Thank you very much for inviting me to share the experience from WHO in the area of animal testing. It is a pity that I was not able to join you in-person, because the program for today is really very interesting and very important for us. Also in the past years, we had lots of discussions on the topic.

I am very pleased to see this issue is taken forward, and there are a number of organizations involved in that initiative. So from a WHO perspective, we would definitely be happy to join this initiative and to contribute from our end.

From the title of the presentation you see that I will basically focus on WHO recommendations and guidelines for vaccines, although we work also on biologicals. I will share with you where we are at the moment and what we plan to do next.

- I will mention briefly about WHO standards to assure quality, safety, and efficacy of vaccines and other biologicals.
- We will then explain how we develop, establish, and facilitate implementation of WHO standards. Then I will show you a couple of issues in the context of animal testing and where we are with recommendations and guidelines on that matter. We will then have a very brief overview of WHO standards serving as the basis for regulatory convergence and a few words about the way forward.

WHO Organizational and Priority Update

On slide number three you can see that we have new leadership at the World Health Organization and highlights of the changes that we are working on together for a healthier world. You see our Director General, who has been very active in promoting the mission of WHO in promoting health, keeping the world safe, and serving the vulnerable.

With the health coverage, health emergencies, and health priorities, you have probably heard that these are now our strategic priorities. We want to have: One billion more people with health coverage, one billion more people to be safer, and also one billion lives improved.

There are lots of initiatives in different areas of our work. The work on the standardization is just one of these initiatives that we have. Our new cluster of access to medicines, vaccines, and pharmaceuticals – this is where we are with the standardization of vaccines and biologicals. You also have a link to the roadmaps on access to medicines and vaccines. That is provided on the slide.
I am now moving to the next slide just to explain that the World Health Organization is a specialized agency of the United Nations. We are serving as a directing and coordinating authority for international health matters and public health on behalf of our 194 member states. Many of you already know that we operate at three levels: ● headquarters in Geneva, where we are ● six regional offices, and ● 150 country offices.

Having the principle objective, which is the attainment by all people of the highest possible level of health, is actually quite challenging. We do have very different requests and different needs expressed by member states. So to meet everyone’s needs is not an easy task. There are common issues, but there are also very region-specific or country-specific issues that we are usually asked to help with.

The setting of norms and standards is one of the original core functions. It has been again recognized as a core function for the 2014 – 2020 period. So there is just some very basic information about WHO.

**Activities to Assist Regulators**

And now on slide 5 I would just like to show that norms and standards are closely related to the regulatory system strengthening. In many of our recommendations and guidelines, we are basically giving recommendations also to regulatory authorities: how to organize themselves and how to conduct certain functions. Many of our activities are also intended to improve expertise in the world and to make regulatory authorities really capable of leading something that we call ‘science-based regulation.’

So the link with regulatory system strengthening is quite strong and important. You probably heard about our benchmarking system, about the regular assessment of regulatory authorities, and all these very relevant issues for further discussions on how to deal with the animal testing.
**Prequalified program:** You already heard from the previous speaker about prequalified vaccines and the WHO role in prequalification. This is basically standards that I will mention in a minute that serve as the basis for vaccine prequalification.

**Safety and vigilance** – there has also historically been quite a strong link between standards and safety evaluation and safety monitoring in the field. So this is just about related initiatives at WHO.

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**WHO Activities to Assist Regulators: Focus on Access and Outcomes:**

