Executive summary

Sector-specific research project: Implications for Switzerland of Regulation (EU) no. 536/2014 on Clinical Trials on Medicinal Products for Human Use

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- In EU Regulation No. 536/2014 on clinical trials on medicinal products for human use (Regulation No. 536), the European Union (EU) consolidates standards for clinical trials in its Member States.
- Through "third country clauses" Regulation No. 536 and its Implementing Regulation 2017/556 set out an indirect extraterritorial effect (that is permitted under international law): under Regulation No. 536, equivalence is always required from Swiss trials if there is a link between human research in Switzerland and the EU legal system. For example, the further use of trial data collected in Switzerland in an EU application dossier for a new clinical trial, the conduct of international multicentre trials (Switzerland-EU) and the marketing authorisation of medicines in the EU that are to be based on Swiss studies are dependent on the recognition of equivalence.
- Clinical research is of considerable economic significance to Switzerland: the report puts the pharmaceutical industry's annual expenditure on research in Switzerland at some CHF 6.9 billion. Of this amount, approximately CHF 2.5 billion is spent on clinical research. Moreover, clinical research is also conducted by small and medium-sized enterprises (SMEs) and within the framework of research programmes initiated by academic institutions.
- In principle, all the analysed organisers of clinical research (multinationals, SMEs and non-industry-sponsored research) are affected by Regulation No. 536, albeit to varying degrees. While multinationals are mostly involved in international multicentre trials and are thus directly affected by EU law, Regulation No. 536 also indirectly impacts the actors predominantly operating in Switzerland through third country clauses.
- An analysis of the legal situation in the EU and in Switzerland reveals that Regulation No. 536, which enters into application in 2020, in some cases sets out more stringent requirements for the conduct of clinical trials than Swiss legislation.
- Conflicts of laws in the proper sense, in other words where Swiss law commands an action that is not permitted under Regulation No. 536, are not apparent.

- The equivalence required under Regulation No. 536 entails systemic risks, however, as compliance with the Swiss Human Research Act in some cases does not satisfy the new requirements of Regulation No. 536 (particularly with regard to the rights and safety of trial subjects, and the reliability and robustness of data generated in clinical trials).
- If, for example, the competent EU authority were to conduct an audit and question the equivalence of a clinical trial conducted according to Swiss regulations, the result of this audit could effectively prejudge similar Swiss situations; indirectly, the equivalence of the Swiss Human Research Act would also be called into question.
- The equivalence required by EU legislation from foreign legal systems and administrative practices (as a requirement for market access and cooperation) constitutes a *legal* concept, but is not free of political expediency, as shown by the issues currently being discussed in connection with recognition of equivalence of the Swiss stock market, electricity market and data protection regulations.
- These risks can be partially minimised or even eliminated if researchers shoulder the comparatively light double burden (given the minimal differences) of complying with two legal systems. The government can make it easier to shoulder this double burden through information campaigns, but also by adapting its own procedures; this could include forms which already incorporate the requirements of EU Regulation No. 536 (noting that non-compliance is immaterial with regard to Swiss procedures).
- Other risks can be minimised through regulatory adjustments. Having said that, the processes around the recognition of equivalence of the legal framework for Swiss stock markets show that even a largely “voluntary alignment” provides no guarantee that the equivalence of Swiss regulations will be recognised. This is because the EU’s equivalence assessments not only apply to the regulations per se (comparison of Regulation No. 536 with Swiss law), but also to the administrative and legal implementation and enforcement of these rules.
- If the aim is to avoid regulatory differences between the Swiss legal system and the new legal situation in the EU, no legal amendments appear to be necessary, rather just isolated changes to ordinances.
- The stakeholder survey reveals that Switzerland is considered an attractive location for research. Respondents emphasised the substantial expertise, the specialisation of research facilities, the high quality of clinical trial execution and the comparatively short approval processes.
- Respondents do not have a uniform level of knowledge. Relevant government measures could improve this situation. Respondents consider the changes brought about by Regulation No. 536 as unproblematic and are thereby underestimating the systemic risks involved.

