Pharmaceutical Patent Law in Times of Crisis: A Comparative Study Part II

David Mulder
Taylor Wessing

Christian Dekoninck
Taylor Wessing

Adrian Toutoungi
Taylor Wessing

Matthew Caskie
Taylor Wessing

Dr Anja Lunze
Taylor Wessing

Dr Angela Knierim
Taylor Wessing

Barbora Dubanská
Taylor Wessing

Dr Agnieszka Sztoldman*
Taylor Wessing; University of Wroclaw

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Abstract

The second part of this article (Part 1 was published in the previous issue)[1] discusses the regulatory framework for conducting clinical trials and obtaining marketing authorisations in emergency situations in view of the corona pandemic of 2020. The authors, having regard for their practical implications, discuss these subjects both from a broader EU law perspective as well as from the national perspective of six jurisdictions, and give their view on the extraordinary measures that have been adopted.

Introduction

In his campaign speeches in 1959 and 1960, John F. Kennedy said that "in the Chinese language the word 'crisis' is composed of two characters, one representing danger and the other opportunity"[2]:

危机

Although the first character of the mandarin word for crisis (*wēi*) indeed means "danger", the second character (*jī*) could also mean something like "crucial point or changing point" besides "opportunity". *Wēijī* is therefore a genuine crisis, a time in which things could go horribly wrong if no action is taken.

Nevertheless, John F. Kennedy was of course right when he said that opportunities present themselves in times of crisis. Where it comes to the regulatory framework for the approval of newfound medicines, such opportunity is seen in the way the various regulatory authorities co-operate. In the European Union, the European Medicines Agency (EMA) has taken the lead by co-ordinating a harmonised approach for the collection of data on COVID-19 clinical trials.[3] In this respect, EMA stressed that clinical trials with relatively small numbers of participants or compassionate use programmes will not generate the data required in the search for effective medicines against COVID-19. EMA furthermore initiated workshops for members to the International Coalition of Medicines Regulatory Authorities (ICMRA) on COVID-19[4] and established a special task force to take quick and coordinated regulatory action.[5] These tasks groups' objectives are to assist EMA's scientific committees or take part on behalf of the scientific committees in early scientific discussions and medicines' reviews.

Also, where it comes to the necessary regulatory approval for conducting studies, clinical trials and applications for marketing authorisations, further co-operation has been established. Initiatives as accelerated scientific advice and protocol assistance, PRIME: priority medicines, accelerated assessment and

* David Mulder, Christian Dekoninck, Adrian Toutoungi, Matthew Caskie, Anja Lunze, Angela Knierim and Barbora Dubanská are attorneys-at-law at Taylor Wessing in Amsterdam (The Netherlands), Brussels (Belgium), London (United Kingdom), Munich (Germany) and Prague (Czech Republic). Agnieszka Sztoldman is an attorney-at-law at Taylor Wessing in Warsaw (Poland) and assistant professor in intellectual property rights at the University of Wroclaw (Poland) (orcid.org/0000-0001-7202-2338; research project: "Freedom of research and patent exclusivity (research exemption)" financed by the National Center for Research on the basis of the agreement with number: 2013/11/N/HS5/03999).

[1] D. Mulder et al, "Pharmaceutical Patent Law in Times of Crisis: A Comparative Study Part I" (2020) 42 E.I.P.R. 556.

[2] cf. the quotations of John F. Kennedy at *https://www.jfklibrary.org/learn/about-jfk/life-of-john-f-kennedy/john-f-kennedy-quotations#C* [Accessaed 25 September 2020].

[3] cf. the press release of EMA of 19 March 2020, "Call to pool research resources into large multi-centre, multi-arm clinical trials to generate sound evidence on COVID-19 treatments", *https://europa.eu/!Nv67qG* [Accessed 25 September 2020].

[4] cf. the press release of EMA of 3 April 2020, "International regulators discuss available knowledge supporting COVID-19 medicine development", *https://europa.eu/!Dg87VH.* [Accessed 25 September 2020].

[5] cf. the press release of EMA of 9 April 2020, "EMA establishes task force to take quick and coordinated regulatory action related to COVID-19 medicines", *https://europa.eu/!kX69pv* [Accessed 25 September 2020].

the possibility to apply for a conditional marketing authorisation were put in place to warrant access to new medicines at the earliest possibility.

In the second part of this two-part study, first the legal framework for conducting clinical trials and obtaining regulatory approval will be set out. It will then be further elaborated which measures have been provided for in legislation for emergency situations, both on a European level and the national level of Germany, the United Kingdom, The Netherlands, Belgium, Poland and Czech Republic. Finally, the EU-wide measures that have been adopted and are in effect will be discussed in more detail.

Clinical trials and regulatory approval under national legislation

European legislation

Clinical trials

In the European Union, various legislation has been put in place regulating how clinical trials should be conducted. The *ICH Guidelines for Good Clinical Practice* have for instance been incorporated in Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use. Furthermore, specific regulations relating to the implementation of good clinical practice in the conduct of clinical trials with humans are found in Directive 2001/20/EC.

Although these attempts at harmonisation have been welcomed, the downside of these means is that applications for clinical trials have to be submitted in each separate Member State where trials are conducted. This causes heavy administrative burdens on sponsors and other stakeholders involved in the conduct of these trials. If trials have to take place in various Member States on a large scale, this means that applications for approval of the trials have to be submitted with each Member State's competent ethics committee(s). Consequently, it is not uncommon that clinical trials already commenced in one Member State, while the application for the very same trial is still under review in another Member State.

