

1 a defined fraction of the production, characterized by its intended homogeneity. The lot size can  
2 be defined either as a fixed quantity or as the amount produced in a fixed time interval.

3 **Lot release:** The process of NRA/NCL evaluation of an individual lot of a licensed vaccine  
4 before approving for releasing onto the market.

5 **Non-compliance:** Failure or refusal to comply with a standard or a set of limits.

6 **OOS:** Out of specification. An OOS result is generated when a vaccine is tested and fails to meet  
7 a pre-defined specification.

8 **Source material/Starting material:** Any substance of a defined quality used in the production  
9 of a vaccine product, but excluding packaging materials.

10 **Spot testing:** An informal test run without elaborate preparation in order to obtain an immediate  
11 sample response.

12 **Summary protocol:** (Also named as 'lot summary protocol'.) A document summarizing all  
13 manufacturing steps and test results for a lot of vaccine, which is certified and signed by the  
14 responsible person of the manufacturing company.

## 15 **10. Abbreviations:**

16 **AEFI:** Adverse Event Following Immunization

17 **DTP:** Diphtheria, Tetanus and Pertussis vaccine

18 **GMP:** Good Manufacturing Practices

19 **HPV:** Human Papillomavirus Vaccine

20 **IS:** International Standard

21 **ISO:** International Standards Organization

22 **MMR:** Measles, Mumps and Rubella vaccine

23 **NCL:** National Control Laboratory

24 **NRA:** National Regulatory Authority.

25 **OPV:** Oral Polio Vaccine

26 **PMS:** Post Marketing Surveillance

27 **QA:** Quality Assurance

28 **QC:** Quality Control

29 **QMS:** Quality Management System

30 **SOP:** Standard Operating Procedures

31 **UN:** United Nations

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41

## 42 **13. Appendix**

43

### 44 **A Model Procedure to Document the Decision Making Process in Lot Release**

45 This section is intended to assist NCLs in the documentation of the information and the process  
46 used in the evaluation of vaccine lot release specific issues. Examples include:

47

- 48 • Release of vaccine lots under emergency situations such as vaccine shortage due to  
49 disease outbreak, natural disaster, manufacturing problems (e.g. out-of-specification) etc.
- 50 • Periodic evaluation of independent testing frequency (to consider modification,  
51 suspension or continuation of current strategy),

- 1 • Periodic evaluation of tests performed for lot release of a particular product (to consider  
2 deletion, inclusion or modification of given tests).  
3

4 An example (in small print) is provided with the aim of illustrating how to utilize the template.  
5 Given that each situation is specific, it is expected that modifications to the structure and content  
6 may be required in order for this template to be applicable to different issues.

7 **1. Issue**

8 Define the problem/issue to be analyzed.

9 **2. Purpose/Objective**

10 Outline the purpose and/or objectives of this analysis, for example to evaluate the consistency of  
11 production of a vaccine, and explore whether changes to the frequency of independent testing or  
12 elimination of a specific test are justified based on the consistency of production.

13 **3. Background**

14 Give brief history of problem/issue and identify critical information.

15 **4. Considerations**

16 Indicate who was consulted for this process and discuss the results of the consultation(s).  
17

18 Identify how the concerns of those consulted were addressed in the proposed approach.

19 **5. Issue analysis**

20 List all key components of the issue to be analyzed, taking into account of relevant information  
21 from NCL/NRA and manufacturers. Justify results/conclusions with regulatory and scientific  
22 data including published and not published information.

23 **6. Options analysis**

24 List all the alternatives considered to address the issue/problem including *Status quo*.  
25

26 List and discuss the positive and negative aspects of each option.  
27

28 Outline the proposed solution or accepted alternative and why it was selected.  
29

30 If relevant, discuss the benefits and costs of the proposed solution compared to the benefits and  
31 costs of the other solutions.

