PEER REVIEWED

Could Re-use of Data Be State-of-the-art for Authorisation Processes?

Everyone is talking about sustainability and the will to replace animal testing with alternative methods, such as New Approach Methodologies (NAMs). But couldn't both issues be realised at once by re-using test data? What if data trading between science and the major regulatory authorities could be harmonised? Would authorisation processes suddenly be simplified and much quicker? In this article, we have summarised how the European authorities EFSA, ECHA and EMA publicly present how they establish the use of NAMs and the topic of data sharing in their assessment processes.

New Approach Methodologies (NAMs)

Looking at the progress for alternative animal testing, one can see strong efforts at all levels. In the scientific community, a great deal of focus has recently been placed on so-called NAMs (New Approach Methodologies). NAMs are computer or lab-based research approaches intended to more accurately model animal or human biology to replace or sometimes at least complement traditional research models. Numerous research funds are offered as prizes (SET Foundation, BMEL Animal Welfare Research Prize, NIH Common Fund Complement-ARIE programme and many others) to promote research into replacement methods or to recognise successful efforts. In addition, databases are created that make it possible to find alternative methods (*e.g.* NAMs Network). On the NAMs Network homepage, *e.g.* 257 different NAMS for hazard characterisation can now be found. These are categorised into organ/systems, guidance, regulations and many more.

The authorities are also recognising more and more alternative methods for authorisation work. Whereas not so long ago, all toxicological tests were still carried out in-vivo, tests such as 'the eye irritation test on reconstructed human cornea-like epithelium' have become established as in-vitro tests for the safety assessment of feed additives, among other things. The EFSA (European Food Safety Authority) has a favourable attitude towards NAMS. The recognition of alternative methods is also laid down in Regulation (EC) 429/2008 Annex 2, Article 3: "In-vitro methods or procedures are recommended which refine or replace the usual studies on laboratory animals or reduce the number of animals used in these studies. Such methods shall have the same quality and validity as the methods they are intended to replace". In addition, EFSA published an activity proposition of the Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment.[1] The roadmap is as follows: EFSA will develop a "guidance on the integration of NAM data into feed and food risk assessment and incorporate the concepts of a weight of evidence approach (as used in traditional human risk assessment) into NAM approaches". They mention that the alternatives to animal testing "have the potential to provide sound, cost-effective, timely and reliable information, but their regulatory acceptance has not yet been established".[1] This guidance might bring more information on that topic.

The ECHA (European Chemicals Agency) also runs workshops on the implementation of NAMs and has established NAMs in various areas of the assessment of chemicals. But at the moment they only accept alternative methods as a direct replacement for animal testing for acute and short-term effects. Examples of this are eye irritation, skin sensitisation or bioaccumulation tests. The ECHA still "considers animal testing to be indispensable, especially for the assessment of long-term effects such as organ damage, weakening of the immune system, development of allergies or asthma or reproductive problems and birth defects".[2]

The EMA (European Medicines Agency) is also open to NAMS. They offer "scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals". The EMA also publishes their opinion on various NAMs that have been shown to be successful in the context of science and drug development.

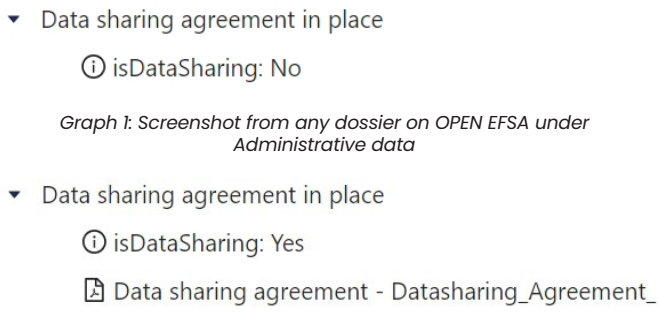
But what about the obvious, the direct re-use of data again. With everyone talking about sustainability, wouldn't that be the non-plus-ultra? Not only does it save animals from experiments, but it also protects the environment, considering the material cost of a new experiment, whether in vivo or in vitro. Not forgetting the time aspect. Every experiment takes time to plan and time again to carry out. If the experiment fails, it has to be planned and carried out again. Let's have a look at three different authorities (EFSA, ECHA and EMA) and how they handle the re-use of data.

EFSA

Chapter IV, Article 20 of Regulation (EC) 1831/2003 states that scientific data and other information for application dossiers are protected from re-use by others for at least 10 years, unless two applicants agree to trade their data between each other. This data trading is particularly welcome for data from toxicological tests on vertebrates so that they do not have to be carried out again. "However, if no agreement is reached on the sharing of the data, the Commission may decide to disclose the information in order to avoid the repetition of toxicological tests on vertebrates (...)". After 10 years, the data is available to the authority for evaluation in favour of another applicant. The following guideline has also been in place since 2008: "Common guidelines on practical arrangements for the sharing of scientific data between the scientific committees and panels of European agencies and the scientific committees of the commission". This states that "the exchange of data/dossiers between scientific committees/panels will take place when the necessity arises, on an ad-hoc and on-request basis, (...)". The data exchange will then be regulated between EMEA, EFSA, ECHA and the Commission. It is not a guideline how applicants can exchange data with each other. There is also no extra guideline on this. If you look at the Open. EFSA portal under Questions (https://open.EFSA.europa.eu) you can see individual applications publicly available in various categories and at various stages of the process. If you then go to the "Administrative data" section of the individual dossiers, you will see the sub-item "Data sharing agreement in place". After we have been monitoring the "data sharing agreement in place" topic since the introduction of the Transparency Regulation (EU) 2019/1381 in March 2021, on July 17th 2024 we saw for the first time that "yes" was clicked and the data sharing agreement