In order to remove this unnecessary burden, the Clinical Trials Regulation (Regulation (EU) 536/2014) was adopted on 16 April 2014. The Clinical Trials Regulation is to repeal Directive 2001/20/EC and provides for a centralised assessment of the application in case of a multinational study. Although originally intended to enter into force in the course of 2018,[6] at present estimations are that the Regulation will enter into force no earlier than in the course of 2021. With the present crisis, however, further delays are not improbable. This means that sponsors and other stakeholders, intending to conduct clinical trials for the treatment of COVID-19, will still have to turn to the national bodies for such applications. EMA, however, did publish guidelines on the management of clinical trials during the COVID-19 pandemic, which will be discussed in more detail below in the third section of this article.

Marketing authorisations

Contrary to the way applications for clinical trials are being handled, applications for marketing authorisations have been fully harmonised in the EU. Directive 2001/83/EC and Regulation (EC) 726/2004 provide rules for the registration procedure of medicinal products for human use. With the centralised, decentralised and mutual-recognition procedures provided for in Regulation (EC) 726/2004, applicants may basically suffice with a single application for a marketing authorisation. According to the European Court of Justice, this harmonised procedure enables cost-efficient and non-discriminatory market access, while ensuring that the requirements of safeguarding public health are achieved.[7]

Where it concerns applications for marketing authorisations in emergency situations, there are various possibilities to speed things up in order to obtain early access to medicines. First, applicants may request the accelerated assessment procedure to be applied in accordance with art.14(9) of Regulation (EC) 726/2004. The accelerated assessment procedure shortens the time-limit for the Committee for Medicinal Products for Human Use (CHMP) of EMA to draw up their assessment report from 210 days to 150 days.

Second, in exceptional circumstances marketing authorisations may be granted even without the submission of a complete dossier on the efficacy and safety of the medicinal product pursuant to art.22 of Directive 2001/83/EC. Marketing authorisations may be granted under such exceptional circumstances and strict conditions: (1) if the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; (2) if in the present state of scientific knowledge, comprehensive information cannot be provided; or (3) if it would be contrary to generally accepted principles of medical ethics to collect such information.[8]

Third, if the availability of a new medicinal product would be of such importance that immediate availability outweighs the risks of less comprehensive data than normally required, a conditional marketing authorisation may be granted pursuant to art.14(8) of Regulation (EC) 726/2004 in conjunction with Regulation (EC) 507/2006. Conditional marketing authorisations issued through the centralised procedure relate to (1) medicinal products

[6] The Clinical Trial Regulation will enter into force after EMA has set up a functional portal and database (the Clinical Trials Information System, "CTIS") for the application and publication of clinical trials in the EU, following art.82 of the Regulation.
[7] European Court of Justice 29 March 2012, *Commission v Poland* (C-185/10) EU:C:2012:181 at [27].
[8] cf. Annex I, Part II, para.6 of Directive 2001/83/EC in conjunction with art.22 of that Directive.

aimed at the treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases; (2) medicinal products to be used in emergency situations in response to public health threats; or (3) orphan medicinal products.[9] Further requirements are that the risk-benefit balance of bringing the medicinal product on the market is positive, that it is likely that comprehensive clinical data will be provided eventually and that unmet medical needs will be fulfilled.[10]

Finally, art.5 of Directive 2001/83/EC provides EU Member States with the necessary instruments to permit the use of medicinal products for which no marketing authorisation has been granted (yet) in order to intervene in times of an epidemic. In situations without an epidemic, compassionate use of medicines, either on an individual level or cohort level, may be permitted after consultation thereof with EMA.[11]

Germany

Clinical trials

In Germany, clinical trials are regulated by the German Medicines Act (Arzneimittelgesetz) and the Ordinance on the Application of Good Clinical Practice in the Conduct of Clinical Trials with Medicinal Products for Human Use (GCP-Verordnung). Before a clinical trial can be commenced, approval must be obtained from the ethics committee and the competent higher federal authority (which is either the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI)). BfArM and PEI have announced several fast-track processes and simplifications for clinical trials in connection with COVID-19. For example, applications for approval of a clinical trial for the diagnosis, prophylaxis or therapy of COVID-19, as well as scientific advice prior to these clinical trials, will be processed free of charge during the pandemic by BfArM. In addition, all applications and notifications of changes in direct connection to clinical trials and drug development on COVID-19 will be processed with priority and flexibility. Applicants are requested to include a short reference to "COVID-19" in the subject line of their application letter. PEI has furthermore announced that it has approved the first clinical trial of a vaccine against COVID-19 within four days.

Apart from that, BfArM and PEI have drawn up a statement[12] regarding the possibility of remote access to source documents and data for monitoring purposes to complement the "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" by EMA.[13]

Regulatory approval

With regard to marketing authorisations, German law provides for a similar tool to the conditional (centralised) marketing authorisation according to art.14(8) of Regulation (EC) 726/2004 in conjunction with Regulation (EC) 507/2006 on a national level. It is applicable if not all documents required for a comprehensive benefit-risk assessment are yet available. In such cases, pursuant to s.28(1) and (3) of the German Medicines Act, the competent higher federal authority may grant a marketing authorisation subject to conditions if there are sufficient indications that the medicinal product may have a high therapeutic value and there is a public interest in its immediate marketing. Such conditions include that further analytical trials, pharmacological-toxicological trials and/or clinical trials will be carried out and that the results will be disclosed. The competent higher federal authority reviews the results thereof annually.