32 **7. Considerations**

33 Identify any additional relevant information, for example, discuss with other NCLs that are  
34 responsible for releasing this vaccine in other countries to share the information regarding  
35 production and quality control of this vaccine.

36 **8. Recommendations**

37 Indicate what the recommendation is and who is responsible for the approval.

38 **9. Implementation and evaluation plan**

39 Show how the proposed changes will be implemented in terms of timing, organizational and  
40 personnel changes necessary, resource allocation, etc.  
41

42 Indicate when and how the proposed change will be evaluated and against what benchmarks

43 **10. References and attachments**

44 Include any references, reports and relevant information used in the risk analysis, such as GMP  
45 inspection report, regulatory post-marketing unit report, quality control product report from NCL  
46 and/or summary of decisions regarding variations submitted for regulatory approval.  
47

48 I approve the recommendation proposed in this analysis,  
49  
50  
51  
52

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- 1 Dr. xxxxxxxx
- 2 Director of National Control Laboratory
- 3

**Distribution: General  
English only**

## **Meeting Report**

### **WHO/Health Canada Consultation on Vaccine Lot Release**

**Ottawa, Canada**

**28 February - 1 March 2007**



## ***Introduction***

The meeting was opened by Dr P Charest (Director-General, Health Canada), who welcomed the delegates and explained that the purpose of the meeting was to review the issues surrounding the lot release process for vaccines which was currently employed by many countries, including Canada. This meeting would consider the scope for a wider international consultation on this subject later in the year.

Dr I Knezevic welcomed participants of the meeting on behalf of WHO and highlighted the importance of having an open discussion among National Regulatory Authorities (NRAs), National Control Laboratories (NCLs), manufacturers and other parties involved in lot release at this point in time. Regarding the venue of the meeting, she reminded the group that Health Canada has a long tradition in hosting WHO consultations on specific topics in the area of biological standardization which is very much appreciated by WHO. One such event was a discussion on Guidelines on Quality Assurance for biological products, held in Ottawa in June 1990. This was supported by the Bureau of Biologics at that time and resulted in the guidance document which among other issues describes duties and responsibilities of National Control Laboratories in the context of Quality Assurance. A more recent event was a consultation on pandemic influenza vaccines and related regulatory issues held last year in March. In addition, the contribution of experts from Health Canada as well as from all other National Regulatory Authorities, to the WHO biological standardization programme, has been recognized as an important factor in setting up global standards. In line with this, Dr I Knezevic supported the idea of WHO meetings hosted by regulators in different countries as a step towards better recognition of the role that regulators play at the national and international level. This statement was followed by an explanation of the meeting objectives and the expected outcomes. Although lot release is long-established and widely assumed to operate effectively, a number of difficulties have been reported at WHO consultations in recent years. This revealed that different approaches in conducting lot release have an impact on the overall regulation and furthermore, on the introduction of new vaccines and the use of existing products. Therefore, a need to review the practical aspects of releasing vaccines and to consider options available for WHO together with NRAs and NCLs



to improve the situation was identified. In response to this, a working group has been set up and the first meeting is an opportunity to have input from every participant. The outcomes of this meeting should pave the path for broader consultation in September 2007 and should also be published in the form of the meeting report to inform a wider audience of this initiative. The experience that participants faced in their routine work would be of great help in understanding current problems, in developing proposals for the future and in identifying goals in coming years.

The meeting appointed Dr Elwyn Griffiths as Chairman and Dr Michael Corbel as Rapporteur.

