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Early and Managed Access to Medicines in Switzerland

Navigating a Challenging National and International Landscape

Claudia Götz Staehelin*
Dr. iur., Advokatin, LL.M., CIPP/E,
Kellerhals Carrard, Basel

Oliver M. Brupbacher*
Dr.iur., Rechtsanwalt, LL.M.,
Kellerhals Carrard, Basel

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Abstract: Early and managed access covers the area "in between" clinical trial research and on-label therapy. It is of increasing importance in particular in light of significant progress in the preventive and curative capabilities of treatments, including through gene therapies, recent advances in the fields of precision and personalised medicine as well as rare diseases, considerable efforts to accelerate the path from innovation to patient and – ultimately – an overall strive towards timely availability of novel pharmaceuticals, biologics and treatments. In line with international developments, Swiss law provides a series of related instruments, including compassionate use, individual and systematic therapeutic experiments, temporary authorisations for life-threatening and debilitating diseases, as well as simplified authorisations for orphan drugs. Their strategic use and implementation requires oversight over broad and diverse regulatory topics and practical experience, but they cover fundamentally all perceivable early and managed access options. Nonetheless, legal challenges remain in at least four main areas: the alignment between early access and reimbursement, the supply chain design, the fragmented regulatory landscape across countries and regions, as well as speed and timely availability. While they have traditionally affected mostly patients with life-threatening or debilitating diseases, the COVID-19 pandemic has brought these challenges to the forefront of a wider public's attention.

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I. Introduction

Instruments that make certain investigational or unapproved medicines and treatments available to patients with an unmet medical need are commonly referred to as *early and managed access*. A number of recent developments have highlighted the relevance and increasing importance of respective programmes and their regulatory environment.

One of these developments is the significant *progress in the preventive and curative* capabilities of modern treatments.[1] Arguably, this progress was never more clearly shown than in the ongoing COVID-19 crisis which was caused by the severe acute respiratory syndrome coronavirus-2 that spread globally since it first emerged in December 2019 and was declared a pandemic by the World Health Organization in March 2020.[2] Already end of 2020, the first temporary authorisations for COVID-19 mRNA vaccines

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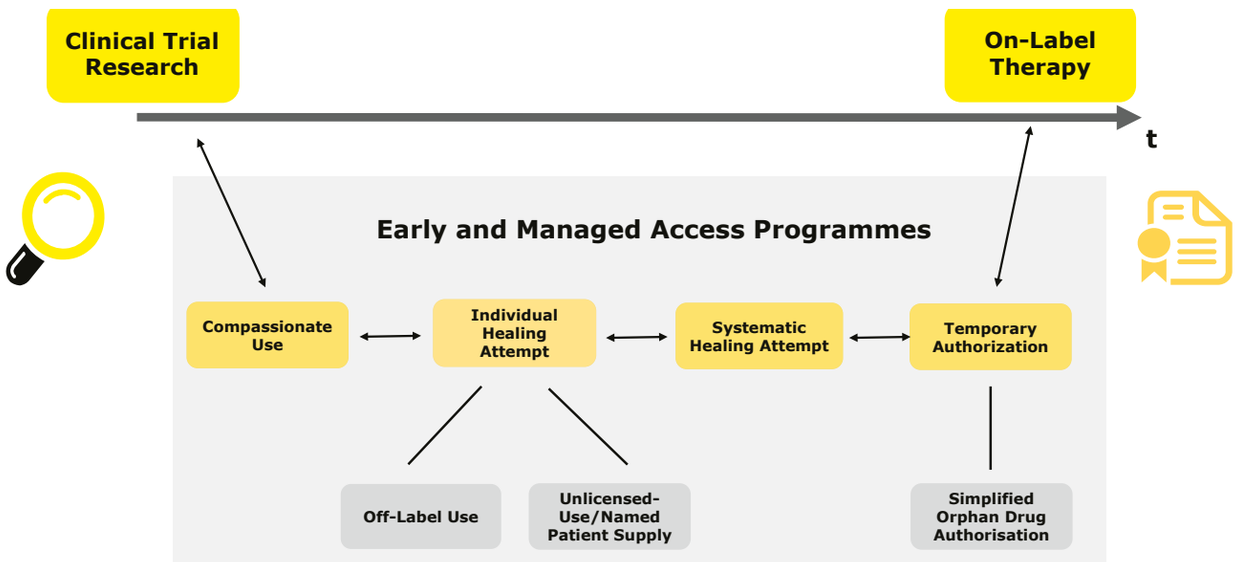
The authors wish to disclose that they advise Moderna in connection with its COVID-19 vaccine.

1 Angelika Batta *et al.*, Trends in FDA drug approval over last two decades: An observational study, in: J Family Med Prim Care, 2020, 105–114, 105.

2 See the official website of the World Health Organization, «WHO announces COVID-19 outbreak a pandemic», available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic (accessed on 24 June 2021).



were obtained. These vaccines contain a novel mechanism of action that is essentially based on a mRNA active substance encoding for the SARS-CoV-2 spike protein that is then recognised by immune cells as a foreign antigen, thereby eliciting immune responses and contributing to protection against COVID-19.[3]
At the same time, the pandemic has led to an unprecedented increase in collaborative research activities to study novel diagnostic and treatment options, and a broad range of experimental treatments have been used to treat severe cases of the coronavirus, often using off-label regimes.[4]
Another important development are the *advances in the fields of precision and personalised medicine as well as rare («orphan») diseases* that have become possible, to a significant extent, due to the abundance of available patient, including genetic, data and the ability to analyse them in a reasonable amount of time.[5] Medical progress in this area causes a swift increase in available drugs and treatment options including for hitherto incurable conditions. Due to the often very high cost of personalised medicines and orphan drugs, such treatments tend to push established conceptions of health insurance reimbursement to, or even beyond, their limits.[6]
In parallel, considerable efforts go into *accelerating the path from innovation to patient*. This is to be seen against the background of the conventional journey from discovery to marketing authorisation for novel drugs and therapies that still remains long, uncertain and expensive. Out of 5,000–10,000 investigational compounds, on average only 12 reach the clinical trial stage, and only one is finally authorised.[7] On average, the development of a new drug takes up to 13 years and requires the involvement of large international research teams. Accordingly, development costs can exceed CHF 2 billion for an authorised new drug, whereby almost two thirds of the costs are incurred in the final stage of development.[8] From the other end, patients and their representatives and organisations push for timely availability of novel treatment solutions, in particular where they are faced with a life-threatening condition or lack approved treatment alternatives.
In light of such developments, this paper provides an overview over the available early and managed access instruments in Switzerland, and addresses the key challenges and questions that arise in this context (see graphic above). For obvious reasons, it focuses on prescription medicinal products.

3 See Steve Pascolo, Sichere und effiziente mRNA-Impfstoffe gegen SARS-CoV-2, in: Schweizerische Ärztezeitung, 2020, 1234–1236, 1234.
4 Jan A. Roth *et al.*, Early off-label treatment during pandemics? A dilemma, in: Swiss Med Wkly 2020, 150. See also the website https://COVID-evidence.org (accessed on 24 June 2021), a continuously updated database of the worldwide available evidence on interventions for COVID-19 that provides information about worldwide planned, ongoing, and completed randomised controlled trials on any intervention to treat or prevent SARS-CoV-2-infections.
5 See Schweizerische Akademie der Medizinischen Wissenschaften, Personalisierte Medizin, Grundlagen für die interprofessionelle Aus-, Weiter- und Fortbildung von Gesundheitsfachleuten, 2019, 11 *et seq.*
6 Articles 71a–71d Ordinance on Health Insurance (OHI); see Bundesamt für Gesundheit, Evaluation der Vergütung von Arzneimitteln im Einzelfall nach den Artikeln 71a–71d KVV: Stellungnahme des Bundesamtes für Gesundheit, December 2020.
7 Barbara Schroeder de Castro Lopes/Judith Schallnau, Life Sciences Law, Zurich/St. Gallen 2019, 44; Vereinigung Pharmafirmen in der Schweiz (vips), Seltene Krankheiten, Fakten & Herausforderungen, 2020, 11.
8 Joseph A. DiMasi *et al.*, Innovation in the pharmaceutical industry: New estimates of R&D costs, Journal of Health Economics, 2016, 20–33, 28.