Furthermore, with s.21(2)(6), the German Medicines Act Germany has made use of the possibility provided by art.83 of Regulation (EC) 726/2004 to make medicinal products available for compassionate use. Such a compassionate use programme has also been applied in relation to treatments for COVID-19.[14]

Apart from that, under certain conditions German law permits the marketing of treatments and vaccines even before a marketing authorisation is granted. Under s.79(5) of the German Medicines Act, competent authorities may allow unauthorised medicinal products to be placed on the market temporarily which are needed to prevent or treat life-threatening diseases or threatening communicable diseases. Section 79(5) of the German Medicines Act is, other than compassionate use, an exceptional (national) permission for times of crisis. Against this background, the government of Upper Bavaria had issued a general ruling allowing clinics and hospitals to import and administer medicinal products for the treatment of COVID-19 to patients notwithstanding the lack of marketing authorisation,[15] even before the COVID-19 compassionate use programme had been started.

[9] cf. Regulation 507/2006 art.2.
[10] Regulation 507/2006 art.4.
[11] cf. Regulation (EC) 726/2004 art.83.
[12] Federal Institute for Drugs and Medical Devices and Paul Ehrlich Institute, Additional Recommendations of BfArM and PEI to the European Guidance on the Management, Version 3, of Clinical Trials during the COVID-19 (Coronavirus) pandemic, *https://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/KlinischePruefung/KPs_bei_COVID-19.html* [Accessed 25 September 2020].
[13] EMA, "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic", version 3 dated 28 April 2020. For the latest version, please visit *https://ec.europa.eu/health/documents/eudralex/vol-10_en* [Accessed 25 September 2020].
[14] cf. German Federal Institute for Drugs and Medical Devices (BfArM), List of confirmed compassionate use programs, *ps://www.bfarm.de/DE/Arzneimittel/Arzneimittelzulassung/KlinischePruefung/CompassionateUse/ Tabelle/_node.html*.
[15] Announcement of the Government of Upper Bavaria of 20 March 2020, rf. 55Ph-2678.Ph_2-40-22-75.

United Kingdom

Clinical trials

In the United Kingdom the process for the approval of clinical trials has been much streamlined in recent years, with the arrival of the single IRAS[16] application. This replaced a previously arduous regime in which those wishing to engage in clinical trials had to navigate a multi-layered system of approval by providing separate applications to each National Health Service (NHS) site that would be involved in the trials (where the NHS organisation has a duty of care to trial participants, either as patients/service users or NHS staff/volunteers). This would be in addition to regulatory approval from the MHRA and research ethics committee approval.

The Health Research Agency (HRA) was established to centralise NHS England assessment of governance and legal compliance and to administer the system of independent Research Ethics Committees. The other home nations of the United Kingdom each have their own body that performs a similar role: Health and Care Research Wales (HCWR) for projects in Wales; NHS Research Scotland for projects in Scotland; and Health and Social Care Northern Ireland for Northern Ireland. The IRAS process co-ordinates between these bodies, providing a permission which applies to research to be conducted in any of the home nations. It also covers regulatory approval by MHRA for a clinical trial of an investigational medicinal product, where required.

In the wake of the COVID-19 pandemic, the HRA has announced a fast-track system for clinical trials. This will involve an IRAS application, but differs from the usual process in that applicants have to contact the HRA in advance of the IRAS application, alerting it of the upcoming COVID-19 related application. Applicants have to create a project ID on the IRAS website, but then need not complete the rest of the online application. Instead, applicants should contact the HRA Director of the Approvals Service by email, following which the Research Ethics Committee of HRA and approvals specialists will do a rapid review of the application. How fast trial applications will then be processed, depends on the urgency. COVID-19 studies identified by the Chief Medical Officer of England to be potentially urgent for public health will be reviewed the most quickly, within 24 hours. Trials not identified by the Chief Medical Officer but relating to fundamental research such as a potential vaccine and immune response will be reviewed within 36 to 72 hours. Less critical research such as the analysis of retrospective data, the mental health impact of COVID-19 and the resulting state measures will be reviewed within one to two weeks. If a fast track review is successful, the applicant will then be encouraged to submit formally through the IRAS portal as quickly as possible. Studies which have only a peripheral connection to COVID-19 will not be reviewed by the fast track system, and a normal IRAS application will need to be made.

Regulatory approval

In the UK, Directive 2001/83/EC and Regulation (EC) 726/2004 were implemented by the Human Medicines Regulations 2012. Early access to unauthorised medicines for COVID-19 is being managed by the Medicines and Healthcare Products Regulatory products Agency (MHRA), the body which approves the marketing authorisation of medicines in the UK. This is being achieved via the MHRA's existing Early Access to Medicines Scheme (EAMS) which was launched in 2014 and operates within the existing regulatory framework. The purpose of this scheme is to provide people with life-threatening illnesses with medicines which have not yet received marketing authorisations where there exists in the words of the MHRA "a clear unmet medical need". The MHRA thereto publicly expressed their desire to approach regulatory issues relating to COVID-19 treatment as pragmatically as possible during this healthcare crisis.