Dr E Griffiths (Health Canada) reviewed vaccine lot release programmes and the challenges they posed. Lot release and laboratory access were two of six critical regulatory functions for WHO and constituted a major focus in the assessment of NRAs/NCLs in the pre-qualification programme. Lot release was a post-licensing activity that involved independent review and approval by the NRA of the summary protocol of manufacturing and all QC processes prior to release. It included targeted testing of lots before release on to the market and was practiced world wide to different degrees. The challenges to present assumptions and practices in regulating biologics had been reviewed in several publications (1, 2). Challenges to present assumptions included the increased volume of vaccines now licensed and in use, the increasing complexity of new vaccines requiring more sophisticated tests, and the increasing globalization of the industry. These factors created an increasing burden for NRAs and for the industry. Questions about the relevance of public sector involvement in the control of biological had been raised. These issues were a particular problem for developing countries with limited regulatory experience and resources and often unable to cope with traditional vaccines let alone new biotechnology products. It could be asked, why have independent lot release by NRAs? This is not done for synthetic drugs so what is its purpose for biological medicines? Was it still relevant in the 21<sup>st</sup> Century? Is it effective? What are its disadvantages and can it be done better?

The argument for lot release was that it was especially important for high risk products such as vaccines. These were important public health tools usually given to large numbers of healthy subjects. Defects in safety or efficacy might not become apparent until long after administration. The consistent safety /efficacy of a vaccine has long been recognized as an essential element in any successful immunization programme and it was vital to maximize this. As products of biological origin, vaccines differed from synthetic drugs in being prepared from inherently variable source materials by complex systems and requiring assay by methods that were themselves subject to variation, using reference materials possessing the same inherent variability. Deleterious effects of synthetic drugs were usually related to their chemistry. Problems with vaccines were usually batch related and caused by complex biological factors such as reversion to virulence or toxicity or loss of immunogenicity. This inherent variability was a fact of life. Independent testing provided a safety net that supported the manufacturer's tests. Although new, high technology products might be expected to be free of such factors, experience showed that this was not the case and similar problems still arose. Historically, lot release arose out the recognition of the inherent variability of biological products as illustrated by numerous adverse events over the years. Some e.g. SV40, were not recognized until years after use of contaminated vaccines.

Lot release was an expensive activity and failures could adversely affect the vaccine supply. Production processes were already lengthy and with vaccines becoming more complex. Failure of a single component of a combination vaccine could lead to rejection of whole batches of complex combinations. This was amplified by current trends to produce large lots (>100,000 doses). The reliability of the lot release process was vital to ensure that poor quality/unsafe lots were detected and to avoid inappropriate rejection of good quality product and disruption of supply. It was important to adapt to changes in technology and to upgrade testing methods appropriately. An independent scientific review (1) had confirmed the need for biological standardization and control to keep pace with science. The WHO Review in 2007 would re-examine issues surrounding lot release. There seemed little argument about the need for independent assessment; the issues were amount and quality of testing, with more emphasis on risk analysis. Intended

outcomes of the consultation were improvement of lot release processes globally, improved opportunities for regulatory cooperation, establishment of an ongoing working group on lot release and benefits to public health and industry.

Dr I Knezevic (WHO, Geneva) presented the WHO perspective on lot release as part of vaccine regulation. She produced a brief resume of the current WHO programme on norms and standards. Lot release was one of the key regulatory functions in vaccine quality assurance. General recommendations were presented in document TRS 822 (4), with listing of tests required in the documents relating to specific vaccines. However, summary protocols did not indicate if tests were obligatory or optional, nor was there specific guidance on tests to be performed by NCLs. Current approaches followed by these included independent testing, review of protocols and a combination of both. The original concept behind lot release was to assure the quality, including potency of each lot, to assure safety of the final product and to assure consistency with clinical trial lots used in efficacy studies. This has changed over time, with more emphasis on consistency of production, GMP and trend analysis. The duties and responsibilities of NCLs had been outlined in 1992 (4). It was expected that they would have the ability to perform all the necessary tests, operate independently of manufacturing activities and be able to advise the NRA on matters relevant to the approval of products and manufacturing facilities. They would also perform pre-licensing testing of products, evaluate shelf life stability and develop and implement test procedures for release. In addition, they should also review quality defects, carry out re-testing of doubtful lots and advise on withdrawal from marketing, perform relevant research, maintain records of all samples examined and have the authority to request samples from manufacturers.