- The stakeholders surveyed predominantly assume that clinical trials conducted in Switzerland will continue to be recognised as equivalent. However, if this is no longer the case, or merely if the impression is created that recognition of the equivalence of clinical trials conducted in Switzerland is realistically jeopardised, the respondents assume that there will be a significant decline in clinical trials in Switzerland.
- Most actors advocate a partial adaptation of Swiss law to EU legislation. In their view, it is primarily the approval process that should be harmonised. The respondents believe that the strengths of current legislation should be retained – short timeframes, broad scope of the HRA (besides clinical trials involving medicinal products, it also covers those involving medical devices, transplant products, gene therapy and trials with genetically modified organisms, therapies involving radiation sources, and in addition to trials on living persons, also those on deceased persons, embryos and foetuses, spontaneous abortions and stillbirths).
- Switzerland as a location for research could also be strengthened through further measures, e.g. better networking of actors, enhanced support of CTUs in hospitals and more centralised ethics committees.
- The following section aims to present possible ways of minimising the risks on the basis of the differences discussed. The question of which measures should be taken is a genuine political decision for which the contractors have no mandate.

Courses of action for the FOPH

The new legal system for clinical trials under EU law is significant for virtually all sponsors of clinical trials in Switzerland, whether because they are involved in multicentre trials in the EU, or because clinical trials conducted in Switzerland may potentially be required as a basis for a drug approval in the EU. The comparative analysis in section 4 showed that although the regulatory differences are small, they entail not insignificant legal risks.

These risks can be partially minimised or eliminated if researchers shoulder the comparatively light double burden (given the minimal differences) of complying with two legal systems. However, the government should do everything it can through information campaigns and by adapting its own procedures to ease this double burden; this may include forms which already incorporate the requirements of Regulation No. 536 (noting that non-compliance is immaterial with regard to Swiss procedures).

Other risks can be minimised through regulatory adjustments. Having said that, the processes around the recognition of equivalence of the legal framework for Swiss stock markets show that even a largely "voluntary alignment" provides no guarantee that the equivalence of Swiss regulations will be recognised.

The following section addresses possible ways of minimising the risks with regard to the differences in the operational arrangements discussed above.

Role of international health legislation, in particular the ICH-GCP Guideline for Good Clinical Practice

In addition to the ICH-GCP Guideline, Regulation No. 536 sets out its own standards regarding good clinical practice, which in some cases stipulate tighter regulations than the HRA. This does not result in a conflict with the Swiss legal system, but requires researchers, sponsors and investigators who 1) wish to participate in an international multicentre trial, who 2) would like to use data collected in Switzerland in a subsequent EU application dossier, or 3) want to get marketing approval for a drug, to comply with the more stringent rules of Regulation No. 536. The tighter EU rules pose systemic risks, particularly for actors who for the time being operate predominantly or exclusively in Switzerland and act in accordance with Swiss legislation on human research, thus mainly in domestic research not sponsored by industry.

In this respect various respondents expressed a wish for government support in tackling the absence of regulatory uniformity resulting from the legal and administrative uncertainty. In this sense, it would be possible, for example, to explicitly include the additional requirements resulting from Regulation No. 536 in forms and other guidance provided (fact sheets, checklists, other specifications, e.g. regarding master files and protocol). Other actors wrongly assume that clinical trials conducted in accordance with the ICH-GCP Guideline satisfy the requirements of Regulation No. 536, and that any aspects which may be classified as non-

equivalent (e.g. liability provisions or the composition of ethics committees) will not be relevant to drug approval in any case. These views do not tally with the legal analysis and reveal a potential danger, which can be minimised or eliminated by providing relevant information and through corresponding regulatory adjustments. Respondents consider any non-equivalence of Swiss regulations as clearly detrimental to Switzerland as a location for research.

Recent experiences indicate that the equivalence of Swiss regulations based on international standards (in this case, the ICH-GCP rules) can be rejected by the EU even if they have been approved for the arrangements of other third countries, although they are based on the same international standards. In any event, the EU authorities involved, together with the EMA, can conduct inspections to verify compliance with EU principles by third party actors on a case-by-case basis.

The survey results suggest that in practice there is still a need for information regarding the more stringent requirements of Regulation No. 536 and the possibility that equivalence may be explicitly denied for the Swiss regulations or the actor in the individual case. .

Various areas of application

Regarding the distinction between clinical trials in general and low-intervention clinical trials under Regulation No. 536 and those in category A of the Swiss Clinical Trials Ordinance ClinO, the requirements and legal consequences are not the same. This does not lead to a conflict of laws, but should be borne in mind by sponsors and investigators who wish to participate in an international multicentre trial.

Design, protocol and other trial documentation

Regulation No. 536 requires more detailed information to be supplied in the application documents to be submitted to the EU licensing authorities than is required under Swiss law. For trial documentation that does not fall within the scope of the MRA Switzerland – EU, Swiss researchers who also wish to conduct research at European locations should supplement the documents – in particular the protocol and master files – with the relevant additional details, or knowingly refrain from doing so; in the latter case, they should be aware that study results may not be recognised as equivalent for a drug approval, for use in a subsequent application dossier for a clinical study in the EU, or in an EU inspection.