Early access under the EAMS scheme is a two-part process. First a medicine must be declared a "promising innovative medicine". This is referred to as a (PIM) designation. Then a positive scientific opinion on the use of the drug in these circumstances must be obtained from the MHRA.

On 26 May 2020, the MHRA approved its first COVID-19 related positive scientific opinion via the EAMS scheme.[17] The effect of such positive opinions is that the path is cleared for individual doctors to prescribe such medicines for eligible patients on a "named patient" or "compassionate use" basis.

The Netherlands

Clinical trials

In The Netherlands, clinical trials are governed by the Medical Research Act (Wet medisch-wetenschappelijk onderzoek met mensen) and underlying legislation. The central body for applications is the Central Committee on Research Involving Human Subjects (CCMO), which supervises the local accredited Medical Research Ethics Committees (MREC).

Since the outbreak of the COVID-19 pandemic, the CCMO and several accredited MRECs have put regulations and procedures in place for fast-track assessment of research files concerning studies on COVID-19. These fast-track procedures apply in particular to studies into a vaccine, but may also be used for other interventions and/or purposes. In situations where the CCMO provides the assessment, the maximum duration of that assessment will be 25 days (instead of

[16] Integrated Research Application System.
[17] cf. the COVID-19 Therapeutic Alert of the MHRA of 26 May 2020, CEM/CMO/2020/025.

35 days). Means have been put in place to facilitate digital meetings, and a number of documents may be submitted at a later stage. For instance, the CCMO released a memorandum giving further guidance on art.6(4) of the Medical Research Act, which provides for deferred consent of human subjects in emergency situations.[18]

Regulatory approval

When a newfound medicine becomes available, early access mostly depends on how fast marketing authorisations are granted. In the absence of such a (conditional) marketing authorisation, art.41 of the Medicines Act (Geneesmiddelenwet) contains the relevant implementation of art.5(3) of Directive 2001/83/EC for emergency situations. According to this article, no one may be held accountable for any harm caused by putting a specific medicinal product on the market which use has been advised or requested by the Minister of Health in times of crisis, except for the Kingdom of The Netherlands itself.

Alternatively, in the absence of such an advice or request, practitioners could decide prescribing certain medicinal products off-label in accordance with art.68 of the Medicines Act. Other than compassionate use, off-label prescription does not have a legal basis in Directive 2001/83/EC. Off-label prescription of medicines is nevertheless permitted insofar certain protocols or standards have been put in place. If these protocols or standards are still under development, the prescribing doctor will have to consult a pharmacist beforehand.[19]

Belgium

Clinical trials

Following the adoption of the Clinical Trials Regulation, the Belgian legislator voted in favour of the Act of 7 May 2017 for clinical trials on medicinal products for human use (the Belgian Clinical Trials Act) in order to ensure a swift implementation of the Clinical Trials Regulation in Belgium. According to the Belgian Clinical Trials Act, the Federal Agency for Medicines and Health Products will be responsible for validating applications. The assessment of these applications will be performed by an ethical committee together with the Federal Agency for Medicines and Health Products, as detailed in an implementing Royal Decree of 9 October 2017. This Act also provides for a federal body that will supervise the accredited ethics committees and be the point of contact for dispatching applications to an ethical committee. The Belgian Clinical Trials Act will, however, only enter into force as from the moment that the Clinical Trials Regulation enters into force, which may take some time as mentioned above.

Up to the entry into force of the Clinical Trials Regulation and the Belgian Clinical Trials Act, the Act of 7 May 2004 on Experiments on Humans, which also covers experiments not specifically relating to medicinal products, remains applicable. Under this current legislation a clinical trial requires approval from an ethics committee and the Minister of Health (de facto the Federal Agency for Medicines and Health Products). Currently there is no central authority supervising the ethics committees, each having their own procedures.

In response to the COVID-19 pandemic, the Federal Agency for Medicines and Health Products has published a new version of the national Belgian directive for management of clinical trials during coronavirus pandemic[20] (providing essentially for expedited procedures) which supplements the European guidelines[21] in this regard. A first clinical trial relating to a vaccine against COVID-19 has been approved recently,[22] and various other clinical trials relating to COVID-19 are pending.[23]

Regulatory approval

According to art.6*quater*, § 1 of the Belgian Act of 25 March 1964 on Medicinal Products,[24] medicinal products that are not authorised (yet) or authorised for another indication may under certain specific conditions nevertheless be made available to patients.

Apart from the exception relating to special needs, as provided for in art.5(1) of Directive 2001/83/EC, this article provides for compassionate use programmemes and medical need programs:

- Under the same conditions as provided in article 83 of Regulation (EC) 726/2004 non-authorised medicinal products may be made available in the context of a compassionate use program.
- In cases where a patient has a chronic disease, a disease with a serious impact or a life threatening disease that cannot be treated satisfactory by a product that is authorised for this indication (and commercially available) in Belgium, medicinal products (that are authorised but

[18] cf. the CCMO Memorandum Flowcharts deferred consent for medical research in emergency situations of 7 April 2020, *https://english.ccmo.nl/publications/publications/2020/04/07/ccmo-memorandum-flowcharts-deferred-consent-for-medical-research-in-emergency-situations* [Accessed 25 September 2020].

[19] According to estimations, about 50% of all medicinal products in The Netherlands are prescribed for indications outside the scope of the original registration text. This would be about 110 million medicines in The Netherlands on a yearly basis. cf. F. Moss, *T&C Gezondheidsrecht, art. 68 Gmw, aant. 1* (Kluwer: 2019).