Another important role of NCLs was the establishment of national reference materials calibrated against International Standards for distribution to manufacturers for routine testing. A multinational or regional approach to establishment and supply was recommended. In practice, this process was currently at an early stage or non-existent in most regions.

Recently, independent testing has been recommended by WHO at the clinical (5) and nonclinical evaluation stages (6). The impression is that this is not widely practiced at present. Ideally, tests selected at the clinical trial approval stage would be validated and used in lot release. This would depend on availability of sample material at the trial stage.

For independent testing, the issues that needed to be considered were: the value of the process; the development and maintenance of laboratory expertise; the testing procedures used and the need to update these; the criteria to be selected for evaluation; the frequency of testing and the reference materials to be used. For protocol review, key issues included; form of protocol, full details of production of lot with testing data or summary protocol or certificate of analysis; lack of expertise in assessing critical issues; basis for setting internal specification for review process; assessment of reagents, reference materials and test methods used by manufacturers; mutual recognition, does it equate with mutual confidence? The advantages and disadvantages of protocol review needed to be discussed, including the implications of releasing vaccines on the basis of protocol review without independent testing.

The difficulties reported to WHO by NCLs included: the expense and complexity of testing; training was needed and was useful but subsequent maintenance of expertise could be difficult; poor communication between NRAs and NCLs; different testing approaches for different products and an unclear message as to which tests were required- currently tests performed ranged from pH measurement to a comprehensive list of assays. The question on what is needed and who decides is another issue raised in this context.

Difficulties reported by industry included: lack of information on lot release requirements in developing countries; high demands for training, reagents and equipment; lack of clarity on added value of independent testing duplicating manufacturers' tests; lack of harmonization of lot release requirements between countries; concern about out of specification results caused by poor competence of NCL; and restriction of availability of products by lot release process.

To help resolve these issues, early and frequent dialogue between NRAs/NCLs and manufacturers from pre-licensing through to post marketing surveillance was recommended.

This workshop was intended to identify areas where further WHO assistance was needed, to define key issues and objectives, to take these forward to a major consultation in September 2007.

### ***Current approaches***

Dr R Gupta (CBER, FDA, USA) presented the regulatory framework for lot release in the USA. Lot release was one component of an overall system for regulation of vaccines to ensure release of safe and effective products. Other components were an extensive licensing process, biennial GMP inspections, review of deviations and supplements to licensing documents. Lot release involved review of protocols and selected testing. Legal requirements were defined in the Public Health Service Act and Code of Federal Regulations (CFR). Only lots released by CBER could be marketed in the USA. Release by other authorities was not recognized. The CFR defined the conditions and authorization for lot release. A lot release system database allowed the tracking of all lots submitted and information pertaining to this, including alerts for issues that could impact on lot release. On receipt, samples and protocols are recorded on the database and the data would be forwarded to reviewers who would decide on subsequent action. Samples could be of bulk components, concentrates or final containers according to license specification. These were recorded and stored for testing if needed. Tests were based on methods validated by the manufacturers. These could include compendial methods (USP), CFR requirements or others. Testing might be performed not only for lot release but in support of license applications or supplements. A decision on testing depended upon the track record of the product. It could be relaxed or re-instated depending on status. Safety issues, complaints or process changes would instigate re-instatement. Some products (but not vaccines) were exempted from lot release. These included certain well-characterized biologicals.

Dr P Richardson (EMA, London, UK) described the Official Control Authority Batch Release (OCABR) process in the EU. This covered vaccines and blood and plasma derivatives as defined by Directive 2001/83/EC amendment Directive 2004/27/EC (7, 8). The OCABR process was part of an overall quality surveillance system which was the responsibility of the European Medicines Agency answerable to the European Commission. Lot release was operated by an interactive network of NCLs coordinated by the EDQM in Strasbourg which was also responsible for testing Centrally Authorized Products not subject to OCABR (rarely includes vaccines) and for EU biological standards. The development of monographs for vaccines and selection of test methods was through the European Pharmacopoeia Group 15.

