World view

By Merel Ritskes-Hoitinga

Medical regulators: look beyond animal tests

Flexible approaches used to accelerate COVID-19 vaccines deserve wider uptake.

Within ten months of scientists identifying SARS-CoV-2, the European Commission and the US Food and Drug Administration (FDA) had authorized vaccines for emergency use, thus beginning immunization programmes that are saving many lives. Regulatory approval for vaccines usually takes ten years. Much of the speed was achieved by prioritizing COVID-19 programmes; another innovation was allowing human studies to begin before all standard animal tests had been concluded.

Before clinical trials of the two messenger RNA vaccines began in 2020, pharmaceutical companies presented regulators with historical data from work on animal models, which studied similar technology in vaccines against diseases including rabies. Other data came from cell-based tests and computational assessments of the experimental vaccines. Non-animal techniques, including the use of monoclonal antibodies, cultured cells and physico-chemical analysis, were also used to ensure the quality of each vaccine batch.

I'm a veterinary physician who specializes in systematic reviews and integrating multiple lines of evidence. Over 15 months, a team and I interviewed regulators, industry scientists and other experts, and examined more than 150 regulatory filings concerning human testing and emergency approval for COVID-19 vaccines, to see how regulatory scientists considered ways to maintain human safety while breaking with tradition (see go.nature.com/3vxw1za).

This mindset should now be applied more broadly. Introducing alternatives to animal testing could, in my view, produce better medical products and reduce the cost and time to bring them to market.

Non-animal technologies and methods for assessing chemical hazards, medical risks and therapies are called new approach methodologies (NAMs). They are already applied to develop consumer products for use outside the body. In 2013, the European Union banned animal tests to assess whether cosmetics were safe. Cell and computational methods filled the gaps. In 2018, a study found that combining non-animal methods to predict skin sensitization works as well as or better than the standard mouse test (N. C. Kleinstreuer *et al. Crit. Rev. Toxicol.* **48**, 359–374; 2018).

Moreover, there is a formalized, overarching approach to assessing risk that involves reviewing existing information and assessing whether extra, targeted NAM testing is required. One analysis found that it flags more chemicals as environmental-safety risks than animal testing does (K. P. Friedman *et al. Toxicol. Sci.* **173**, 202–225; 2020). Multinational company Unilever and the US Environmental Protection Agency are collaborating to test 40 chemicals using this next-generation risk-assessment approach, which should provide insight for regulatory policy.

> "Scientists considered ways to maintain safety while breaking with tradition."

Many current safety-testing requirements came about because of tragedy and atrocities: the FDA, for example, gained many of its powers in the 1930s, after people were poisoned by an antibiotic dissolved in antifreeze. Other rules were put in place to avoid repeats of brutal Nazi medical experiments and the fetal-development problems caused by the drug thalidomide. But the technology in use when requirements were introduced does not remain state of the art, and policy has not caught up.

In the past decade or so, alternative testing methods have become much more sophisticated, including use of 3D cell cultures, organoids, bioprinted tissues, computer models and 'organs on a chip', which can mimic interactions such as those between the digestive and immune systems.

Last year, the European Pharmacopoiea, which sets quality standards for drug companies on the continent, announced that it would, over five years, replace the conventional animal test to detect fever-inducing compounds. In the new standard test, medicines are added to vials of human blood and monitored to see whether they activate monocytes, a type of immune cell. The irony is that this alternative has been validated much more thoroughly than has the original rabbit test, which was developed in the early twentieth century and was incorporated into regulatory requirements by default. It has taken more than a decade of dialogue between academic and industry scientists, risk assessors and regulators to move forwards with a test that is more efficient, more accurate and more ethical.

Both the US Congress and the European Parliament are working on legislation to reduce animal studies in testing. Regulators have established working groups to support alternative methods, but there are no clear, effective ways to progress. One crucial step will be creation of a formal, streamlined path to lay out criteria for validating NAMs.

This should not simply require strict fidelity to the animal tests that the NAMs would replace; whenever possible, they should be compared directly with human data. Some critics assert that the best way to predict safety and efficacy for humans will always be testing in another mammal. But my work and that of others suggests that animal studies sometimes fail to predict toxicity in humans (in a probiotic treatment for acute pancreatitis, for example; see C. R. Hooijmans *et al. PLoS ONE* **7**, e48811; 2012), or predict toxicity that is not observed (some antibiotics are toxic for guinea pigs, but not for humans). So existing animal tests should also go through rigorous assessment.

Appropriate criteria would reassure both the public and regulators, and would produce preclinical assessments grounded more in evidence than in tradition.

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