This paper starts with an outline of the basic principle of *prior marketing authorisation* (ch. II) and the basic exception of *early patient access in clinical trials* (ch. III). It then explores the instruments «in between» that are commonly employed by early and managed access programmes, including – in loose chronological order – compassionate use (ch. IV.B), individual and systematic therapeutic experiments (chs. IV.C and IV.D), temporary authorisations for life-threatening and debilitating diseases (ch. IV.E), and simplified authorisations for orphan drugs (ch. IV.F). It subsequently adds the reimbursement perspective that provides another crucial element of early and managed access (ch. V), before it concludes with an outlook and an overview over remaining challenges (ch. VI).

II. The Principle: Patient Access Follows Marketing Authorisation

In the medicinal products field, access normally requires *prior review and authorisation:* In principle, before a medicinal product, together with its corresponding drug information, can be placed on the market, it requires an official review and marketing authorisation by a competent authority. This corresponds to a generally accepted standard and is intended to protect the public from dangerous, ineffective or insufficiently tested medicinal products and to prevent incorrect or improper use. The approval process is generally based on the objective criteria of quality, safety and efficacy.[9]

In Switzerland, as a general rule, ready-to-use medicinal products may only be distributed and dispensed if authorised by the Swiss Agency for Therapeutic Products (Swissmedic; article 9 para. 1 Therapeutic Products Act, TPA).[10] The marketing authorisation is granted if, in case of medicinal products with indications or procedures, the applicant can prove that they are of *high quality, safe* and *effective,* or, in case of complementary medicines without indication, if the applicant can prove at any time on the basis of documentation that they are of high quality and if it can be credibly demonstrated that the medicinal product in question does not pose a risk to the safety of consumers.[11] The quality of a medicinal product generally requires proof of compliance with applicable Good Manufacturing Practice guidelines and Pharmacopeia. Whether the drug is safe and effective is tested in preclinical studies and clinical trials, often over many years: In the preclinical phase, substances undergo laboratory testing on cell cultures and in animals to collect basic feasibility, iterative testing and safety data. Meanwhile, clinical research in its Phases I-III seeks to understand how the substances will interact with the human body and to further evaluate their safety, tolerability and efficacy in increasingly large patient groups.[12] Post marketing, the safety of a medicinal product is subject to continued safety monitoring based on adverse event documentation and reporting.

Marketing authorisations are *specific:* They are issued for a specific composition and galenic form, for defined indications respectively fields of application, and for specified dosages. Regulatory extensions (*e.g.* a new galenic form of a drug, new indications) require a new approval procedure.[13] In fact, most approvals are granted for such extensions. Of the multitude of «new» drugs that are approved by Swissmedic every year, only few contain genuinely new molecules and, hence, represent new active pharmaceutical ingredients.[14] Approval orders are issued in the name of a specific marketing authorisation holder.[15] As a general rule, marketing authorisations are valid for five years. They can be renewed as long as the conditions for issuing the marketing authorisation are met.[16] Authorisations are valid for the entire territory of Switzerland.[17]

Marketing authorisation holders in Switzerland must have an *establishment license* to manufacture, import or conduct wholesale trade as well as a registered address, seat or branch office in Switzerland.[18]

9 See *e.g.* Gail A. Van Norman, Drugs and Devices: Comparison of European and U.S. Approval Process, in: JACC: Basic to Translational Science, 2016, 399–412, 403 f. For a comparison of Swiss approval times with the EU and the USA, see: Swissmedic, Benchmarking 2020 – Comparison of Swiss approval times for human medicines with the EU and the USA and analysis of national authorisation procedures, available at: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/studie-zulassungszeiten-ham-schweiz-2020.html (accessed on 24 June 2021).

10 This applies irrespective of whether the medicinal product requires a prescription or can be sold over the counter. Exceptions apply to the principle of prior authorisation, including for medicinal products prepared on a small scale according to specific instructions and for a small group of patients, medicinal products intended for clinical trials and medicinal products which cannot be standardised (article 9 para. 2 TPA).

11 See article 10 TPA. In the authorisation process, Swissmedic obtains advice on scientific matters from expert committees, the «Swissmedic Medicines Expert Committees» (SMEC). A negative opinion is often accompanied by questions or new requirements for the applicant who can then respond, improve the application and re-submit it.

12 See e.g Interpharma, Erste Schritte zum neuen Medikament, available at: https://www.interpharma.ch/themen/fuhrend-in-forschung-entwicklung/der-weg-eines-medikaments/forschungsfragen-zu-beginn/ (accessed on 24 June 2021); U.S. Food & Drug Administration, Learn About Drug and Device Approvals, available at: https://www.fda.gov/patients/learn-about-drug-and-device-approvals (accessed on 24 June 2021).

13 See Articles 24 *et seq.* Ordinance on Medicinal Products (OMP); Swismedic Wegleitung Änderungen und Zulassungserweiterungen HMV4, 1 June 2021.

14 See *e.g.* Swissmedic, Annual Report 2019, 29.

15 See BSK HMG-Peter Mosimann/Markus Schott, Art. 9 N 16.

16 Articles 16 *et seq.* TPA.

17 Peter Mosimann/Makus Schott (footnote 15), Art. 9 N 20 *et seq.* with further references.

18 Article 10 TPA.

These requirements represent additional hurdles for market access, especially for pharmaceutical start-ups and first market entries. It essentially means that, in parallel to obtaining a marketing authorisation for a medicinal product, the respective applicant has to obtain approval for the relevant parts of its supply chain and the respective organisation and processes. If timing is of the essence to provide patients with much-needed therapies, this may raise significant challenges, as may be exemplified by the biotechnology company Moderna and its recent – successful – efforts to have the active pharmaceutical ingredient for its COVID-19 mRNA-vaccine manufactured in Switzerland and to bring the finished product to market here, all in the record time of less than a year. The establishment licence was granted to Moderna Switzerland GmbH on 9 January 2021.[19]

While *ethical standards* and *economic considerations* are not relevant criteria for the granting of a marketing authorisation or establishment license,[20] they play a significant role when it comes to early access to medicinal products. Clinical trials that enrol patients *«must demonstrate, in particular, that tests on humans have been conducted in accordance with the recognised rules of Good Clinical Practice»*.[21] This includes compliance with the ethical rules (see below ch. III). When it comes to drug reimbursement and the respective inclusion of a medicinal product on the List of Pharmaceutical Specialities (SL), the Swiss Federal Office of Public Health (FOPH) weighs the benefits of a treatment against its risk and cost for the society as a whole (see below ch. V).

Switzerland broadly distinguishes between *ordinary, simplified* and *accelerated authorisation procedures*.[22] The ordinary marketing authorisation procedure, and the barriers to market entry it creates, do not appear to be proportionate for all medicinal products. Hence, a simplified authorisation procedure may apply in particular to generic, co-marketing and orphan (see below ch. IV. F) drugs, in cases of a temporary authorisation (see below ch. IV. E) as well as to certain drugs that have been pre-approved in an EU or EFTA country, as long as this is compatible with the quality, safety and efficacy requirements according to law or international agreements.[23] Meanwhile, an accelerated authorisation procedure may be requested for a medicinal product for human use where it is a promising prevention or therapy against a serious, disabling or life-threatening disease, if there are no or only unsatisfactory treatment options with approved medicinal products, and if the use of the new medicinal product is expected to have a high therapeutic benefit. The request for an accelerated authorisation procedure must contain the same scientific documentation, and is assessed according to the same criteria, as an application submitted in the ordinary authorisation procedure. However, it must be made in advance to Swissmedic, within the framework of an accelerated application hearing, and the implementation must be approved by Swissmedic, allowing for a targeted advance planning of resources and enabling a streamlining of the review process.

III. The Exception: Patient Access in Clinical Trials

Clinical trials are research projects in which persons are prospectively assigned to a health-related intervention in order to investigate its effects on health or on the structure and function of the human body.[24] They are generally designed to evaluate the tolerability, safety and efficacy of an investigational medicinal product with a view to fulfilling the conditions of its ultimate *marketing authorisation*.

Conversely, from the perspective of the individual patients, participation in a clinical trial offers an opportunity to *access new treatments before they are authorised* and made available to the general public. The respective information is generally publicly available because authorised clinical trials have to be registered, prior to their commencement, in a publicly accessible international online registry and additionally in the Swiss National Clinical Trials Portal (SNCTP).[25] The SNCTP offers various functions for both generally interested persons and researchers, so that patients who would like to participate in a study can search for suitable clinical trials. Researchers, for their part, can easily obtain a picture of current research activities in a subject area.