To avoid the use of different controls in each member state, a unified codified system was developed prescribing the optional possibility of member states to require OCABR but with the obligation of mutual recognition and not to unnecessarily repeat tests already performed by an NRA in the EU.

The lot release of vaccines required QC by the manufacturer but independent testing could be done subsequent to or in parallel with this. The outcome of tests was communicated between NCLs and release certificates were mutually accepted. The NCL needed to have Official Medicine Control Laboratory (OMCL) status and certain requirements had to be met to achieve this. For specific products, the OMCL designated for lot release was identified at licensing stage and proposed in the application. The proposed release tests were also approved at this stage. The OCABR process was supposed to embrace more than lot release and to take into account information on production, QC and GMP. New vaccines were providing new challenges e.g. in relation to adjuvant formulation or vaccine design and new test methods. There were also proposals in place in some jurisdictions to reduce release testing and to give more responsibility to manufacturers.

Dr H Rode (Health Canada) presented the Canadian regulatory framework for batch release. Each lot of certain biological products including immunizing agents (vaccines)

is subject to a risk-based lot release programme that has been outlined in a Guidance to Industry document. Lot release for the highest category of biological required submission of protocols and samples. The decision on whether to release on protocol review alone or to require testing in addition depended on estimated risk. Vaccines were generally considered as high risk but could be assigned to a lower risk category on the basis of post licensing experience. Any safety concerns would lead to reversal of this process. Tests were targeted to relevant release tests identified pre-licensing and focused on safety and potency.

### ***Challenges of lot release programmes in developing countries***

The regulatory perspective on lot release in developing countries was considered. Ms T. Jivapaisarnpong (NCA, Thailand) described the development of the lot release system in Thailand. Biological products used in Thailand, including vaccines, comprised those from locally produced commercial and non-commercial sources as well as imported materials. From 1990 to 1998 lot release was restricted to locally produced products but was extended in 1998 to include those from all sources. Protocol review was applied to all products with testing restricted to local products until 2003 when test samples of imported products also had to be submitted. The objectives of lot release include assurance of product quality and provision of a means of controlling changes in products. This was supported by the licensing process and GMP backed up by trend analysis. The lot release process involved review of the lot summary protocol according to a check list, recoding of all data relating to product quality, quality control testing, trend analysis of manufacturer's and NCL quantitative test results to establish the acceptance range. Variation in the quality of protocols was a problem and it had proved difficult to persuade some manufacturers to provide sufficient detail. For out of specification results, the manufacturer is notified by an official letter and is required to investigate and identify the cause. Typical causes included changes in equipment, source materials, test specifications and test methods. The appearance test had proved problematic as there were no clear criteria for lot release by NCL. Adjuvant sensitivity to freeze-thawing could also cause changes in appearance. Visual inspection followed the Ph Eur method. Examples of problems encountered included small white particles in some Japanese

encephalitis vaccine lots, subsequently identified as endogenous protein. Black and white particles, fibres were found in DTP, hepatitis B and rabies vaccines, and turbidity in Hib vaccine. Other problems detected have included incorrect product description, non-compliance with GMP, unsatisfactory transportation conditions, and un-notified changes in stoppers/containers.

Lot release of vaccines in Latin American countries was discussed by Dr M A Cortes Castillo (PAHO, Washington DC, USA). This function is included in the regulatory frameworks of most Latin American countries as part of post licensing monitoring activity, especially in relation to vaccines. In 2003-4, 19 NRAs in the Region were evaluated by PAHO. Of these, 15 regularly undertook review of summary lot protocols and eight performed at least two laboratory tests. A common problem experienced by NRAs was that manufacturers' protocols varied widely in content and detail. Testing practice also varied widely between countries in the Region. For example, in Venezuela, 51% of EPI vaccine lots and 25% of privately purchased vaccine lots were tested. For blood derivatives, the proportions were 90% and 25% respectively. In Cuba, on the other hand, 19.9% of vaccine lots were tested.