[20] Federal Agency for Medicines and Health Products, Coronavirus: new version of Belgian directive for management of clinical trials during coronavirus pandemic, 29 April 2020, *https://www.famhp.be/en/news/coronavirus_new_version_of_belgian_directive_for_management_of_clinical_trials_during* [Accessed 25 September 2020].

[21] EMA, *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic*, version 3, dated 28 April 2020. For the latest version, please visit *https://ec.europa.eu/health/documents/eudralex/vol-10_en* [Accessed 25 September 2020].

[22] Federal Agency for Medicines and Health Products, press release of 19 June 2020, *https://www.fagg.be/nl/news/coronavirus_vergunning_voor_eerste_klinische_proef_met_covid_19_vaccin_in_belgie* (in Dutch) [Accessed 25 September 2020].

[23] An overview of the pending clinical trials can be consulted on the clinical trials database, available at *https://databankklinischeproeven.be/en* [Accessed 25 September 2020].

[24] Which mainly transposes art.5 of Directive 2001/83/EC into Belgian law.

not for the relevant indication) may be made available for the non-authorised indication in the context of a medical need programme. It is however required that:

— an application to obtain authorisation for the indication in question is pending; or
— the indication has been authorised but the product is not yet commercially available in Belgium; or
— clinical trials are ongoing or clinical trials have demonstrated the relevance of the use of the medicine in the envisaged indication.

It should be noted that this exception relates to the making available of medicinal products by the holder of the marketing authorisation. In view of their therapeutic freedom, including the freedom to choose the best possible means to treat their patients, physicians may decide to prescribe certain medicinal products off-label, even if the above conditions are not met, provided that the patient is informed thereon. As physicians do not have to specify the indication in their prescription, it is in most cases impossible to verify whether a prescription relates to an off-label use. Although the physicians thus have the freedom to prescribe such off-label use, guidance may nevertheless be issued. As such, the Federal Agency of Medicines and Health Products, based on the recommendations of the institute of public health, Sciensano, has strongly discouraged the off-label use of hydroxychloroquine to treat COVID-19.[25]

Finally, art.6*quater*, § 1, 5° of the Law on medicinal products of 25 March 1964 allows the Minister of Public Health or his delegate to authorise the distribution of unauthorised medicines in order to fight against serious threats for the public health. The implementing Royal Decree explicitly provides that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product under these conditions.

Poland

Clinical trials

The conditions for conducting clinical trials of medicinal products in Poland are regulated by the Polish Pharmaceutical Law of 6 September 2001.[26] Each clinical trial may only be conducted on the basis of a prior authorisation issued by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, in combination with a positive opinion of the Bioethics Committee. The President of the Office shall record the clinical trial in the Central Register of Clinical Trials. According to the Polish Pharmaceutical Law, a clinical trial of an investigational medicinal product is conducted in accordance with Good Clinical Practice, providing a standard for planning, conducting, monitoring, documenting and reporting the results of clinical trials conducted on humans.[27]

According to the Statement of the President of the Office for Medicinal Products, Medical Devices and Biocidal Products of 19 March 2020 regarding clinical trials conducted during the pandemic,[28] investigators, sponsors and other persons/entities involved in conducting clinical trials are advised to introduce amendments arising from the need to adapt to the epidemiological situation and to consider them as urgent safety measures (in accordance with art.37y of the Polish Act Pharmaceutical Law of 6 September 2001). Article 37y provides the facility to abstain from conducting a clinical trial in accordance with the applicable protocol if any event that is likely to affect the safety of participants to the clinical trial occurs.[29] On 29 May 2020, a further statement was communicated that an inspection on the safety monitoring systems for medicinal products will be carried out until further notice by means of electronic communication.[30]

It is furthermore noteworthy that, in view of the spread of the SARS-CoV-2019 pandemic in Poland, an industry association of medicinal product manufacturers (POLCRO,[31] GCPpl[32] and INFARMA[33]) developed a document entitled "Good practices of clinical trials during the COVID-19 epidemic".[34] This document contains recommended good practices and available solutions which can be considered and adapted to any clinical trial (commercial and non-commercial) in order to eliminate