**Ensuring normative and technical excellence drives impact at country level**

<table>
<thead>
<tr>
<th>Technologies, Standards and Norms</th>
<th>Regulatory Systems Strengthening</th>
<th>Prequalification Programme</th>
<th>Safety &amp; Vigilance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Set global norms and standards (written &amp; physical) and nomenclatures</td>
<td>• Set effective and efficient regulatory systems in LMICs through collaborative &amp; harmonized approaches with reliance principles</td>
<td>• Assure safety, quality, efficacy &amp; appropriateness of medical products used in LMICs: vaccines, medical devices, cold chain equipment, vector control products &amp; in vitro diagnostics</td>
<td>• Increase knowledge of real life adverse events and coordinate actions taken against adverse events</td>
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<tr>
<td>• Increase common understanding on regulatory requirements by authority and manufacturer</td>
<td>• Increase confidence in medical products produced in LMICs</td>
<td>• Increase competition to shape the market</td>
<td>• Mitigate risks and protect against substandard / falsified products</td>
</tr>
<tr>
<td>• Standardize approach used by quality control labs</td>
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<td>• Contain antimicrobial resistance</td>
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**Norms and Standards**

**Guidance Documents**

And now on slide 6 you can see that we actually have 97 documents, recommendations, and guidelines. Those that are general documents applicable to all vaccines are there as well. Among them you have for instance: • ‘stability and evaluation of vaccines’ • ‘nonclinical evaluation of vaccines’ • ‘clinical evaluation of vaccines.’ Principles described in these guidance documents apply to all vaccines.

But then there are vaccine-specific documents, 66 of them that actually have a unique feature in the world, because they all contain technical specifications and guiding principles for quality assessments, nonclinical and clinical evaluation of a huge variety of vaccines.
So all vaccines mentioned by the previous speakers, we do have guidelines for them starting with diphtheria, tetanus, and pertussis being a kind of basis for vaccines. But also for those that were developed in the past decade – like HPV vaccines or rotavirus vaccine or even more recent like malaria vaccines – for all of these we have a recommendation for a guideline, and currently we are working on the new guideline for R&D vaccines.

These documents were actually developed in-line with the development of vaccines. And when it is demonstrated in clinical trials that they are most likely to be confirmed in terms of efficacy and safety, then these guiding principles are actually provided as the basis for licensing, but also for post-licensure evaluation of the impact.

**Measurement Standards**

Very important also are the measurement standards that many of you are probably familiar with. These standards also have a unique feature because they define biological activity in the international units. That is a great value for potency testing, also for clinical trials, and for development. Both measurement and written standard scientific evidence is of critical importance.

In many cases, of course, with new vaccines we don’t have sufficient scientific evidence. Then we need to work with experts in the world to reach consensus and to move on, at least to provide the basis for further development of these products.

And of course as part of that, and I will mention later on more specifically – animal testing being part of the development of all vaccines, but also being part of evaluation at different levels, is actually quite important and is also part of this scientific evidence that we are talking about here.

**Collaborating Partners**

[There are several] collaborating centers that are working closely with us. It is not just the team of us here where we have basically eight people – five scientists and three secretaries working with us. But there is also a really big team of experts in our collaborating centers, starting with NIBSC [National Institute for Biological Standards and Control] that is the leading center for measurement standards in the UK.

We also have CBER being a longstanding collaborating center helping us with the development of guidance and recommendations for vaccines and other biologicals.

We also have TGA [Therapeutic Goods Administration] in Australia, and NIID [National Institute of Infectious Diseases] in Japan. They also have very long records of serving as a collaborative center for biological standardization. In the past 15 years we have established collaborating centers in South Korea MFDS [Ministry of Food and Drug Safety]. There is one in Canada, Health Canada, NIFDC [National Institutes for Food and Drug Control] in China, and Paul-Ehrlich Institute in Germany.

So all of these eight centers are really playing an important role in the standardization. We think that they will all actually help in taking this issue of optimizing animal testing and improving the situation with animal testing for vaccine evaluation, because some of these centers also play a role of national control authority, while the others are national regulatory authorities. So this regulatory oversight of vaccines is actually quite important.

**Implementation of Standards**

And then what you can see on the screen is just very brief information about the implementation of standards. So once we have standards adopted by the Expert Committee on Biological Standardization, which is our decision making body, these standards become available to all WHO member states.
But the role of implementing these standards into regulatory or manufacturing practices is actually with regulators and manufacturers. WHO’s role is to facilitate this process of implementation, but we cannot implement this without having key players at the country level.