Clinical trials in humans contain strict selection criteria, as defined in an investigation plan or a study protocol,[26] on who can, and who cannot, participate in the studies. Phase I clinical trials usually include a

19 See https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/zulassung-covid-19-impfstoff-moderna.html (accessed on 24 June 2021).

20 See Peter Mosimann/Markus Schott (footnote 15), Vor Art. 8–17 N 10.

21 See article 5 Ordinance on the Requirements of Marketing Authorisation of Medicinal Products (OMAMP).

22 See articles 9 *et seq.* and 14 *et seq.* TPA; Ordinance on the Simplified Marketing Authorisation Procedures (OSMA); article 7 OMP.

23 See articles 9a, 13, 14 para. 1 TPA; articles 12 *et seq.* OSMA.

24 Article 2 lit. a Ordinance on Clinical Trials (ClinO).

25 See articles 64 *et seq.* ClinO. On www.kofam.ch (accessed on 24 June 2021), patients and other interested parties can obtain information on approved studies in Switzerland. Currently, information on approximately 55,000 studies in Switzerland and neighbouring countries can be inspected; see https://www.bag.admin.ch/bag/en/home/medizin-und-forschung/forschung-am-menschen/schweizerisches-studienportal.html (accessed on 24 June 2021). For reasons of patient protection, Phase I clinical trials, *i. e.* trials in which the investigative medicinal product is being administered to adult persons for the first time, can be registered by researchers with a time delay (article 65 para. 2 ClinO).

26 Barbara Schroeder de Castro Lopes/Judith Schallnau (footnote 7), 43.

small number of mostly healthy individuals, except in the case of known toxic substances such as chemotherapeutics that may be tested as an experimental therapy in very sick patients where treatment alternatives are lacking.[27] In Phase II, the investigational medicinal product or treatment is administered to a still small group of individuals, *i. e.* usually 20–300, to evaluate therapeutic effects and side effects as well as to determine the optimal dosage.[28] From this phase on, the study participants are normally individuals suffering from the disease for which the drug is being developed.[29] In Phase III clinical trials, the investigational medicinal product or treatment is administered to much larger groups of individuals, *i. e.* usually 300–3,000. This phase is generally designed to confirm the efficacy and safety of the new substance in relation to clinically meaningful endpoints, as compared with an established standard of care or, in the absence thereof, a placebo.[30] Information is also collected to enable the substance or treatment to be used in a way that provides the greatest benefit to patients.[31]

The investigation plan and study protocol define the *study population* using inclusion and exclusion criteria such as age, gender, and type of disease, as well as stage of disease, previous treatments, other medical conditions, and results of laboratory tests.[32] This means that patients must normally fulfil additional characteristics beyond the actual disease in order to participate in a clinical study. To ensure comparability of the study results, the selection criteria must be strictly adhered to, and exceptions generally cannot be made for «almost matching» patients. For example, if a patient fulfils only 4 out of 5 inclusion criteria, he or she normally cannot participate in the clinical study.

Clinical trials with therapeutic products are tightly regulated to ensure the *protection of human dignity, personality and health* in research and, also, to create favourable conditions for research, while ensuring its quality and transparency.[33] A clinical trial may generally only be carried out if it has been previously audited and approved by an independent supervisory body. In Switzerland, in principle, clinical trials require prior authorisation by Swissmedic[34] and independent Cantonal Ethics Committees (CECs) for research involving human subjects.[35] While the task of Swissmedic is to review applications for clinical trials of therapeutic products with regard to the Good Manufacturing Practice (GMP) compliance as well as the safety and quality of the investigational medicinal product used,[36] the CECs primarily examine whether the ethical, legal and scientific requirements are met, in particular with regard to scientific relevance (including integrity and independence), subsidiarity (*i. e.* the need to involve persons) and proportionality (*i. e.* the risk-benefit ratio), respect for the participants' right to self-determination, and requirements of particularly vulnerable persons.[37]

The use of strict inclusion and exclusion criteria, the tight regulation of clinical trials and the primacy of the interests, health and welfare of the research participants over the interest of science and society[38] mean that *clinical trials may be, but not always are, an option* for patients with diseases for which there are no approved medicinal products yet or for whom all approved therapeutic options have been exhausted. Limitations on patient access in clinical trials also result from the prohibition of pre-approval promotion. In Switzerland, professional promotion for a medicinal product may only be made after it has received marketing authorisation from Swissmedic. While pharmaceutical companies may inform healthcare professionals and the media about medicinal products, new indications, possible applications, dosages, and pharmaceutical forms that have not yet received

27 Schweizerische Akademie der Medizinischen Wissenschaften, Forschung mit Menschen. Ein Leitfaden für die Praxis, 2nd ed., 2015, 101.

28 Barbara Schroeder de Castro Lopes/Judith Schallnau (footnote 7), 43; Schweizerische Akademie der Medizinischen Wissenschaften (footnote 27), 101.

29 Barbara Schroeder de Castro Lopes/Judith Schallnau (footnote 7), 44; Schweizerische Akademie der Medizinischen Wissenschaften (footnote 27), 101.

30 Schweizerische Akademie der Medizinischen Wissenschaften (footnote 27), 101.

31 Barbara Schroeder de Castro Lopes/Judith Schallnau (footnote 7), 44. See also «What is a clinical trial and how does a trial work?» available at: https://www.roche.com → Research & Development → Who we are and how we work → Research and clinical trials (accessed on 24 June 2021).

32 See US National Library of Medicine, Learn About Clinical Studies, available at: https://www.clinicaltrials.gov/ct2/about-studies/learn#WhoCanParticipate (accessed on 24 June 2021).

33 Article 1 Human Research Act (HRA). Pertinent regulations for Switzerland are found in the TPA, the Human Research Ordinance (HRO), the ClinO, as well as directly or indirectly applicable international regulations such as the Declaration of Helsinki, the Guidelines for Good Clinical Practice of the International Conference on Harmonisation in the version dated 9 November 2016 (ICH GCP Guidelines; see article 5 para. 1 ClinO) and the Convention on Human Rights and Biomedicine (ratified on 24 July 2008). Sector-specific regulations for certain kinds of research activities apply in particular under the Transplantation Act (TransPA), the Stem Cell Research Act (SCRA), the Reproductive Medicine Act (RMA), the Human Genetic Testing Act (HGTA), and the Radiological Protection Act (RPA).

34 Article 54 para. 1 TPA.

35 Articles 45, 47 HRA; articles 24 *et seq.* ClinO. The Ordinance on Organisational Aspects of the Human Research Act (OrgO-HRA) defines the organisation of the CECs and of the Coordination Office for Research Involving Human Subjects (kofam).

36 Article 54 para. 1 TPA. An exception applies in the case of category A clinical trials, *i. e.* clinical trials involving authorised medicinal products administered in accordance with the approved conditions of use (article 54 para. 2 lit. a TPA). In certain cases, the research project must also be submitted to the FOPH for comment or approval.

37 See articles 24 *et seq.* ClinO.

38 Article 4 HRA.

marketing authorisation from Swissmedic, no promotion for these medicinal products is allowed.[39]
It is these limitations imposed on patient access by the principle of prior marketing authorisation and by the regulatory restrictions on clinical trials that are *addressed by early and managed access* instruments, as shall be set out in the following.

IV. The Options «in Between»: Early and Managed Access in Switzerland

A. Terminology

Instruments that make certain investigational or unapproved treatments available to eligible patients with an unmet medical need are usually categorised as *early access* (focussing on the patient's perspective) or *managed access* (focussing on the industry's or health system's perspective).
The terminology varies. The European Medicines Agency (EMA), for example, is *«committed to enabling early patient access to new medicines, particularly those that target an unmet medical need or are of major public health interest»,* noting that *«the European Union (EU) pharmaceutical legislation includes several provisions to foster patients' early access to new medicines that address public health needs and are eligible for the centralised procedure such as accelerated assessment, conditional marketing authorisation and compassionate use».*[40] The US Food and Drug Administration (FDA) considers *«expanded access … a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.»*[41] The industry, meanwhile, uses various terms, including *«Managed Access Programs (MAPs)»* [42] and *«Pre-Approval Access (PAA)».*[43]

In Switzerland, the following can generally be considered to constitute early or managed access instruments: *Compassionate use* (article 9b para. 1 TPA;[44] see below ch. IV.B), *off-label use* and *unlicensed use* or *named patient supply* (article 20 TPA; see below ch. IV.C), and *temporary authorisation* (article 9a TPA; see below ch. IV.E).