Protocol review was not sufficient in itself and needed to be supplemented by testing. There was no clear guidance on the critical elements of protocol review nor was the content of protocols stipulated e.g. manufacturers were not required to mention repetition of tests.

Lot release was important in the Region as many vaccines in use were no longer an issue for developed countries e.g. DTP, OPV. It was not clear who ensured the quality of these lots. Even for vaccines from pre-qualified manufacturers, lot to lot variation was a problem that could not be addressed by the pre-qualification process alone. Lot release was needed to support this. Another issue was that some products e.g. rotavirus vaccines, had been used for the first time in the region even though the NRA in the country of origin had not tested the virus content. It was the intention of PAHO through the Regional Network of Quality Control Laboratories to support and strengthen those



laboratories capable of performing reliable lot release testing and thereby generating data valuable for the region as a whole. One recent example had been the organization of an international workshop to provide training in rotavirus vaccine testing. PAHO was also establishing Regional Standards for testing, beginning with the PAHO First Regional Standard for Pertussis Vaccine. PAHO intended to continue to support lot release activities in the region through such facilitating processes.

### *Manufacturers perspective*

The perspective of the developing countries manufacturers was presented by Dr S S Jadhav, (DCVMN). The manufacturers were not opposed to lot release if properly conducted and in fact they considered that it provided advantages to the manufacturer in terms of protection from improper claims, reassurance of the public, and in building confidence in products. A lot release system was defined as an integrated system of testing, documentation and review parameters which ensures compliance with Quality Assessment (QA and QC) of a product as laid down under GMP, pharmacopoeia and WHO requirements before release on the market. A lot release policy should state in writing the procedures and methods to be adopted to achieve this. The tools for a lot release system included written controlled statements, formats and templates which ensure implementation of the system. Detailed flow diagrams showing examples of the operation of these were presented. The role of the National Control Laboratory (NCL) as exemplified by the Indian NCL was described. The expectations of the manufacturer from the NCL included: provision of training, including updates, according to WHO norms; guidelines for assay validation, training on characterization, standardization and establishment of in-house reference materials, meetings to discuss product quality reviews; discussion on test specifications for new products, conducting collaborative studies on new reference materials; harmonization of test protocols; guidance on procedures during new product development; supply of reference cultures, cell lines and reagents; guidance on adverse event management.

Dr A Sturgess (IFPMA) presented the views of the International Federation of Pharmaceutical Manufacturers Associations, representing manufacturers in developed

countries. Current practice meant that a vaccine may be delivered to more than 100 countries for which there were a variety of different release approaches. Lot release requirements are usually country-specific. In addition to release testing by the company, release testing by the National Regulatory Authority (NRA) was typically required. Lot release protocols were usually country-specific and varied widely in format and details were required. Some markets require testing of final packing lots, or testing on importation causing further delay. The process could be extremely complex and a product lot intended for multiple markets could undergo multiple series of tests. This could take 6 to 12 months off the shelf life in some cases. This was a major problem for vaccines with short shelf lives. False positive out of specification results could also cause delay or release problems in other markets. NRAs may use different assays from manufacturers with limited concordance testing. Batch release by multiple NRAs could impose heavy financial/resource burdens on producers. The complexity of testing meant that not all NRAs would have resources to keep up with technological development. This could further increase risks of false out of specification results and compromise access of vaccines to some markets. The releasing authority needs to have access to a complete view of manufacture from GMP inspections through file registration/ product license variations.

Sample retention was resource demanding and the need to test multiple lots by multiple NRAs meant additional sample material needed to be retained.

Manufacturers considered that multiple testing of the same lots did not increase product quality. An option to reduce the testing burden needed to be considered. This included the exemption of Testing on Import where shipping validation data were provided and the recognition of independent testing laboratories.