That is why we actually established in 2008 a new mechanism to promote use of standards. So these implementation workshops that you might have heard about or might have participated in were actually devoted to difficult issues that either regulators or manufacturers or both, usually, are struggling with.

Guiding principles that are not easy to implement, or that people need some kind of practical advice or illustration in providing examples, or for instance, getting some case studies that they can understand practicality of application of certain principles. That was actually seen as a very good mechanism for countries to update the standards and to use them and to update their national regulatory requirements in line with WHO standards.

Current Practices and Regulatory Divergence for Animal Testing

This is also something that we can think about in the context of animal testing, because we have several recommendations in different documents that are basically giving guidance on how to reduce animal testing.

This issue has been discussed for a long time, and the view from countries is different. So, it is not always easy to implement, even when we are giving very clear guidance and we actually show the benefit of using certain testing approaches. It is not straight forward for countries to apply that.

Now what you can see on your screen is some issues in terms of current practices for animal testing [see slide #9]. In the past 15 years we had quite a lot of discussion in terms of when the animal testing is really needed and what is the scientific rational for certain tests.

We did identify that a number of tests were actually done for historical reasons. Updating national regulatory requirements is also a top process, because sometimes this is really deeply integrated in national regulations and is not an issue of deleting the text and saying this is no longer applicable.

We basically found that animal testing during the entire lifecycle of vaccines is starting with the vaccine development – a lot of testing for the purpose of evaluating cell substrates, for vaccine characterization, proof of concept, and basically all steps of vaccine evaluation. I am sure that you will hear more about that during the day from the other speakers.

Then in the context of licensing, it is part of quality assessment focused in on safety testing. It is also part of nonclinical evaluation.

And of course, a huge undertaking in terms of animal testing is vaccine lot release. This is an area that has been identified as potentially the most important one if we want to make an impact and really help countries change the current practice.

And also in the context of post-approval changes – that topic has not been discussed very often in WHO consultations. But this is now becoming more and more important, because we established a few years ago a guideline for post-approval changes of vaccines. We already had one implementation workshop two years ago, and another one is planned in July of this year. And this will also probably address the issue of animal testing.

So you can see that I am conveying the message that there are different practices in WHO member states, and that is actually creating **regulatory divergence** in terms of national requirements for animal testing.
We usually hear from manufacturers about these differences, but also sometimes countries are reporting to us. And this is one of the proposals that we would like to make in terms of setting the kind of forum where regulators can share their experience. And of course, we can ask manufacturers to help providing examples to help moving forward without having unnecessary animal testing and without reducing confidence in vaccines quality and safety.

And here I am just showing the top of the paper that we published in 2011 showing basically some changes that were made in WHO documents [see slide #10]. And then there are examples also with respect to DTP testing. There was neurovirulent a safety test that we elaborated on as well.

Then there was also discussion on lot-release potency test and the bridge from full-dilution to single-dilution assay as one of the approaches for reducing animal testing. And then the example of several vaccines were given, and different initiatives were mentioned.

**Rabies Vaccine**

Since then we actually have had quite a lot of discussion of these issues, and I will just show a couple of points regarding the rabies vaccine. What you can see on the screen is just a list of relevant documents – the old requirements for rabies vaccines and then those that were updated, and the most recent one from 2007. There was also a report from the expert consultation on rabies and a position paper on rabies vaccines from 2018. You can find a lot of details in these documents [see slide #11].

Now what you can see is just a list of quality control tests on the final product of rabies vaccines [see slide #12]. You can see a lot of tests and also a number of potential areas for reducing animal testing. You can see in bold the innocuity test, because I will talk about that in a minute and will show you what is kind of the WHO approach on that.

So when it comes to the potency testing of rabies vaccines, you know that the famous specification of 2.5 international units per dose has been very well implemented in all countries. This serves as the basis of vaccine potency tests.