B. Compassionate Use

1. Nature and Delimitations

Compassionate use refers to the administration of medicinal products that are not yet approved, but that are tested in clinical trials – usually in Phase III – on a defined group of patients. It provides a mechanism whereby such unapproved medicinal products can be provided *outside clinical trials* to individual patients who would potentially respond to the drug, but who are not enrolled, or can no longer be enrolled or treated, in the clinical trial. Compassionate use programmes are typically funded by the trial sponsor, respectively the drug manufacturer.
Alongside Switzerland, in particular the USA, Canada and the EU have introduced compassionate use regulations.[45] They are *applied widely.* Most recently, the demand for treatments of the COVID-19 infection rose sharply during the pandemic while approved options were still unavailable. For example, the drug remdesivir was made available to patients through compassionate use programmes.[46]
Compassionate use is different from *clinical trial research* on the one side and *off-label use* on the other side.[47] While being comparable to a clinical trial in that it involves the use of an investigational drug the efficacy and safety of which has not yet been demonstrated, compassionate use programmes pursue primarily therapeutic purposes and thus constitute, by their very nature, a treatment, and not research.[48] Other than with off-label use where, by definition,

39 Article 32 para. 1 lit. c TPA; article 5 para. 1 and article 16 para. 1 Ordinance on Advertising of Medicinal Products (OMPA); sections 23.1, 26.2 Code of Conduct of the Pharmaceutical Industry in Switzerland (Pharma Code).
40 See EMA, Support for early access, at: https://www.ema.europa.eu/en/ → Human-regulatory → Overview → Support for Early Access (accessed on 24 June 2021).
41 See FDA, Expanded Access, at: https://www.fda.gov/news-events/public-health-focus/expanded-access (accessed on 24 June 2021).
42 See *e. g.* https://www.novartis.com/files/novartis-position-pre-approval-access.pdf; https://www.sanofi.com/en/science-and-innovation/clinical-trials-and-results → Managed Access Programs (MAPs) (all accessed on 24 June 2021).
43 See *e. g.* https://www.roche.com/dam/jcr:035f3847-505e-484c-b5f6-f666790791de/en/24_Position_Pre_Approval_Access_Investigational_Medicinal_Products_reviewed_April_2020.pdf; https://www.takeda.com/what-we-do/access-to-medicines/ → Pre-Approval Access (all accessed on 24 June 2021).
44 The notion of compassionate use in Swiss law has undergone a change, respectively clarification, with the amendment, as per 1 January 2019, of the old article 9 para. 4 TPA.
45 Jan Borysowski *et al.,* Ethics review in compassionate use, BMC Medicine, 2017, 1.
46 Giuseppe Lapadula, Five reasons why data on compassionate use of remdesivir deserved publication (and are worth reading), in: Swiss Medical Weekly, 2020, 1; See https://www.admin.ch/gov/en/start/documentation/media-releases.msg-id-79746.html (accessed on 24 June 2021). Note that, once Gilead had filed a request for an authorisation in Switzerland, it was allowed to market the drug based on article 21 para. 1 Covid-19 Ordinance 3, *i. e.* pending the authorisation process and without having to rely on compassionate use under article 9b para. 1 TPA (see below IV. E. 3).
47 See also Heidi Bürgi, Die Voraussetzungen des Off-Label Use von Arzneimitteln in der Schweiz, Basel 2013, 61 *et seq.*
48 In this sense also explicitly EMA's Guideline on Compassionate Use of Medicinal Products pursuant to Article 83 of Regulation (EC) No 726/2004, developed by the Committee for Medicinal Products for Human Use (CHMP), 3.

an otherwise authorised medicinal product is prescribed outside of its label for an indication, or to a patient, the product is not (yet) approved for, compassionate use programmes administer medicinal products that are not (yet) authorised and, accordingly, do not (yet) have a label.

2. Regulation

The regulatory requirements for compassionate use programmes in Switzerland are strict. Specifically, patients may be treated with an unproven investigational medicinal product outside of a clinical trial if it is identical to a medicinal product used in at least one clinical trial approved in Switzerland (see article 9b para. 1 TPA and articles 52 *et seq.* Medicinal Products Licensing Ordinance, MPLO). For this purpose, the sponsor of the clinical trial may apply to Swissmedic for a *temporary authorisation* to use the respective investigational medicinal products for a limited number of patients that do not qualify for inclusion in the clinical trial. The authorisation is subject to strict preconditions. Importantly, the general marketability of the product is neither assessed nor decided at this stage.

The *preconditions* include justification by the sponsor of every deviation from the most recently approved study protocol, and specification of the conditions under which the medicinal product will be used.[49] In addition, the sponsor must also justify the non-inclusion of the patients in the clinical trial, state the reasons why the use is likely of major therapeutic benefit, and prove that there is no alternative and equivalent medicinal product authorised in Switzerland.[50] The sponsor must also obtain a preliminary opinion on the aforementioned requirements from the CEC which approved the reference trial or, in the case of a multi-centre clinical trial, from the lead CEC.[51]

After its authorisation, significant changes to a compassionate use programme must be submitted to Swissmedic, together with a rationale from the sponsor. Furthermore, patients have to be informed about the risk associated with the use, including the fact that the medicinal product is only authorised based on a special licence. All adverse reactions and events that occur during the compassionate use programme must be reported to Swissmedic. Finally, the sponsor must submit an annual safety report to Swissmedic that summarises the current status of knowledge and describes the identified and potential risks of the medicinal product.[52] If Swissmedic eventually authorises the marketing of the medicinal product, the temporary compassionate use authorisation ends as soon as the product is actually supplied.[53]

3. Challenges and Limitations to Access

In terms of *patient access,* the scope of compassionate use programmes is *limited.* In view of their preconditions, they are geared towards situations where there is both a clear *health need* and an *absence of marketing purposes*.[54] Practically, therefore, they focus on an individual patient or a set of individual patients who have a serious or life threatening disease or condition for which no satisfactory alternative therapy exists and who, at the same time, cannot enter an existing clinical trial.

As much as compassionate use programmes cannot, by their definition, serve investigational purposes, they may not be used for *commercial* pre-approval activities. Pre-approval promotion of a medicinal product by means of a compassionate use programme is impermissible.[55] Equally, pharmaceutical companies are barred from working, and seeking to occupy, the market through compassionate use programmes, as they may be tempted to do seeking to early on increase the threshold to market entry for competitors. Accordingly, article 52 para. 1 lit. e MPLO requires that the sponsor must demonstrate that no alternative and equivalent medicinal product is authorised and available in Switzerland.[56]

In sum, if a new product or treatment shall be made available to patients on a larger scale, there is *no way around the proper market access pathway* of obtaining a prior marketing authorisation. Conversely, if the patient population of a clinical trial is to be enlarged, there is no way around recruiting more patients that fulfill the inclusion criteria.

C. Individual Therapeutic Experiment

Individual therapeutic experiments (also called individual healing attempts) are located in the area between research and therapy. They refer to the use of a medicinal product – whether authorised or not – in an area of application that is in any case not covered by an authorisation, *i. e.* where a patient has no conventional opportunity of being treated or cured, on the basis of an individual therapeutic decision together with a risk-benefit assessment by the treating physician.[57] Accordingly, they follow the regulations applicable to the *doctor-patient relationship*.

49 Article 52 para. 1 lit. b MPLO.
50 Article 52 para. 1 lit. c, d and e MPLO.
51 Article 52 para. 1 lit. i MPLO.
52 Article 54 MPLO.
53 Article 55 para. 3 MPLO.

54 See Janine Reudt-Demont, Totalrevision der Verordnung über die Bewilligungen im Arzneimittelbereich, in: Life Science Recht, 2018, 261–266, 262.
55 Article 32 para. 1 lit. c TPA; article 5 para. 1 and article 16 para. 1 OMPA.
56 Bundesamt für Gesundheit BAG, Erläuterungen zur Verordnung über die Bewilligungen im Arzneimittelbereich (Arzneimittel-Bewilligungsverordnung, AMBV), 2018, 18.
57 Alexander Meier *et al.,* Pharmarecht. Arzneimittel- und Medizinprodukterecht, 2nd ed., München 2018, 37; Franziska Sprecher, Patientenschutz ade? Verschiedene Massstäbe beim Patientenschutz bei individuellen Heilversuchen im Vergleich zu systematischen klinischen Studien, in: Sicherheit & Recht, 2009, 76–80, 76.

