vaccine development in the EU and which already existed prior to the Covid-19 crisis:

- the PRIME scheme (predominantly suitable for treatments and vaccines in earlier stages of development);
- the conditional marketing authorisation procedure.

## Q.3 What about fast-track procedures in Switzerland?

A.3: With its Ordinance on Measures to Combat the Coronavirus (COVID-19)("**COVID-19 Ordinance 2**") published on 13 March 2020 (as later updated), the **Swiss Federal Council** has granted some exceptions to the standard requirements for the authorisation of medicinal products intended to treat Covid-19 (art. 4 l). Provided that an application for an authorisation of a medicinal product containing one of the listed active substances has been filed, such product may indeed be placed on the market without authorisation, pending Swissmedic's decision. The Swiss Federal Agency For Therapeutic Product, may permit a relaxation of the relevant requirements on the basis of a risk-benefit analysis.

Additionally, according to the recent "**Joint Guidance of Swissmedic and swissethics** on the management of clinical trials with medicinal drug products in Switzerland during the COVID-19 pandemic", applications for clinical trials with medicinal drug products to treat Covid-19 are expressly prioritised by the authorities.

Last but not least, as of 1 January 2020, the **application of art. 13 TPA has been extended subject to certain conditions**. Upon request, Swissmedic may scale back its own review procedure related to medicinal products with new active substances indicated for the prevention of a severe communicable disease like Covid-19, by relying on corresponding foreign review results. The main conditions are that the medicinal product **has been already authorised by the European Commission or the US FDA** and the proposed **indication is identical to the indication approved by the reference authority**.

Swissmedic may also grant a "**temporary authorisation**" for the use of a human medicinal product. The **revised Swissmedic guidance** dated 1 April 2020 provides more details on the legal requirements to allow patient to have access to a drug before an ordinary approval procedure may occur. The applicant may only require a temporary authorisation where, for example, there is a short term risk of death and where less scientific evidence is available. The use of this temporary authorisation only works under strict conditions, laid down under art. 9a TPA and art. 18 – 22 of the Ordinance from Swissmedic on the simplified procedure on human medicinal products and the authorisation of medical product based on a declaration (only available in DE/FR/IT).

## Q.4 What legal grounds may doctors use to provide off-label medicines to treat patients who are affected by Covid-19?

A.4: There are essentially two general legal grounds under which patients can access medicines not intended for a certain disease or use: through regulated clinical trials and through a so called "compassionate use". We already mentioned above the clinical trial path and the prioritization granted to studies concerning the new coronavirus both in the EU and in the Swiss system.

By **compassionate use** we refer to those set of programs intended to give patients with a life-threatening, long-lasting or seriously disabling disease and no available treatment options, access to treatments that are still under development and that have not yet received a marketing authorisation. They are set up at the level of individual countries also within the EU Member States.

**Europe**

At an EU level, however, among EMA's initiatives for acceleration of development support and evaluation procedures for Covid-19 treatments and vaccines, EMA has clarified that it can provide **recommendations for a "group of patients"** on a medicinal product (eligible to the centralised procedure), in order to favour a common approach across Member States. Requests for opinion on a compassionate use shall be presented to EMA by the national competent authorities and not directly by the applicants. The Agency can accelerate the procedure and issue an opinion in a short timeframe, depending on the urgency of the situation and the amount of data available.

**Switzerland**

In Switzerland, Swissmedic expressly declared that it is permissible to use authorised medicinal products which, in the light of initial experience abroad, might be suitable for the treatment of Covid-19 on an off-label basis – i.e. for an indication other than the approved one(s). Responsibility lies in such case with the treating physician, who is required by law to inform patients about the off-label use of the medicine concerned and to obtain their informed consent after having discussed the connected risks and side effects. The deviation from the use of a product as indicated in the medicinal product information authorised by Swissmedic may relate to the indications, uses, dosage or type of administration or to use in a specific group of patients.

## Q.5 Can medicine manufacturers apply changes in the manufacturing or the supply chain of Covid-19 medicines to avoid disruptions and prevent shortages of these medicines?

A.5: **Europe**: The **EMA** has issued a **Guidance** on adaptations to the regulatory framework to address challenges arising from the Covid-19 pandemic, with a particular focus on crucial medicines for use in Covid-19 patients. An exceptional change management process ("**ECMP**") to Marketing Authorisation Holders ("**MAHs**") of crucial medicines for treatment of Covid-19 permits the swift implementation of **changes to suppliers and/or manufacturing/control sites** necessary to reduce the risks of shortages under certain conditions intended to ensure the quality of the medicinal product, while deferring the full assessment of the variation.

Under the ECMP, MAHs will be able to exceptionally source starting materials, reagents, intermediates or active substances from suppliers not specifically mentioned in the marketing authorisation if that is necessary to prevent/mitigate shortages of supplies in the EU. MAHs will be also able to use manufacturing sites or sites responsible for quality control that are not specifically mentioned in the marketing authorisation in cases where the use of an alternative site is necessary to prevent/mitigate shortages of supplies in the EU.

Other exceptions and adaptations concern the **importation** of finished products, GMP and GDP issues, quality variations and the flexibility granted to labelling and packaging requirements in order to facilitate the movement of medicinal products within the EU.

**Switzerland**

In Switzerland, according to art. 4l of the **COVID-19 Ordinance 2**, Swissmedic may, on the basis of a risk-benefit analysis, permit **changes to the manufacturing process** approved within the framework of the authorisation of medicinal products used to prevent and treat the Covid-19. Further, under art. 4m para. 3 of the same Ordinance, Swissmedic can approve the **import** of essentially identical medicinal products as a short-term solution for any temporary non-availability of medicinal products. The products may only be distributed to hospitals. Swissmedic also has the power to grant exemptions for the import and the authorisation of medicinal products whenever the epidemiological situation demands it.