The NIH test is also used for determination of potency, and for stability testing. It was used for the calibration of secondary reference preparation against the WHO International Standard. There is currently available the 7th International Standard adopted by the Expert Committee on Biological Standardization last year in October [2018].
This is actually an area that worked quite well. The issue with standards is not causing a problem. But what is causing the problem is the actual NIH tests. Manufacturers were encouraged to develop alternative in vitro assays, but this initiative was not really straightforward.

There were lots of difficulties—interpretation of the results, different initiatives. There are still studies going on. The one dilution assay that was actually recommended was well received, we think, as a kind of principle. But then still there was a question of full dilution assay is needed for licensing. And also from time-to-time they need to repeat full dilution assays. Nobody really wants to use traceability of international units when they are using one dilution assay.

There are always pros and cons and issues that need to be handled in the context of changes.

**Discontinuance of Innocuity Test**

And now we are moving to the innocuity or abnormal toxicity tests—because the last expert committee meeting in October 2018 came to the decision that this test should be discontinued. I will just give you a bit of history of that. You will also see different terminology. It is also called an ‘abnormal toxicity test’ or ‘general safety test.’

That general safety test as a name was particularly misleading, because in a number of countries people were taking this as a really high-level safety assurance. And for that reason, it was really difficult to remove the test, even when we gave them or provided some kind of flexibility for that.

So the history is that at the beginning, tests were really intended to ensure the safety and consistency of production of sterile products. It became later on a general safety test to detect extraneous contaminants in all biological products. I am sure you all know the history of that test.

But then in the past decade, or even longer, there was a question about the value of that test, both from the perspective of regulatory science and also in the context of principles of animals used.

The specific request that we received from the IABS conference held in 2015 on the 3Rs concept was a formal request to WHO to initiate steps to delete the innocuity test from all WHO recommendations. And also a number of other international initiatives have been taken in the same direction—US FDA in 2015 and the European Pharmacopeia Commission decision in 2017, with the effects from January 1, 2019.

All of these events were actually very good for reopening this discussion with the committee, because we already proposed two or three times actually in the past 15 years to discontinue these tests. But it was very difficult, because there are countries that really want to keep this, and in some cases, is not really for scientifically justified reasons. It is really just for the purposes of showing: ‘we have a lab and we have to do something, and we cannot do more sophisticated tests, so let us just do something in two guinea pigs and five mice.’

That was not a good rationale for performing the tests, but it was actually seen as a kind of safety assurance—so a bit of perception that was also very difficult to deal with, and still it is an issue.

Before 2000 the test was required of each final lot, with subsequent guidance indicating that the test could be omitted during routine lot release once consistency of production had been established.

Since 2000, there were a number of efforts made to reduce animal testing at all levels of production and overall evaluation, including innocuity tests. So a lot of calls to national control labs to change the practice of lot release. WHO guidelines on lot release were also conveying the same message—that if countries do not have a reliable laboratory where such testing for lot release for vaccines could be performed, then it is better to rely on the results from another lab or to apply some kind of recognition or reliance concept rather than insisting on their own testing.
In 2015, the WHO expert committee advised that the need to test final vaccine lots for unexpected toxicity using the innocuity test should be agreed with the NRA. We were actually hoping at that time that most of the national regulatory authorities will actually wave this and will say it is not really needed. But we found that still a number of regulatory authorities actually kept doing this by themselves and asked manufacturers to do this as well.

The current manufacturing processes that include implementation of GMP and comprehensive quality control measures were basically considered as more appropriate than the innocuity test itself in assuring the quality and safety of vaccines. This concept can also be applied to other tests.

Where we are now is basically with the decision from the expert committee from October last year [2018]. When the scientific rationale for the impurity was discussed in-depth, the committee concluded that complete omission of the innocuity test would not compromise the quality and safety of vaccines and other biological products.

They recommended the immediate discontinuation of the inclusion of the innocuity test in all future WHO recommendations, guidelines, manuals, and documents published, and in the Technical Report Series. And further recommendation was made that the inclusion of this method in previously published WHO technical reports be disregarded.