Individual therapeutic experiments do not follow the requirements of the Human Research Act because they do not aim at obtaining scientific knowledge. Rather, the focus is on the treatment of the patient, the therapeutic purpose and the possible cure.[58] The relevant differences to a *research* situation are that patients treated in the context of clinical trials enjoy *inter alia* comprehensive information rights, an unconditional right to withdraw from the trial at any time, and comprehensive insurance coverage. Clinical studies must also generally be reviewed and approved in advance by competent authorities and ethics committees (see above ch. III).

In comparison to established on-label *therapies,* individual healing attempts are always a subsidiary option and are to be understood as «ultima ratio attempts».[59]

It is to be expected that individual therapeutic experiments will gain in importance in particular in the context of developments in personalised medicine.[60] Among such individual healing attempts, a distinction is usually made between *off-label use* (see below ch. IV. C. 1) and *unlicensed use* or *named patient supply* (see below ch. IV. C. 2).[61]

1. Off-Label Use

The term off-label use describes the use of a medicinal product authorised in Switzerland in a manner that *deviates from the approved conditions of use*.[62] The deviations may refer to the indications, field of application, dosage, modes of administration, or the use in certain patient groups.

Off-label use is *widespread* in practice. Especially in the field of cancer therapy and paediatrics, medicines have always and to a considerable extent been prescribed off-label or even unlicensed.[63] Paediatric off-label use is very important because there are far fewer medicines on the market for use in children than in adults. While the figures on off-label use vary, it is assumed that up to 60% of the drugs used in oncology are applied off-label, and even up to 90% of the drugs in paediatric oncology.[64] Overall, around 70% of medicines are assumed to be prescribed and administered off-label in children, although according to other studies, the figures may be much higher.[65] For adults, the overall proportion of off-label use is estimated to be around 15%.[66] In particular in the field of rare diseases, many applications remain experimental because the case numbers are too small to meet the methodological requirements for studies.[67]

2. Unlicensed Use or Named Patient Supply

Unlicensed use or named patient supply is generally understood to mean the use of a medicinal product that, while being subject to mandatory authorisation, is available and applied in a ready-to-use form even though it has *no marketing authorisation*.[68] It enables healthcare professionals, on behalf of their patients, to access medicinal products approved, or nearing approval, in other countries before a marketing authorisation has been granted in their home country. Accordingly, it requires the prior import of such products by a healthcare professional for specific patients.

In Switzerland, access to medicines in form of unlicensed use or named patient supply by importing small quantities of ready-to-use medicinal products that are not authorised in Switzerland is permitted, and *regulated under tight conditions,* in article 20 paras. 2 and 2bis TPA as well as articles 48 and 49 MPLO. Thereby, a distinction is to be drawn between drugs that are (see below ch. IV. C. 2. a)), and that are not yet (see below ch. IV. C. 2. b)), approved abroad.

a) Named Patient Supply for Drugs Approved Abroad

For medicinal products and indications that are unapproved in Switzerland, but that are *approved in another country with a drug regulatory system comparable* to the one in Switzerland, such as the EU or the US, the import of a medicinal product by a medical professional or by the responsible pharmacist in a hospital pharmacy is permitted in principle.

Specifically, a medical professional who holds a cantonal dispensing license or a pharmacist with pharmaceutical responsibility in a hospital pharmacy may import a ready-to-use human medicinal product that

58 «Heilversuche», Bericht des Bundesrates in Erfüllung der Motion 11.3001 – «Heilversuche» der Kommission für Wissenschaft, Bildung und Kultur des Nationalrates, Bern, 11. Dezember 2015, 9; Isabel Baur, Personalisierte Medizin im Recht, Humanforschung – Quo vadis? Zürich 2019, 223.

59 Article 16 i) Biomedicine Convention. See also «Heilversuche», Bericht des Bundesrates in Erfüllung der Motion 11 (footnote 58), 9; Isabel Baur (footnote 58), 225.

60 See Isabel Baur (footnote 58), 223.

61 Isabel Baur (footnote 58), 223.

62 BGE 134 IV 175, E. 4.1 *et seq.;* See also Heidi Bürgi (footnote 47); Philippe Fuchs, Produkthaftungsrechtliche Aspekte des off-label-use von Arzneimitteln, in: Life Science Recht, 2018, 7–11, 7.

63 Ermindo R. Di Paolo *et al.,* Unlicensed and off-label drug use in a Swiss paediatric university hospital, in: Swiss Medical Weekly, 2006, 218–222, 218; Thomas Von Stokar *et al.,* Equal and Secured Access to Cancer Drugs for Off-label Use, Summary of the Final Report, 27 May 2013, 7; Beat Kipfer/Carsten Witzmann, Die Vergütung von Arzneimitteln im Einzelfall nach Art. 71a-d KVV, in: Life Science Recht, 2019, 89–109, 92.

64 Beat Kipfer/Carsten Witzmann (footnote 63), 92.

65 Virgilia Rumetsch, Medizinische Eingriffe bei Minderjährigen, Basel 2013, 134.

66 Christopher Geth, Off-label-use von Arzneimitteln und strafrechtliche Produkthaftung, in: recht, 2013, 122–134, 123.

67 Isabel Baur (footnote 58), 230.

68 Schweizerische Akademie der Medizinischen Wissenschaften/Verbindung der Schweizer Ärztinnen und Ärzte, Rechtliche Grundlagen im medizinischen Alltag, Ein Leitfaden für die Praxis, 2020, 65 *et seq.;* Ermindo R. Di Paolo *et al.* (footnote 63), 218.

is not authorised in Switzerland, provided that: (a) the medicinal product is intended for a specific patient or for emergencies; (b) the medicinal product is authorised by a country with comparable drug control,[69] *e. g.* by the EMA or FDA; and (c) for the medicinal product in question, there is no alternative medicinal product authorised in Switzerland, an alternative medicinal product is authorised in Switzerland, but is not available on the Swiss market, or a treatment change to a drug approved and available in Switzerland is not appropriate. The import is only permitted in small quantities and for a specific patient, respectively for own customers, or for emergencies.[70]

b) Named Patient Supply for Unapproved Drugs

For *unapproved* medicinal products and indications, the import by a treating physician with a cantonal professional licence or by the responsible pharmacist in a hospital pharmacy is in principle permitted if the relevant product respectively indication has been *authorised for use in a clinical trial* by a country with a comparable drug regulatory system, such as the EU or the US.

Specifically, treating physicians with a cantonal professional license may import ready-to-use human medicinal products that are not authorised in Switzerland if: (a) they have carried out a risk analysis to confirm the appropriateness of use and reported its conclusions to the competent cantonal authorities before importation; (b) the medicinal product is intended for a specific patient or for emergencies; (c) for the medicinal product in question, there is no alternative medicinal product authorised in Switzerland, an alternative medicinal product is authorised in Switzerland, but is not available on the Swiss market, or a treatment change to a drug approved and available in Switzerland is not appropriate; and (d) the medicinal product has been approved for use in a clinical trial by a country with comparable drug control. Again, the import is only permitted in small quantities and for a specific patient, respectively for own customers, or for emergencies.[71]

3. Challenges and Limitations to Access

Off-label and unlicensed use are legally permitted in Switzerland as long as the treating physicians observe their general legal *duty of care*.[72] That said, especially with named patient supply of unapproved drugs, there are undoubtedly certain challenges associated with risk-benefit analyses in connection with the appropriateness of use being carried out by the treating physicians alone. While the physicians have to report their conclusions to the competent cantonal authorities before the drug import,[73] there is no pre-approval by an independent authority (such as an ethics committee), and the information of the patients is the sole responsibility of the treating physician. This matters because, in practice (see below ch. IV. D), the boundaries between individual healing attempts and treatment activities on the one side and the various forms of clinical trial activities on the other side can be fluid. This places high demands on patient education and consent in these cases.

From a *commercial* perspective, it should be remembered that medicinal products may only be promoted for the indications approved by Swissmedic, and that off-label advertising for medicinal products is generally prohibited.[74] Scientific communication about possible off-label use is, however, permitted in principle.