was publicly available. It is obviously possible to say "yes", but it is common knowledge that clicking "no" does not involve any major action or consequences. The applicant can simply say "no" without any further questions (Graph 1 and 2). It is questionable whether this could change in the near future and what will be changed then.

A call for data sharing and a demand that the initiation of animal testing is seen as the last possible resource to prove the efficacy and safety of a substance does not seem to exist on the part of EFSA for the time being.



Graph 1: Screenshot from any dossier on OPEN EFSA under Administrative data

Graph 2: Screenshot from the dossier found on 17 July 2024

ECHA

In comparison to EFSA, the topic of "data sharing" has long been established at ECHA. There is not only explicit guidance on the topic of data sharing and the so-called REACH Regulation (Regulation (EU) 2016/9), but also a notice directly on the homepage to all applicants:

"Registrants must make every effort to share data on intrinsic substance properties in a fair, transparent and non-discriminatory manner. This applies in particular to information on tests on vertebrate animals. In this way, registrants reduce registration costs and avoid unnecessary testing, especially on vertebrate animals. If the parties cannot reach an agreement, ECHA can assist in resolving data sharing disputes as a last resort".[1]

Article 2 of Regulation (EU) 2016/9 establishes the transparency of data sharing: "Where multiple registrants of the same substance or participants in a Substance Information Exchange Forum (SIEF) are obliged to share information in accordance with their duties under Regulation (EC) No 1907/2006, they shall make every effort to reach an agreement on the sharing of the information (...)". 1, In addition, Article 3 also regulates the "one substance, one assessment" policy. The Agency should ensure that there is only one application for a specific substance. Without ever having submitted a separate application to the ECHA, this gives the impression that the registrants could already have the option of planning animal tests together, should they be necessary. This obviously saves animal testing, resources and time for everyone.

How all this is and can be implemented in practice needs to be examined elsewhere. However, the efforts are recognisable and the fact that this direction is being taken can only be welcomed.

EMA

The EMA uses so-called catalogues and has replaced the old register (European Union electronic register of post-

authorisation studies (EU PAS Register®)) with the publication of the HMA-EMA catalogue.

"The HMA-EMA Catalogues are repositories of metadata collected from real-world data (RWD) sources and RWD studies. They are intended to help regulators, pharmaceutical companies and researchers to identify and use such data when investigating the use, safety and effectiveness of medicines".[5]

The following purpose shall be fulfilled with the catalogue:

- "Facilitate the discoverability of adequate data sources to generate real-world evidence for regulatory purposes (*e.g.*, identification of RWD data sources suitable for investigating a specific research question);
- Aid in the suitability assessment of data sources by providing clear and easy access to information from the study protocol and study report;
- Improve interoperability between studies and data sources;
- Improve transparency"

The Catalogues have the **FAIR** (**F**indable, **A**ccessible, **I**nteroperable and **R**eusable) data principles. With that those data are fully searchable, and it is even possible to export the data. The EMA states that "the Catalogues implement globally unique and persistent identifiers, ensuring data accessibility and interoperability".

The following types of studies should be included in this catalogue:

- "Non-interventional post-authorisation safety studies (PASS)
- Required non-interventional PASS
- Any other real-world data (RWD) study conducted by MAHs, regulators, academia or research organisations"

The extent to which an actual re-use of data is guaranteed later on was not pursued further at this point. The fact is that the catalogue at least provides a tool that the industry can use to obtain marketing authorisations and possible PASSs certainly help to assess the potential risks of a new medicinal product.

Summary

Each of the authorities has its own provisions, regulations and approaches to establishing new products and prove their individual safety. A harmonisation of these regulations is not apparent, at least at a first glance. After all, data sharing among the authorities seems to be established. As a citizen, it is difficult to judge what this looks like in reality, at least at the moment. While the industry is trying to close the gap of missing databases for commercial issues and set up databases themselves (e.g. 4ReValue GmbH), the consortia have always helped their members to exchange data internally. It will be interesting to see what further developments emerge on the part of the authorities.

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Dr. Regina Ohlmann

The veterinarian Dr. Regina Ohlmann was working as a consultant in the feed industry, when she realised that the introduction of the Transparency Regulation not only meant more work for the EU approval of feed additives, but also an opportunity to introduce data sharing. With that in mind, Dr. Ohlmann founded the 4ReValue GmbH together with Dr. Schreiner. She is enthusiastic about the idea of reducing animal testing through her work.

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