It was considered that these recommendations represented a significant step towards science-based regulation and regulatory convergence at the global level, but as mentioned we need to work on the actual implementation of that recommendation.

**Regulatory Convergence**

So just a quick review of regulatory convergence – what are the opportunities and challenges?

We have been promoting this science-based WHO standard for science-based regulation and the common tools, hoping that if all countries are using the same WHO standards, there should not be as much divergence in the regulation. But we still see quite a lot of space and opportunity to improve the situation and move from divergence to convergence by using the definitions that WHO provides, international standards, and also more and more educational and training tools for improving expertise. Because the expertise of regulators in countries is really critical.

Without the expertise, people are reading WHO documents as principles carved in stone, which is not the intended use. With the relevant expertise, people can actually apply some flexibility. They can think in the context of case-by-case scenarios and make relevant decisions for each case of vaccine evaluation.

And also, many international and regional initiatives we see as opportunities for taking this issue forward. I just listed a number of associations that we have been working with: DCVRN [Developing Country Vaccine Regulator’s Network], PANDRH [Pan American Network for Drug Regulatory Harmonization], AVAREF [African Vaccine Regulatory Forum], ASEAN [Association of Southeast Asian Nations], APEC [Asia-Pacific Economic Cooperation] Harmonization Center, IPRF [International Pharmaceutical Regulators Forum] is now actually IPRP [International Pharmaceutical Regulators Programme] – and also manufacturers associations like IFPMA [International Federation of Pharmaceutical Manufacturers and Associations], DCVMN [Developing Countries Vaccine Manufacturers Network], and a number of others. Pharmacopeias are also very good collaborators in these areas of work. Successful cooperation with IABS in a number of areas is also a very good opportunity.

We are also looking for new opportunities in the area of training because it is something that countries always ask for.
Optimizing Testing in Animals

A way forward in optimizing testing in animals: What we think is very much needed is to conduct a review of the kinds of approaches in the WHO member states. It has actually been planned for several years but was postponed due to the lack of resources. The way that we would do it would be through a WHO working group on that topic that needs to be established and needs to initiate the kinds of systematic work with regulators, manufacturers, academia, and other relevant expert groups.

And then another issue is the further development of alternative assays that can actually replace in vivo potency assay by introducing novel methods, such as serological assays, ELISA, or biochemical methods. All of this is on its way, but I think we need to also promote use of these alternative assays.

Further development and implementation of methodological advances such as synthetic manufacturers have been working on, involving the replacement of animal-based substances with synthetic materials – some of them have made very good progress. But this is still something that should continue, especially for cell substrates and the overall production actually.

And then in the area of detection of advantageous agents in cell substrates, next generation sequencing and new methodologies could potentially replace quite a number of animal tests. That would make a difference, so we have been involved in that for several years. It is now at the stage where we think that regulators need to get more involved, not just in the discussion, but really in better understanding how to interpret the results and move the tools from research to regulation.

Our activities to facilitate implementation of up-to-date standards, including recommendations for discontinuation of the innocuity tests and to measure impacts of that change at the guidance level, are other steps forward that we are planning to do. I envisage a number of collaborative efforts and participation with other bodies and organizations in coming years to promote science-based regulation and optimal testing.

The concept of reliance could be expanded to avoid redundancy and duplication of animal tests. This concept of reliance has been actually really discussed a lot in the past years. ICDRA— the International Conference of Drug Regulatory Authorities— recognized this as a very important mechanism for regulators to work together and also to reduce redundancy and duplication at all levels – not just in the context of animal testing, but really in all areas of regulatory function.

That is basically where we are at the moment. I would just like to thank:

- Our colleagues on my team….We hope that we will have a lot more activities in the coming years comparing to the past years.
- And also to thank members of our drafting and working group, who were very helpful in the development and implementation of standards, especially at the collaborating centers.
- And really a huge numbers of individual experts. Some of them are also included as speakers at this conference, and they all provided really a lot of help and guidance to us but also our member states. Thank you very much.