Finally, as for compassionate use programmes (see above ch. IV. B. 3), individual therapeutic experiments are *no alternative route to the proper market access pathway:* If a new product or treatment shall be made available to patients on a larger scale, there is no way around obtaining a proper marketing authorisation.

D. Systematic Therapeutic Experiment

This is where the *boundaries are blurring* between individual healing attempts (see above ch. IV. C) and systematic therapy respectively research, both of which would require prior authorisation (see above chs. II and III). In contrast to individual therapeutic experiments, a systematic therapeutic experiment treats several patients off-label or unlicensed in a research-oriented manner, albeit outside of a somehow recognised standardised procedure. This form of therapeutic experiment may be considered closer to research because of its planned and structured approach.[75]

In this grey zone, whether a therapeutic trial exists, be it an individual or systematic one, is to be established according to the circumstances in each individual case. If a systematic therapeutic experiment is qualified as *research,* it is subject to the respective statutory requirements for clinical trials (see articles 11 *et seq.* HRA), including prior approval by Swissmedic and competent CECs (article 54 para. 1 TPA; articles 45 *et seq.* HRA).[76] Otherwise, the general rules of the *doctor-patient relationship,* specifically in connection with the general duty of care (articles 3, 26 TPA), apply. However, a certain degree of legal uncertainty remains. This is mainly because there is no consensus on how to clearly distinguish clinical ex-

69 See Swissmedic, Verzeichnis Liste Länder mit vergleichbarer Humanarzneimittelkontrolle HMV4.
70 Article 49 paras. 1, 3 MPLO.
71 Article 49 paras. 2, 3 MPLO. Hospital pharmacists have additional options pursuant to article 49 para. 3 MPLO.
72 Articles 3 and 26 TPA. See Peter Mosimann/Markus Schott (footnote 15), Art. 9 N 21.
73 Article 49 paras. 5, 6 MPLO.
74 Article 5 para. 1 and article 16 para. 1 OMPA.
75 Isabel Baur (footnote 58), 227.
76 Isabel Baur (footnote 58), 227.

periments from individual healing attempts.[77] From a legal perspective, as the group of patients treated off-label or unlicensed for a specific condition increases in size, the more the physicians will be called by their duty of care to base their treatment decisions on robust evidence established in respective clinical trials, in particular as their patients do not profit from the protective requirements applicable to clinical trials.

E. Temporary Authorisation for Medicines for Life-Threatening or Debilitating Diseases

1. Regulation

In Switzerland, medicinal products for life-threatening or debilitating diseases can be temporarily authorised, provided their use is expected to have a major therapeutic benefit and is compatible with the protection of health, and no authorised alternative or equivalent medicinal product is available in Switzerland. Such a temporary authorisation follows a *simplified procedure* with *reduced requirements* for marketing authorisation as compared to the normal procedure (articles 9a, 14 *et seq.* TPA; articles 18–22 Ordinance on the Simplified Marketing Authorisation Procedures [OSMA]).[78] A temporary authorisation is granted for a maximum of two years.[79] The transfer to a full marketing authorisation is subject to the fulfilment of the conditions imposed by Swissmedic. All documents relating to such conditions must be submitted to Swissmedic for assessment within a maximum of two years after the temporary authorisation, together with an application for the granting of a full marketing authorisation.[80] In principle, the temporary authorisation provides the same rights as an ordinary authorisation. Accordingly, off-label use of temporarily authorised medicinal products is generally allowed, too.[81]

2. Challenges and Limitations to Access

Studies performed in the EU relating to the equivalent European early access option, *i. e.* the conditional marketing authorisation,[82] show that, while the instrument is frequently used as a «rescue option» when the available evidence is not sufficiently persuasive for regular authorisation of a medicinal product, it does not necessarily result in promising products entering the market earlier.[83] Experience suggests that this may be particularly due to *reimbursement* challenges. In many countries, simplified or accelerated market access does not automatically amount to simplified or accelerated reimbursement (see below ch. V). In Switzerland, the relevant legislation, in particular the Ordinance on Health Insurance (OHI), does not contain specific provisions on the reimbursement for medicinal products that have been temporarily authorised. This does not mean, however, that a temporary admission would not be sufficient for an inclusion in the SL. Rather, article 65 para. 1 OHI requires a *«valid authorisation of the institute»,* which can also be understood as a (temporary) authorisation according to Art. 9a TPA. One of the relevant aspects for access here, however, may be the lack of synchronization between the temporary authorisation and the reimbursement, which may lead to a delay until a reimbursement decision is obtained.[84] In practice, in such situations, the costs are often borne by marketing authorisation holder until the final reimbursement decision.

The situation around temporary authorisations and reimbursement has presented itself somewhat differently during the COVID-19 pandemic in Switzerland, due to the direct procurement of essential medical goods, in particular vaccines, by the federal government including the Armed Forces Pharmacy.[85] On 19 December 2020, Swissmedic granted a temporary marketing authorisation to Pfizer/BioNTech's corona vaccine Comirnaty, followed by a temporary marketing authorisation to Moderna's mRNA platform-based COVID-19 vaccine on 12 January 2021. On 22 March 2021, a temporary marketing authorisation was granted for the «COVID-19 Vaccine Janssen», a human adenovirus-based vector vaccine developed by Johnson & Johnson. On 25 November 2020, Swissmedic granted a temporary authorisation in accordance with article 9a TPA for Gilead's remdesivir.

3. Authorisations Based on «Emergency» Law

In exceptional circumstances, temporary authorisations may also be granted based on «emergency» law. In terms of a recent example, medicinal products containing one of the active substances listed in the Ordinance 3 on Measures to Control Coronavirus (Covid-19 Ordinance 3) may be *placed on the market before*

77 «Heilversuche», Bericht des Bundesrates in Erfüllung der Motion 11.3001 (footnote 58), 19; see also Franziska Sprecher (footnote 57), 76.

78 See also Swissmedic, Wegleitung Befristete Zulassung Humanarzneimittel, 1 July 2021, 4 *et seq.*

79 Article 21 para. 1 OSMA.

80 Swissmedic (footnote 78), 8.

81 Peter Mosimann/Markus Schott (footnote 15), Art. 9 N 56: Pascal Lachenmeier, Die Anwendung «nicht zugelassener» Arzneimittel in der Krebstherapie nach schweizerischem Recht («off-label use»), Jusletter vom 11. Mai 2009, Rz. 48.

82 Other instruments are the authorisation under exceptional circumstances and the accelerated assessment. See also the official website of the EMA: https://www.ema.europa.eu/en/ → Human-regulatory → Marketing Authorisation → Conditional Marketing Authorisation (accessed on 24 June 2021).

83 Jorge Martinalbo *et al.,* Early market access of cancer drugs in the EU, in: Annals of Oncology, 2016, 96–105, 98.

84 On the question of the interplay between access and cost, effectiveness/safety evidence and societal value, see also Andreja Detiček *et al.,* Patient Access to Medicines for Rare Diseases in European Countries, in: Value Health, 2018, 553–560.

85 Article 14 Covid-19 Ordinance 3.

completion of the authorisation procedure if Swissmedic has received an application for authorisation.[86] This measure is intended to ensure that effective and safe medicinal products that are considered promising on the basis of the available experience can be made available to patients as quickly as possible. Irrespective, Swissmedic prioritises and appropriately accelerates applications for authorisation of medicinal products for the prevention and treatment of a pandemic disease.[87] Hence, it is not necessary to apply for an accelerated authorisation procedure in accordance with article 7 Ordinance on Medicinal Products (OMP) as Swissmedic examines all applications against the background of the pandemic with the indicated acceleration.

For example, remdesivir, a drug originally proposed by Gilead as a treatment for Ebola, has been considered as one of the most promising treatments of COVID-19, based on efficacy data derived from *in vitro* data and animal models.[88] Swissmedic decided on 30 June 2020 that, on the basis of article 21 para. 1 Covid-19 Ordinance 3, remdesivir may temporarily be placed on the market in Switzerland pending marketing authorisation approval (as powder for a concentrate, and as concentrate, for the preparation of a solution for infusion). This applied from the date of submission of a complete marketing authorisation application until Swissmedic would decide on the marketing authorisation or until the corresponding emergency legal basis would be lifted. In this case, a final decision to grant a temporary authorisation in accordance with article 9a TPA was issued on 25 November 2020.