***Potential implications of changes in the approach to lot release***

The implications of vaccine lot release programs for impact on public health were considered by Dr M J Corbel (NIBSC, UK) who identified the primary purpose of lot

release as to ensure consistency of production lots with the MA specification and with clinical trial lots used to support licensing. This provided additional assurance of safety, permitted monitoring of potency or correlates of efficacy and helped to maintain quality. Lot release was necessary because vaccines were complex biological products that required potency and safety testing by methods that were subject to variation. Independent testing provided an additional layer of assurance and provided data that were useful for investigation of any subsequent problems. Even well-established manufacturers could experience problems with consistency of production. Examples detected by NIBSC had included, in the case of DTwP, persistent problems with low potency for several products. Excessive toxicity was manifested in the mouse weight gain test, including massive ascites production in the case of vaccines from one source, or as high levels of pertussis toxin and endotoxin. Products made by more advanced technology were not exempt from problems. In the case of a DTaP combination, the detection of excessive histamine sensitizing activity had been challenged by the manufacturer but confirmed by independent NCLs. A similar situation had occurred for persistent low diphtheria potency. Excessively high or low viable counts were a frequent problem for BCG vaccines, probably reflecting the nature of the current assays. Problems of resurgence of Hib disease in infants had also raised issues about vaccine quality. Investigation of vaccine quality, including re-examination of batch testing data and further testing on retained samples, had shown that the Hib vaccines used during the period in question had been very consistent in quality and also remarkably stable. In this case, lot release testing had vindicated the manufacturers. Subsequent investigation had shown that the resurgence of Hib disease was attributable to a complex of factors including loss of natural boosting through reduction in carriage caused by the initial intensive vaccination campaign, and adoption of a less immunogenic acellular pertussis-based combination.

Lot release testing had detected these issues and had helped to resolve some problems and to avoid others. It was to the advantage of both manufacturers and vaccine recipients and played an important role in promoting public confidence in vaccines.

Dr P Christian (NIBSC, UK) reviewed the issues surrounding post approval introduction of new assays and the maintenance of expertise in vaccine testing. In the EU context, the introduction of variations or improvements to existing assays is not usually difficult but requires close collaboration with the manufacturer. The licensing authority will usually accept the changes and a variation to the license may not be required. However, the introduction of entirely new assays can be problematic. This will usually require the cooperation of the manufacturer, the licensing authority and the European Pharmacopoeia and EDQM. Examples have included the replacement of challenge assays for diphtheria and tetanus toxoid potency with serological endpoints and the replacement of the monkey neurovirulence test with a transgenic mouse test. In the first instance all parties were supportive but the whole process took a minimum of 13 years, in the second case it took 16 years. In situations where there is no cooperation from the manufacturer, change is only likely to be implemented by the NRA if there are major safety issues. Usually the NRA will only request implementation of new methodology if accepted by the pharmacopoeia but the latter is usually only reactive to changes in license requirements. Maintenance of expertise can be a problem where the throughput of batches is small e.g. because of low demand or because production batches are large. Changes in immunization policy may also exclude certain types of product e.g. replacement of DTwP by DTaP may eliminate expertise in the pertussis potency test. Similarly a switch from OPV to IPV may lead to too few batches to maintain competence in the neurovirulence test. Other examples have included loss of capacity to test rabies and yellow fever vaccines because of change in manufacturer. These problems can at least be partially obviated by quality systems that monitor maintenance of competence and by designation of centres of excellence that specialize in certain types of assay.

Dr M Baca Estrada (Health Canada) considered the issues surrounding the updating of tests for new and established vaccines. Ideally a lot release test should be relevant to protection /safety in humans. It should be sensitive and able to detect all possible causes of production failure. It should also perform consistently to ensure validity of results. In practice, most tests fell short of these requirements. For many vaccines there were no tests relevant to protection in humans. There was also pressure to eliminate animal test.