[25] Federal Agency for Medicines and Health Products, press release of 8 June 2020, *https://www.famhp.be/en/news/coronavirus_hydroxychloroquine_off_label_use_strongly_discouraged_and_new_benefit_risk* [Accessed 25 September 2020].
[26] Pharmaceutical Law (Prawo farmaceutyczne) of 6 September 2001 (Dz.U.2020.944 of 2020.05.27).
[27] Regulation of the Minister of Health on Good Clinical Practice (Rozporządzenie Ministra Zdrowia w sprawie Dobrej Praktyki Klinicznej) of 2 May 2012 (Dz.U.2012.489 of 2012.05.09).
[28] Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych; cf: *http://urpl.gov.pl/pl* [Accessed 25 September 2020].
[29] See also: Communication of the President of the URPL of 19 March 2020 on clinical trials conducted during the pandemic (in Polish: *Komunikat Prezesa z dnia 19 marca 2020 r. w sprawie badań klinicznych prowadzonych w warunkach pandemii*), *http://www.urpl.gov.pl/pl/komunikat-prezesa-z-dnia-19-marca-2020-r-w-sprawie-badań-klinicznych-prowadzonych-w-warunkach* [Accessed 25 September 2020].
[30] Communication of the President of the URPL of 29 May 2020 on inspections of clinical trials and control of medicinal product safety monitoring systems (in Polish: *Komunikat Prezesa z dnia 29 maja 2020 w sprawie inspekcji badań klinicznych i kontroli systemów monitorowania bezpieczeństwa produktów leczniczych*), *http://www.urpl.gov.pl/pl/komunikat-prezesa-urzędu-z-dnia-29-maja-2020-r-w-sprawie-inspekcji-badań-klinicznych-i-kontroli* [Accessed 25 September 2020].
[31] This means *Polski Związek Pracodawców Firm Prowadzących Badania Kliniczne na Zlecenie* (in English: Polish Association of Employers of Companies Conducting Clinical Investigations on Request); see *http://www.polcro.pl* [Accessed 25 September 2020].
[32] This stands for *Stowarzyszenie na Rzecz Dobrej Praktyki Badań Klinicznych w Polsce* (in English: Polish Association of Clinical Research Organizations); see *https://www.gcppl.org.pl* [Accessed 25 September 2020].
[33] This stands for *Stowarzyszenie Przedstawicieli Innowacyjnych Firm Farmaceutycznych* (in English: Employers' Union of Innovative Pharmaceutical Companies); see *https://www.infarma.pl* [Accessed 2 October 2020].
[34] Good clinical practice of medicinal products during the COVID-19 pandemic of 13 May 2020 (English version), *https://www.infarma.pl/assets/files/2020/Good_Clinical_Practice_Recommendations_v3.pdf* [Accessed 25 September 2020].

the risks associated with conducting clinical trials during the COVID-19 pandemic, as well as clinical trials on medicines for the disease caused by this virus. In particular, the following has been adopted: (1) legal security of conducted clinical trials; (2) liaising with the bioethics committees; (3) liaising with the Office for Medicinal Products, Medical Devices and Biocidal Products; (4) clinical activities and management of ongoing studies; (5) managing the investigational medicinal product; and (6) data reliability (quality, continuity, assurance, confidentiality).

Regulatory approval

In Poland, there are no new special registration procedures for medicinal products in connection with the COVID-19 pandemic. The EMA guidelines for the modified registration path will apply, including where these relate to rapid scientific advice, rapid agreement of a paediatric investigation plan, rapid compliance check, rolling review and marketing authorisation. A national regulation applicable in the fight against a pandemic is that the Minister responsible for health and veterinary medicinal products may, at the request of the Minister responsible for agriculture, authorise medicinal products without a permit for a limited period of time in the event of a natural disaster or other threat to human life, health or to the life or health of animals.[35]

In exceptional circumstances, the President of the Office for Medicinal Products, Medical Devices and Biocidal Products may decide, after consulting the market authorisation holder, to apply fast-track authorisation. This is, however, only if such a fast-track authorisation complies, within a prescribed period, with the conditions laid down on the basis of the requirements of Annex I to Directive 2001/83/EC and, in the case of a veterinary medicinal product, on the basis of the requirements of Annex I to Directive 2001/82/EC. Above all, this means that the safety of the medicinal product should be warranted, that adverse effects relating to the product should be reported and that specific action have to be undertaken in such cases (which therewith is a flexible equivalent of art.14(8) of Regulation 726/2004).[36]

The Polish Office for Registration of Medicinal Products promotes the use of off-label prescription, compassionate use and sometimes Randomized Clinical Trials in combating COVID-19. For the time being, there are no known examples of drugs marketed in Poland by leading pharmaceutical companies ("known drugs") and registered in Poland under the "accelerated pathway" in connection with COVID-19. There are, however, rolling reviews ongoing and off-label prescription appears to occur more frequently.

Czech Republic

Clinical trials

The Czech Act on Pharmaceuticals (*zákon o léčivech*)[37] and Decree on Good Clinical Practice (*vyhláška o správné klinické praxi*)[38] govern the rules for approval, start and execution of clinical trials. A clinical trial requires an approval from the ethics committee and an approval from the Czech State Institute for Drug Control (*Státní ústav pro kontrolu léčiv* or SÚKL).

In response to the COVID-19 pandemic, SÚKL published recommendations on clinical trials[39] which follow guidelines issued by EMA[40] (in a shortened manner with amendments reflecting specifics of Czech law) and are continuously amended to reflect the development of the pandemic situation. In the latest statement following the improvement of the pandemic situation in the Czech Republic, SÚKL cancelled its previous recommendation not to start new clinical trials and imposed a set of rules for ensuring safety of clinical trials.

In its statement, SÚKL announced that applications for starting clinical trials on medicinal products connected to COVID-19 will gain priority assessment in shortened time. Multicentre ethics committees have also promised to assess these applications with haste.

Regulatory approval

The Czech Act on Pharmaceuticals[41] provides several means concerning how to achieve early access of medicinal products needed by patients. Among these are specific treatment programmes (compassionate use); temporary approval of distribution, sale and use of an unregistered medicinal product; and prescription by a doctor (off-label use).

In cases stated in art.83 of Regulation (EC) 726/2004 or in case of an extraordinary need when no registered medicinal product is available for effective patient treatment, prophylaxis and the prevention of infectious diseases, there is a possibility to permit the use, distribution and sale of an unregistered medicinal product within a specific treatment programme.[42] A specific treatment programme can be conducted with prior approval of the Ministry of Health based on an application stating a description of the programme, including the group of patients concerned, means of monitoring and/or the facility where the programme should be conducted.