F. Special Case: Simplified Authorisation for Orphan Drugs

1. Rare Diseases and Orphan Drugs

Rare diseases are diseases that affect only a comparatively small number of people. Today, around 6,000 to 8,000 rare diseases are known worldwide, of which about 80% are genetic.[89] New research suggests that approximately 4% of the global population is affected by a rare disease at any given time.[90] According to estimates of the University of Lausanne, about 7% of the Swiss population suffer from a rare disease, *i. e.* about 600,000 people.[91]

Patients with rare diseases mostly face similar *challenges* relating to diagnosis, availability of relevant information and access to specialist physicians.[92] On average, patients see seven doctors until they receive the correct diagnosis after an average of five years and one misdiagnosis.[93] Such patients encounter particular challenges with respect to, *e. g.,* access to qualified specialist facilities, general social and medical support, effective cooperation between the different actors such as hospitals and general practitioners, continued social and professional integration, and maintaining independence.[94] Children with rare diseases regularly are in a particularly challenging situation given that there are often not enough patients to conduct the necessary clinical studies. If there is a lack of study results, there are no new drug approvals and thus no reimbursement from basic insurance.[95]

Orphan drugs are medicines for the treatment of diseases that are so rare that sponsors, *i. e.* mostly pharmaceutical and biotechnology companies, traditionally have been reluctant to develop them on normal market terms. To spur on research and development in the area of orphan drugs, government agencies introduced regulatory incentives for the healthcare and biotechnology industries. The beginnings thereof date back to the introduction of the US Orphan Drug Act in 1983.[96] Europe introduced an EU regulation for orphan drugs in 2000.[97] Already in 1997, the French Ministry of Health and the Institut national de la santé et de la recherche médicale (INSERM) initiated Orphanet, a database that pools resources on

86 Article 21 para. 1 and Annex 5 Covid-19 Ordinance 3: casirivimab/imdevimab; bamlanivimab/etesevimab. Articles 71a–71d OHI do not apply to the coverage of the costs of medicinal products used for the treatment of COVID-19 and containing active substances listed in Annex 5 of Covid-19 Ordinance 3 (see article 71e OHI).

87 Swissmedic, Wegleitung Zulassungsverfahren für Covid-19 Arzneimittel im Pandemiefall, 15 May 2021, 5.

88 Giuseppe Lapadula (footnote 46), 1.

89 See Schweizerische Akademie der Medizinischen Wissenschaften, Empfehlungen: «Seltene Krankheiten»: Geltungsbereich eines nationalen Konzepts sowie Rahmenbedingungen für die Schaffung und den Betrieb von Referenzzentren, 2014, 1; Vereinigung Pharmafirmen in der Schweiz (vips) (footnote 7), 7.

90 Laura Joszt, Not so rare: 300 Million People Worldwide Affected by Rare Diseases, in: AJMC, 7 November 2019, available at: https://www.ajmc.com/view/not-so-rare-300-million-people-worldwide-affected-by-rare-diseases (accessed on 24 June 2021) with reference to Stéphanie Nguengng Wakap *et al.,* Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, in: European Journal of Human Genetics, 2020, 165–173.

91 Interpharma, Rare Disease Day: Seltene Krankheiten sind nicht selten, available at: https://www.interpharma.ch/blog/rare-disease-day-seltene-krankheiten-sind-nicht-selten/ (accessed on 24 June 2021).

92 See Orphanet Switzerland, http://www.orpha.net/national/CH-DE/index/%C3%BCber-seltene-krakenheiten/ (accessed on 24 June 2021).

93 Vereinigung Pharmafirmen in der Schweiz (vips) (footnote 7), 9.

94 See Orphanet Switzerland, http://www.orpha.net/national/CH-DE/index/%C3%BCber-seltene-krakenheiten/ (accessed on 24 June 2021).

95 Vereinigung Pharmafirmen in der Schweiz (vips) (footnote 7), 13.

96 Orphan Drug Act of 1983, PUBLIC LAW 97–414—JAN. 4, 1983.

97 See Regulation (EC) No 141/2000 on orphan medicinal products; Regulation (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‹similar medicinal product› and ‹clinical superiority›.

the diagnosis, care and treatment of rare diseases.[98] Today, Orphanet is operated by a consortium of European partner countries under French leadership, with funding from the EU.

2. Regulation

In Switzerland, orphan drugs are defined in the TPA.[99] Swissmedic recognises the *orphan drug status* upon application if it can be proven that the respective medicinal product is indicated for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating disease affecting no more than five in 10,000 people in Switzerland when the application is submitted. The criterion of rarity of the disease refers in each case to the disease in its entirety, including all its stages, and not to an isolated stage in the course of the disease or a subgroup defined by molecular genetic markers.[100] Alternatively, it must be proven that the medicinal product or its active substances have received orphan drug status by a country with comparable drug control.[101] Most applications today are based on the prior orphan drug recognition by the competent authority of a country with comparable drug control, in particular the EMA or the FDA.[102] A list of medicinal products that have received orphan drug status in Switzerland is published by Swissmedic on the internet.[103]

Medicinal products that have received orphan drug status are amenable to *authorisation in a simplified procedure*.[104] An orphan drug authorisation can be granted in parallel with, or after, the recognition of the orphan drug status.[105] In principle, the approval procedure for drugs with orphan drug status corresponds to the procedure provided for the respective drug category.[106] Proof of safety, quality and efficacy must also be provided for orphan drugs.[107] Thereby, the aspect of rarity is taken into account, which includes in particular the limited number of patients and the increased difficulty in the conduct of clinical studies.[108] If the medicinal product is already authorised by another country with comparable drug control, the applicant may submit to Swissmedic the quality, toxicology and clinical documentation that formed the basis for the foreign authorisation, as long as these documents are written in a Swiss national language or in English.[109]

98 See https://www.orpha.net (accessed on 24 June 2021).
99 See article 4 para. 1 lit. a^{decies} (in force since 1 January 2019), article 14 para. 1 lit. f TPA.
100 Swissmedic, Wegleitung Orphan Drug, 1 March 2021, 3.
101 Swissmedic (footnote 100), 2. In case of diverging decisions of two countries with comparable drug control see article 4 para. 3bis OSMA.
102 Swissmedic, Geschäftsbericht 2019, 24.
103 See article 7 OSMA.
104 Article 14 para. 1 lit. f TPA and articles 24 *et seq.* OSMA.
105 See article 4 para. 3 OSMA.
106 Swissmedic (footnote 100), 5.
107 Articles 3 *et seq.* OMAMP; article 25 OSMA.
108 Article 26 para. 1 OSMA; Swissmedic (footnote 100), 5.
109 Article 26 para. 2 OSMA.

3. Challenges and Limitations to Access

While the *simplified authorisation procedure* removes significant hurdles to the approval of orphan drugs, major access challenges for patients remain. As with the temporary authorisation for life-threatening and debilitating diseases (see above ch. IV. E. 2), simplified access does not automatically imply simplified reimbursement. This is because the criteria for access to basic insurance do not readily supplement the simplified authorisation for orphan drugs.[110] Such reimbursement, however, is essential for patient access, in particular in the orphan drug field where drug prices are often very high. To address this point, access reimbursement under mandatory health insurance may be available under certain conditions for individual cases of hardship (see below ch. V).[111]

V. Reimbursement

In Switzerland, as a principle, the obligation to reimburse medicinal products and treatments under the mandatory health insurance only extends to medicinal products that are listed in the SL (see above ch. II). Specialties are only included in the SL where the pharmaceutical manufacturers or importers submit a respective application (article 52 para. 1 lit. b Health Insurance Act, HIA).[112] This amounts to a significant hurdle for early and managed access programmes, given that the process for inclusion in the SL can take a long time, in particular where high drug prices are in question, and that the health insurance regulation in Switzerland has to date made no provision for a simplified or accelerated reimbursement decision in step with temporary respectively simplified authorisation procedures (see above chs. IV. E. 2 and IV. F. 3).