Protection of trial subjects and informed consent

The differences between Regulation No. 536 and Swiss human research legislation relate primarily to the form of the duty to provide information. Regulation No. 536 sets out higher requirements with regard to the inclusion of particularly vulnerable populations in clinical trials; this group includes subjects not able to give informed consent, minors, pregnant or breastfeeding women and emergency patients.

Under Regulation No. 536, either the subject themself or a legally designated representative must be informed and give their informed consent. Under Swiss law, it is not the maturity but the state of capacity that determines whether an individual is authorised to give informed consent. In order to minimise the risk that cases of informed consent permissible under Swiss law do not satisfy the claim to equivalence of Regulation No. 536, it could be possible to establish a deputyship in accordance with the Swiss Civil Code for adults lacking the capacity to consent who are to take part in a clinical trial so that the consent of the deputy makes it possible to exploit the results of the clinical trial.

Regulation No. 536 sets strict limits on financial compensation of trial subjects by prohibiting *undue* influence being exerted on trial subjects. For particularly vulnerable subjects it additionally stipulates that financial inducements or other incentives beyond compensation for expenses and loss of earnings are not permitted. Meanwhile, the HRA only states that no person may receive payment or any other non-cash advantage for participation in a research project with an expected direct benefit. However, participation in a research project with no direct benefit may be remunerated “appropriately”. Regulation No. 536 does not contain any provisions on *permitted* remuneration for subjects who are not vulnerable.

Nonetheless, the stated discrepancies between Regulation No. 536 and Swiss human research legislation with regard to informed consent remain limited. An adjustment could be made without difficulty through a corresponding amendment of ClinO.

As revealed by the survey, Swiss actors are aware that Regulation No. 536 raises the level of protection of the previous EU Directive, particularly with regard to vulnerable subjects, such as minors. The potential legal consequences of non-compliance with the level of protection required in Regulation No. 536 (despite adherence to Swiss human research legislation) are not always perceived or at least not seen as an issue. To counter such systemic risks, it is advisable to make the aforementioned amendments to the ClinO and to review compliance of Swiss human research legislation and Regulation No. 536 with adult protection legislation in a timely manner.

Databases

Besides recording clinical trials (and therefore to ensure transparency), the EU database also facilitates the further use of data in drug approval procedures and in application dossiers for future clinical trials in the EU. Because the format and scope of data stored in databases under Swiss law differ from those in the EU database, the documentation transmitted and registered on clinical studies cannot be used without adaptation for subsequent marketing authorisations or application dossiers in the EU, which in the case of applications in the EU will result in additional administrative effort for applicants from Switzerland. If there is a desire to prevent

this additional effort, Swiss data collection in terms of the format and scope of data stored in the database could be adapted to reflect EU law as a voluntary alignment.

Transparency issues

Under Swiss law, data generated from clinical trials are not subject to the same transparency requirements as data that are entered in the EU database. If the EU were to consider access to the data generated from clinical trials (application dossier, requests for authorisation, data and reports on clinical trials) as fundamental to the robustness of the data or to the protection of public health, the lack of an equivalent transparent database in Switzerland could jeopardise recognition of the equivalence of the clinical trials on which the data are based. Any concerns related to equivalence would be dispelled if the EU were to take the preferable view that the transparency provisions should not be deemed regulations that constitute good clinical practice in accordance with Regulation No. 536, and that they should not be considered essential to the robustness of data generated from clinical trials. As it cannot be ruled out at this stage that the competent EU authorities will take the former view, there is a need for action with regard to ensuring equivalence if the risk of non-compliance is to be eliminated.

In the case of clinical trials in Switzerland that are part of a multicentre trial led by a sponsor that is based or represented in the EU area, the sponsor is in any case required under Regulation No. 536 to enter all Swiss data including the master file in the EU database via the EU portal. If the clinical trials in Switzerland are conducted according to the same protocol, but organisationally separate, the deviations from EU law have a negative effect as Swiss legislation stipulates less extensive requirements regarding data availability than EU law. If the sponsor in Switzerland has failed to ensure that the requirements of EU law are fulfilled and that the relevant information is compiled and available, recognition of equivalence may depend on how detailed and complete the access to these data is required to be.

The data disclosure obligation under Regulation No. 536 may be problematic for Swiss companies and researchers if it takes precedence over the more restricted Swiss disclosure obligations. This problem could be avoided if the transparency requirements of Swiss legislation were adapted to those of Regulation No. 536.

