"Quality inadequate" – the perspective of a member of an animal testing committee

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Switzerland is proud of its position in the world of research; by its own assessment, it is a location where world-beating research is being carried out. It also celebrates its animal protection law and regards that too as a world leader. There is a strict licensing procedure in place in relation to animal experiments. On looking closer, however, it transpires that this area involves an immense administrative cost and is understandably regarded as a burden by researchers, but from an animal protection and scientific viewpoint, it presents barely any barrier to some questionable research projects. This situation is legally unsustainable, as illustrated below.

Because animal welfare and the dignity of animals are constitutional rights, and therefore rank the same as fundamental rights and other national objectives, any infringement of the relevant protective interests is only permissible if this is required by an "overriding interest" in that specific individual case. Research projects involving animals are therefore subject to approval. Approval for an experiment that is associated with stress for the animals involved in that experiment is dependent on a variety of different conditions. In particular, the trial must be proportionate; a test of whether the animal experiment is suitable and absolutely necessary, or even mandatory, in order to achieve the goal of the research must therefore be carried out. The interest in the experiment and its results must therefore be weighed against the stress it causes to the animals. The experiment may only be approved if the benefit gained from the experiment clearly outweighs the damage to the wellbeing and dignity of the animal. As part of the approval proceedings, the three steps of suitability, necessity and proportionality (balance of interests) in the narrowest sense must therefore be taken into account by law – in addition to some preliminary questions, such as training for the staff, infrastructure and general conditions. The current system fails at all three levels, which means that the legal requirement to link animal experiments to the "unavoidable level" will not be fulfilled.

In practice, a standard has become established on the balance of interests level in the approval process for animal experiments over the years. This is no longer subject to any serious scrutiny, even though the animal protection law requires continuous critical scrutiny and a repeated weighing up of interests. This is regardless of the fact that the relationship between the interests has undergone considerable change, to the benefit of the animals, especially in view of the confirmation of the dignity of the animal in the applicable animal protection law in 2008. Switzerland also lags far behind other countries in the meaning of "necessary" and the associated basic requirement for alternative research methods. Cantonal authorities rely on the Confederation who, in turn, expect that this subject will be tackled by the research community.

In this case, however, the focus is on the evaluation of the quality and validity of animal experiments in Switzerland. Legally speaking, we are working on the standard of the eligibility, which the approval authorities and the animal testing committee views in relation to their goal for the long term – and which is always put forward as a justification in the balance of interests – but which is not normally discussed, on purely pragmatic grounds. For example, the question of whether a frustrated mouse can really be used to investigate the causes and mechanism of depressive illnesses is never discussed. The question of suitability is – with very few exceptions – placed trustingly in the hands of the applicant. This is understandable, in the face of the veritable flood of applications. Given the current situation where about 1000 new applications are received throughout Switzerland, together with many more additional applications for revisions and supplementations per year, it is impossible to examine them all. Even with the large number of people currently dealing with this issue (in Zurich alone, there are three officers at the veterinary office and eleven members of the animal testing committee who are responsible for animal experiments; the institutions' own internal animal welfare officers are also involved in each case), it is still impossible to examine fundamental questions carefully. In addition, the research community itself only seems to ask itself these questions sporadically and inadequately. Research groups place their trust in the results they have obtained over many years and even decades, and dive into ever newer and more exciting research problems, apparently without normally questioning their models and processes in any depth.

Dozens of questions come up and need to be taken into account in regard to the appropriateness of animal models – and neither the applicants nor their teams, nor the committee, nor approval authorities are fully equipped for this task. Particularly because of the fact that an animal can only be a fragmentary aid to solve a complex problem, at best, many influences and interfering factors may have a significant influence, e.g. when the animals are handled, the environment in which they are handled, anaesthesia, analgesia, etc. Experience has shown that these are only partially considered during the experiment planning stage, and many of them are simply ignored altogether. Even Switzerland's much-vaunted cutting-edge research makes use of more or less untested established models from all around

the world, without tapping the full potential of their spirit of innovation. Meanwhile, the fact that there must be something wrong with current practice is evidenced by the feeble rates of transmissibility and reproducibility. These do not just affect the foreign competition.

I believe that the Canton of Zurich's Cantonal Committee on Animal Testing provides an important 3R / 1R (Refinement) service. Experts from various specialist sectors endeavour to refine the planning of experiments so that the stress suffered by the affected laboratory animals is minimised, without affecting the goals of the research. However, the committee fails in its efforts to evaluate the suitability and necessity for animal experiments in relation to the long-term aims of the tests – and a Cantonal Committee on Animal Testing may also simply not be able to provide this service. The two studies currently under consideration (Vogt et al., 2016; Reichlin et al., 2016) mention deficiencies but do not concern themselves with the suitability of animal models in terms of the long-term goals, such as the ongoing advancement of medical standards. On the contrary, this question touches an even more basic level, i.e. the suitability of the specific experimental concept in relation to the knowledge immediately under investigation. The deficiencies revealed by both of these studies are a problem for Zurich too. They seem to be a component of a system that has not been examined seriously for many years. From what I have observed, there are several reasons why the committee frequently fails to investigate the associated quality-relevant questions:

1. The current practice is established. It's done like this "everywhere". The animal testing committees know no other way. They are mainly made up of researchers who work in this way themselves. Outsiders without any experience of research are unaware of the critical areas.
2. Different standards apply in basic research compared with applied or "application oriented" research; the normal quality directives are often viewed with less precision, as this type of research is much more open, and less likely to be directed towards a specific goal. It seems that this area generally tolerates more freedom with regard to research creativity.
3. If appropriate statistical sample sizes are investigated, the committee is also faced with the worry that the numbers of animals may actually increase, because the samples are frequently too small. A (too) small number of animals is therefore often preferred in comparison with more solid results, which leads to a mistrust of either the anticipated research results or the statistical calculations.
4. Biomedical research (and research involving animal testing in particular) incorporates many elements of uncertainty, which would be regarded as grey areas of research. It is generally accepted that many aspects are not subject to control, despite standardisation in some selected areas.

Scientifically speaking, biomedical research is facing a crisis in current practice. Despite the deficits that were revealed years ago (see e.g. Ioannidis JPA (2005), Why Most Published Research Findings Are False, in: *PLoS Med 2(8),* e124.) this sluggish system continues to crank along in its usual fashion. Researchers regard themselves as a part of the system, and do not regard it as their responsibility to change anything fundamental. Neither the donor institutions nor the authorities nor the politicians have the confidence to evaluate the situation. Only some of the criticism with regard to flaws affects research involving animal testing while other areas of research are also affected by quality deficiencies. This is alarming enough in view of the fact that it is impossible to use the immense resources invested in this research appropriately. In the animal testing area, the identified deficiencies are particularly controversial because they involve living beings whose welfare and dignity should be protected under Swiss law. We will fail to honour this requirement if we stubbornly continue to ignore the quality problems throughout an entire sector.

The two studies both show that Switzerland is not an outstanding research location in terms of the quality of research. As a consequence, we are faced with a flood of publications with results that are extremely difficult to judge in terms of value. Meanwhile, important attainments, such as the protection of the welfare and dignity of animals, may well be put forward as a guarantee of an ethically justified orientation, but they are not consistently implemented.