Further, reimbursement under compulsory health insurance is, in principle, *limited to the indications and conditions of use authorised* by Swissmedic.[113] The use of a medicinal product outside the authorised indications and conditions of use would make it, in principle, a non-compulsory service.[114] However, the Federal Supreme Court has developed criteria according to which, in exceptional cases, the compulsory health insurance must also assume the costs of a drug if it is dispensed for an indication outside the conditions of use approved by Swissmedic.[115] An important field of application have been rare diseases as

110 Vereinigung Pharmafirmen in der Schweiz (vips) (footnote 7), 19.
111 See, *e. g.*, the original price point of USD 2.1 million in connection with the approval of the one-time gene therapy Zolgensma in 2019.
112 See BGE 139 V 375, E. 5.1.
113 BGE 139 V 375, E. 4.3 with reference to BGE 130 V 532, E. 5.2.
114 BGE 136 V 395, E. 5.1; BGE 130 V 532, E. 3.2., E. 3.4.
115 BGE 130 V 532, E. 6.; dazu Bernhard Rütsche, Vergütung von Heilmitteln im Einzelfall: Für eine allgemeine Härtefallklausel im Krankenversicherungsrecht, in: recht 2019, 72–80, 75.

the authorisation procedure may not be considered commercially worthwhile in a small country such as Switzerland.[116] In this context, it is not the marketing authorisation fees themselves, but rather the costs associated with the entire marketing authorisation procedure, which can sometimes deter pharmaceutical companies from submitting marketing authorisations for rare diseases.

Today, the criteria developed by the Federal Supreme Court for *reimbursement of medicinal products in individual cases of hardship outside the SL* are codified in articles 71a-71d OHI (off-label use, unlicensed-use and *hors-list* use).[117] A case of hardship exists if, either, the use of the medicinal product forms an indispensable prerequisite for the performance of another service covered by the health insurance, and the latter is clearly in the foreground (treatment complex), or the medicinal product is necessary for the treatment of a serious disease, has a major therapeutic benefit, and no other effective and approved treatment method is available.[118]

While article 71a OHI states that the health insurer determines the reimbursement for *off-label use* after consultation with the marketing authorisation holder, article 71c OHI provides for the case of *unlicensed use* of a ready-to-use medicinal product that has not been approved by Swissmedic and that may be imported in accordance with the TPA as long as the product has been approved for the relevant indication by a country with an equivalent drug approval system. Finally, article 71b OHI regulates the reimbursement for the *hors-list* use of a ready-to-use medicinal product that has been approved by Swissmedic, but is not included in the SL. As the SL admission procedure often takes a long time, or the marketing authorisation holder may shy away from the respective effort, this opens up an access to reimbursement in particular for orphan drugs for which the SL admission may be considered unattractive by a market authorisation holder.[119]

In a decision of 7 August 2018,[120] the Federal Supreme Court extended the provisions on individual case reimbursement *per analogiam* to medicinal products that are exempt from approval (so-called *Magistralrezepturen*[121]). According to doctrine, this case law should be taken to mean that the regulations on individual case reimbursement (articles 71a *et seq.* OHI) are to be applied to all types of therapeutic products.[122] Accordingly, these regulations are to be regarded as an expression of a general unwritten hardship clause in Swiss health insurance law, which aims at ensuring equal access to effective treatment methods.[123] It remains an open question what this means for early and managed access, *e.g.* whether there is a right to individual reimbursement where the conditions of articles 71a *et seq.* OHI are not fulfilled, or even a right to a hitherto uncodified simplified or accelerated reimbursement process in connection with temporary or simplified marketing authorisations.

VI. Conclusions and Outlook

Early and managed access covers a wide range of instruments that make certain investigational or unapproved medicines and treatments available to eligible patients with an unmet medical need. They are of increasing importance in particular in light of significant progress in the preventive and curative capabilities of treatments, including through gene therapies, recent advances in the fields of precision and personalised medicine as well as rare diseases, considerable efforts to accelerate the path from innovation to patient and – ultimately – an overall strive towards timely availability of novel pharmaceuticals, biologics and treatments.

Early and managed access programmes cover the area «in between» clinical trial research and on-label therapy. In line with international developments, Swiss law provides a series of related *instruments,* including compassionate use, individual and systematic therapeutic experiments, temporary authorisations for life-threatening and debilitating diseases, as well as simplified authorisations for orphan drugs. While their strategic use and implementation requires oversight over broad and diverse regulatory topics and practical experience, they cover fundamentally all perceivable early and managed access options. In that sense, there is no «gap» in the Swiss regulatory landscape. That said, *legal challenges* remain in at least four main areas:

First, a *lack of alignment between early access and reimbursement* can be observed. There is no equivalent to the temporary and simplified marketing authorisations in the reimbursement field. Also, the conditions for reimbursement of medicinal products in individual cases of hardship may not always be fulfilled, and open questions remain in light of recent developments in case law. However, early access without reimbursement by mandatory health insurance all too often remains a privilege of the wealthy few.

Second, the *supply chain design* may in practice stand in the way of early access. Marketing authorisation holders in Switzerland must have an establishment li-

116 Bernhard Rütsche (footnote 115), 75; Vereinigung Pharmafirmen in der Schweiz (vips) (footnote 7), 19.
117 See also on the whole topic, Beat Kipfer/Carsten Witzmann (footnote 63), 89 *et seq.*
118 Article 71a para. 1 OHI.
119 Hans-Jakob Mosimann, Off-Label-Use von Arzneimitteln, in: SZS, 2020, 240–247, 242.
120 BGE 144 V 333.
121 Article 9 para. 2 lit. a TPA.
122 Bernhard Rütsche (footnote 115), 80.
123 Bernhard Rütsche (footnote 115), 80.

cense to manufacture, import or conduct wholesale trade. Delays in obtaining the requisite establishment license may lead to subsequent delays in marketing authorisation. However, market access without an established supply chain is of little value.

Third, despite joint efforts, in particular in the EU, the fragmented regulatory landscape across countries and regions and the continued *lack of full international coordination* on early access and reimbursement constitute a significant hurdle for therapies to reach patients with unmet needs. This means that companies bringing novel treatments to market are held to decide, in advance and for each country individually, whether or not a local marketing is feasible. The medicinal product is then subjected to a range of varying country-specific procedures, which bind significant management efforts and have the potential to delay access.[124] However, local unavailability, or delayed availability, is the opposite of what early and managed access programmes set out to achieve.

Finally, *speed and timely availability* are an issue especially for patients with urgent needs. While this has traditionally affected mostly patients with life-threatening or debilitating diseases, the COVID-19 pandemic has brought timing to the forefront of a wider public's attention. The astonishing and unprecedented achievements in bringing respective vaccines to market in less than one year from the outbreak of the disease demonstrate the as yet not fully exploited potential in this respect, including in Switzerland. However, as far as things currently stand, timing can be expected to remain a significant, if not the core, challenge for early and managed access programmes in the future.

124 See Andreja Detiček *et al.* (footnote 84), 553–560, 554.

Reporter
Dr. iur. Barbara Abegg, MJur, Rechtsanwältin, Lenz & Staehelin; Dr. iur. Martina Braun, Rechtsanwältin, Wenger Plattner; Stefan Hubacher, MLaw, Rechtsanwalt, FMP Fuhrer Marbach & Partner; lic. iur. Markus Kaiser, LL.M., Rechtsanwalt, TIMES Attorneys; Dr. iur. Felix Kesselring, LL.M., Rechtsanwalt, Bratschi AG; Dr. rer. nat. Michael Kock, Patentanwalt, European Patent Attorney, dr. kock consulting; Dr. sc. nat. ETH Alfred Köpf, Patentanwalt, Rechtsanwalt, Rentsch Partner AG; lic. iur. Peter Ling, LL.M., Rechtsanwalt, Lenz & Staehelin; lic. iur. Eric Noël, Rechtsanwalt, Katzarov SA; Janine Reudt-Demont, MLaw, LL.M., Rechtsanwältin, Niederer Kraft Frey AG; lic. iur. Judith Schallnau, LL.M., Rechtsanwältin, Legal Officer, World Intellectual Property Organization (WIPO); Dr. iur. Richard Stäuber, LL.M., Rechtsanwalt, Homburger AG; Magalie Wasem Tréguer, MLaw, Rechtsanwältin, Pharma Law Solutions GmbH; Dr. Andreas Welch, Europäischer und Schweizer Patentanwalt, Hepp Wenger Ryffel AG; Marion Wyler, MLaw, Rechtsanwältin, CMS von Erlach Partners AG; Dr. iur. Daniel Zimmerli, LL.M., Rechtsanwalt, Walder Wyss AG.

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