Data protection

Both Regulation No. 536 and the HRA contain specific data protection provisions and refer to the relevant data protection laws (FADP, GDPR); data protection is considered an element of the protection of trial subjects. The stakeholders surveyed do not see any significant problems regarding the EU data protection requirements. In addition, the pharmaceutical companies are free to adapt to the more stringent EU legislation regarding transparency; for global pharma companies this would in any case be normal practice.

To determine whether additional data protection requirements can be derived from Regulation No. 536 for actors operating in Switzerland, a comparison would have to be carried out – which goes beyond the scope of this report – of the European data protection regime with the applicable human research legislation and with Switzerland's general data protection legislation, including the planned revision of the Swiss Data Protection Act. One of the aims of the planned revision of the Swiss Data Protection Act is to follow developments in the EU to ensure that data can continue to be transferred between Swiss companies and those in the EU.

Liability, liability guarantee and damage compensation

For category A clinical trials involving minimal risks and burdens under ClinO, simplifications apply (exemption from Swissmedic licence requirement, exemption from liability under certain conditions, and exemption from the liability guarantee). But there are no requirements that conflict with Regulation No. 536. The investigator or sponsor in Switzerland is therefore not precluded from following the rules of Regulation No. 536.

Regulation No. 536 is limited to the obligation of Member States to ensure that systems are in place to compensate subjects for any damage, to guarantee such damage compensation and to inform trial subjects about it. Exemptions from liability and the liability guarantee, which are provided for under ClinO but not under Regulation No. 536, could raise equivalence questions, however. These exceptions result in a lower level of protection for trial subjects in Switzerland, which, in the event of a tactical restrictive interpretation, could call into question the equivalence of the Swiss regulations.

Organisation and procedure

Finally, differences in organisation and procedure exist with regard to the composition of ethics committees (mandatory layperson representation), the independence of persons validating and assessing applications (more extensive and more stringent requirements), as well as the obligations of the sponsor regarding timely reporting to the Member States concerned on the progress of the clinical trial, regarding safety reporting to the European Medicines Agency and regarding annual reporting on the safety of each investigational medicinal product used in the clinical trial to the EU Agency. These deviations from Swiss law do not result in any legislative conflicts. They could only jeopardise the recognition of equivalence if the conditions for equivalence are subject to a tactical restrictive interpretation: if Member State authorities or the EU Commission take the view that these differences have an impact on the protection or rights of trial subjects, or on the reliability and robustness of the data generated, they could then become relevant for Switzerland from an equivalence perspective.

At this point it makes sense to work to clarify that the Swiss regulations satisfy the EU requirements in an equivalent manner.

The lack of subdivision of trial applications and requests for authorisation as stipulated in Parts I and II of Regulation No. 536, and the differences with regard to the division of responsibility between the lead committee and other ethics committees involved in Switzerland and between the reporting Member State and Member State concerned under Regulation No. 536 are unproblematic from an equivalence perspective, provided the trials *as a whole* are equivalent with regard to the rights and safety of trial subjects and the reliability and robustness of the data generated from the clinical trials. The lack of a national contact point to handle the procedures set out in Chapters II and III (evaluation of clinical trials and evaluation of substantial modifications) in Switzerland does not pose a problem from an equivalence perspective either, and the same applies to the lack of a single payment body.

Whether and to what extent the coexistence of different organisational and procedural arrangements in the EU and in Switzerland influences the number of clinical trials in Switzerland cannot be conclusively stated from a health economics perspective based on developments since 2014. While the EU could become more attractive on account of the centralised applications, Switzerland still also possesses many comparative advantages in terms of the quality of trial execution, the expertise of researchers and the comparatively short timeframes. The fear expressed by some stakeholders that Switzerland has already become less attractive as a location for clinical drug trials in recent years, and that this could result in a sustained decline in the number of clinical studies, was not confirmed by analyses of the available data sets.

There is some uncertainty among respondents as to whether a sponsor from Switzerland can submit an application for a clinical trial in the EU and thus gain access to the EU portal from Switzerland. The same applies to the question of whether BASEC (*Business Administration System for Ethics Committees*) documents can be entered via the new EU portal. In this respect, there is a need for information in terms of practical application, especially as there are fears that Switzerland would become less attractive as a location for clinical research without access to the EU portal. In this context, a number of respondents would like to see a shared portal for ethics committees and Swissmedic. At the very least, they believe it would be preferable for Swissmedic to have access to the portal of the ethics committees as they would have to carry out inspections of all clinical trials – including those that do not require authorisation from Swissmedic. A solution in terms of direct access to the EU portal would probably only be achievable through an international treaty and thus seems unlikely.