[35] Polish Pharmaceutical Law of 6 September 2001 (Dz.U.2020.944) art.4(8).
[36] Polish Pharmaceutical Law of 6 September 2001 (Dz.U.2020.944) art.23b.
[37] Act No.378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals).
[38] Decree No.226/2008 Coll., on good clinical practice and detailed conditions of clinical trials on medicinal products, as amended.
[39] Statement of the department for clinical trials of SÚKL for ongoing clinical trials and clinical trials which have yet to commence in connection with COVID-19 from 14 May 2020, *http://www.sukl.cz/leciva/stanovisko-odboru-klinickych-hodnoceni-lecivych-pripravku* [Accessed 25 September 2020].
[40] EMA, *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic*, version 3 dated 28 April 2020. For the latest version, please visit *https://ec.europa.eu/health/documents/eudralex/vol-10_en* [Acessed 25 September 2020].
[41] Act No.378/2007 Coll. on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals).
[42] Czech Act on Pharmaceuticals art.49.

In addition to the options under art.83 of Regulation (EC) 726/2004, the medicinal products do not need to be the subject of an application for a marketing authorisation or to be undergoing clinical trials in order to be included in the specific treatment programme. Czech law therewith provides for a much wider form of compassionate use.

In the case of an expected or confirmed spread of a cause of a disease (i.e. also in the case of a pandemic), the Ministry of Health can, based on an expert opinion of SÚKL, temporarily allow the distribution, sale and use of an unregistered human medicinal product.[43] In such cases, the marketing authorisation holder, manufacturer and healthcare providers cannot be held liable for the consequences of such use of the medicinal product. This procedure has already been used with respect to several medicinal products during the COVID-19 pandemic.

An attending doctor can prescribe or use an unregistered medicinal product with the objective of providing optimal healthcare, provided that a registered medicinal product is not available on the Czech market and the product to be used is already registered in another state. Furthermore, the use should be based sufficiently on scientific knowledge and the medicinal product should not contain genetically modified organisms.[44] Such use must be notified to SÚKL without undue delay by the prescribing doctor. However, the doctor may be held liable for any harm caused due to the prescription or use of an unregistered medicinal product in such situations in the absence of prior approval of the Czech Ministry of Health.

EU-wide measures that have been put in place

Guidance by EMA on clinical trials

As briefly addressed in the introduction of this article, ever since the COVID-19 outbreak EMA has taken the lead when it comes to overseeing various regulatory aspects both within and outside the EU. One of the many international challenges in this regard is the fact that a very large number of ongoing or planned clinical trials, not related to COVID-19, have been delayed, suspended or even discontinued.[45] According to an overview of BioWorld, no fewer than 419 clinical trials were disrupted due to the coronavirus on 23 June 2020.[46]

With its Guidance on the management of clinical trials during the COVID-19 pandemic, the last update at the time of writing of this article dating from 28 April 2020,[47] EMA introduced a number of regulatory flexibilities for the duration of the crisis. The guidance is applicable until its revocation[48] and Member States are *encouraged* to implement the guidance to the maximum extent possible. After all, as discussed previously, the national bodies of Member States remain competent for assessing applications for clinical trials until the entry into force of the Clinical Trials Regulation.

The guidance covers both changes to the initiation of new trials and ongoing trials. One of the main changes addressed regarding ongoing trials is that urgent safety measures no longer need prior notification to the competent authorities. Such urgent safety measures find a legal basis in art.10 of the Clinical Trials Directive, which article nevertheless requires that the competent authorities and Ethics Committee shall be informed of the measures taken without delay. The guidance furthermore stipulates that the justification for such delay in the notification needs to be documented in the trial master file.

Another significant change, which also applies to new trials relating to COVID-19, is that informed consent may be acquired later on in case of acute life-threating situations, where it is not possible within the therapeutic window to obtain such prior informed consent. However, such a delay in obtaining consent is permitted only when this is explicitly provided for by national legislation. After all, the prohibition to conduct clinical trials on patients without their prior informed consent is strictly forbidden in accordance with art.7 of the International Covenant on Civil and Political Rights (ICCPR), while exceptions should only be permitted in circumstances where this would be either in the interest of the individual concerned or public health.[49] It therefore remains of crucial importance to verify beforehand whether or not the national legislation of the jurisdiction, where the trial is conducted, actually included such an exception and what policy the ethics committees adopt when it comes to the COVID-19 crisis. Where, for instance, deferred consent is indeed permitted under extraordinary circumstances in The Netherlands, Czech Republic, Poland and Germany, the laws of other jurisdictions may not provide for such an exception.

Finally, according to the report of the ICMRA of 18 March 2020,[50] various flexibilities were agreed upon where it concerns the data required for first-in-human clinical trials for vaccines for COVID-19. Although the exact extent of pre-clinical data required remains the (exclusive) authority of the competent national body, it

[43] Czech Act on Pharmaceuticals art.8(6).
[44] Czech Act on Pharmaceuticals art.8(3).
[45] cf. the press release of EMA of 15 June 2020, "Global regulators work towards alignment on policy approaches and regulatory flexibility during COVID-19 — update #4", *https://europa.eu/!Yt83rm* [Accessed 25 September 2020].
[46] cf. the overview of clinical trials of biopharma products affected by COVID-19 of BioWorld, available at *https://www.bioworld.com/COVID19clinical-affect* [Accessed 25 September 2020].
[47] EMA, *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic*, version 3 dated 28 April 2020. For the latest version, please visit *https://ec.europa.eu/health/documents/eudralex/vol-10_en* [Accessed 25 September 2020].
[48] Which will only be when there is consensus that the period of the outbreak in the EU has passed.
[49] cf. the Annotation to art.7 of the draft international covenants on human rights, Travaux Préparatoires to the ICCPR (1 July 1955), A/2929, p.88, *https://hr-travaux.law.virginia.edu/international-conventions/international-covenant-civil-and-political-rights-iccpr* [Accessed 25 September 2020].
[50] Summary report of the ICMRA on the Global regulatory workshop on COVID-19 vaccine development of 18 March 2020, available at *https://europa.eu/!bt88MW* [Accessed 25 September 2020].

may for instance no longer be required to demonstrate the efficacy of a candidate in animal challenge models. Also, with respect to toxicology data, data accrued with other products using the same platform technology may suffice as support for first-in-human clinical trials.

At the moment of the writing of this article, EMA reported that it had no less than 34 potential COVID-19 vaccine candidates under investigation, as well 132 potential candidates for the treatment of COVID-19.[51] A complete and up-to-date overview of all clinical trials is available in the EU Clinical Trials Register (EU CTR).[52]

Further regulatory measures

Ever since the outbreak of the new coronavirus, EMA has been actively pointing out the possibilities for developers and manufacturers to apply for conditional marketing authorisations. This has eventually resulted in a first application[53] and recommendation for a conditional authorisation for remdesivir.[54] The application for the conditional authorisation followed directly after a rolling review during the further development of this medicinal product.

While, at the time of the writing of this article, a conditional marketing authorisation for remdesivir for the treatment of COVID-19 has yet to be granted, EMA in the meantime explicitly points towards the possibility of its compassionate use.[55] In the view of the authors, further recommendations of EMA and other national bodies on compassionate use should be strongly encouraged. After all, without such (centrally overseen) recommendations, member states might be inclined to make use of the exotic exception of art.5(3) of Directive 2001/83/EC motivated by political reasons instead of scientific arguments. Compassionate use, on the other hand, requires that (the regulatory bodies of) Member States inform EMA of their intent to make use of such compassionate use programmes, providing the CHMP with the possibility to give further advice.[56]

Compassionate use is available as long as a medicinal product has not received a (conditional) marketing authorisation.[57] This also means that if the indications for which a marketing authorisation has been granted diverge from the conditions and indications defined in the marketing authorisation, compassionate use is no longer an option. In these situations, the most obvious alternative would be to dispense medicines by means of off-label prescription instead (insofar the national laws of a Member State permit such off-label prescription and use).

It will be interesting to see if EMA will also recommend the compassionate use of other medicinal products in the near future and if the medicinal products, for which compassionate use is recommended, indeed prove to be effective in the treatment of COVID-19. In this regard it may be noteworthy that, other than in the case of a Member State recommending the use of an unauthorised medicinal product pursuant to art.5(3) of Directive 2001/83/EC, the manufacturer of the medicinal product remains liable under civil law and criminal law in case of compassionate use programmes.[58] While the threat of liability should warrant that manufacturers only put promising medicinal products on the market, this may also cause the same manufacturers to be reluctant to do so. At the same time compassionate use should not be regarded as an adequate substitute for the (conditional) marketing authorisation. After all, as has been stressed by EMA on multiple occasions, the collection of robust data on the safety and effectiveness of medicinal products remains absolutely crucial in the long run when it comes to the search for new medicines.

Conclusion

The legal framework applicable to clinical trials and regulatory approval provides sufficient basis for flexibilities in times of a crisis. With EMA leading the way and national bodies implementing its guidance, a large number of promising clinical trials are ongoing. Although the removal of the administrative burden for sponsors of having to apply for administrative approval in each individual Member State through the entry into force of the Clinical Trials Regulation would have been most welcome, the present co-operation on an international scale is unprecedented.

Furthermore, with all measures adopted both by EMA and the various national regulatory bodies, early access to new treatments and a vaccine appears to be warranted. Until then, the "new normal" and the "one and a half metre" society is likely to remain part of everyday life, and hopefully may prevent multiple waves of outbreaks both inside and outside the EU.

[51] cf. the overview of Treatments and vaccines for COVID-19 of EMA, available at *https://europa.eu/!vC48Mf* [Accessed 25 September 2020].
[52] Accessible through *https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19* [Accessed 25 September 2020].
[53] cf. the press release of EMA of 8 June 2020, EMA receives application for conditional authorisation of first COVID-19 treatment in the EU, available at *https://europa.eu/!Bg44fT* [Accessed 25 September 2020].
[54] cf. the press release of EMA of 25 June 2020, First COVID-19 treatment recommended for EU authorisation, available at *https://europa.eu/!bj93dr* [Accessed 25 September 2020].
[55] cf. the Summary on compassionate use of remdesivir Gilead of 3 April 2020, available at: *https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf* [Accessed 25 September 2020].
[56] Regulation (EC) 726/2004 art.83(3) and 83(4). Such advice was for instance requested by Estonia, Greece, The Netherlands and Romania.
[57] Regulation (EC) 726/2004 art.83(2).
[58] Regulation (EC) 726/2004 art.83(7).