Theme Papers

New challenges in assuring vaccine quality[*]

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In the past, quality control of vaccines depended on use of a variety of testing methods to ensure that the products were safe and potent. These methods were developed for vaccines whose safety and efficacy were based on several years worth of data. However, as vaccine production technologies have developed, so have the testing technologies. Tests are now able to detect potential hazards with a sensitivity not possible a few years ago, and an increasing array of physicochemical methods allows a much better characterization of the product. In addition to sophisticated tests, vaccine regulation entails a number of other procedures to ensure safety. These include characterization of starting materials by supplier audits, cell banking, seed lot systems, compliance with the principles of good manufacturing practices, independent release of vaccines on a lot-by-lot basis by national regulatory authorities, and enhanced pre- and post-marketing surveillance for possible adverse events following immunization. These procedures help assure vaccine efficacy and safety, and some examples are given in this article. However, some contaminants of vaccines that can be detected by newer assays raise theoretical safety concerns but their presence may be less hazardous than not giving the vaccines. Thus risk–benefit decisions must be well informed and based on scientific evidence.

Keywords: drug evaluation, methods and trends; drug monitoring; legislation, drug; quality control; vaccines, standards.

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Introduction

The quality control of vaccines has always relied on three components: control of the starting materials; control of the production process; and control of the final product. For "traditional vaccines", for which there is a vast production experience and a long history of use, considerable emphasis is placed on a bioassay for potency testing of the final product, often in animals. Tetanus and diphtheria toxoids and whole-cell pertussis vaccines belong to this category. Their efficacy and safety have been demonstrated by extensive experience in the field, through post-marketing monitoring of case reduction and adverse reactions.

Serological markers of protection in humans exist for some of these vaccines. For example, the protective role of tetanus antitoxin antibodies is well established. However, the protective level was set in a somewhat arbitrary way — as $\geqslant 0.01$ IU/ml serum. This level was based on animal studies that established a correlation between antitoxin antibody levels and either the appearance of tetanus symptoms or death. The experience in humans is, however,

more limited and there are cases in which individuals with titres as high as 0.16 IU/ml developed tetanus. Although an absolute protective level has not yet been established for humans, there is a clear correlation between antibody titres and severity of tetanus (*1, 2*). For diphtheria toxoid the situation is similar: it has been shown that titres <0.01 IU/ml are clearly non-protective, while individuals with titres $\geqslant 0.16$ IU/ml are protected. There is some variability, since in different individuals the same antitoxin levels can confer different degrees of protection (*3*).

In the case of whole-cell pertussis vaccine, an animal potency test is available, the results of which correlate with protection in humans. Thus, vaccine lots having potency $\geqslant 4$ IU per human immunizing dose confer protection in children (*4*). These vaccines, if they are produced and tested according to the above-mentioned criteria, have been used safely in humans. However, the immunological correlates of protection by whole-cell pertussis vaccine in humans are not well defined.

For vaccines produced in animal or human-cell substrates, great emphasis has been placed on a testing programme to ensure the absence of contaminating viruses that could cause disease in humans. In the case of oral poliovirus vaccine produced in primary monkey kidney cells, for example, there are a number of tests that are undertaken to ensure the absence of contaminants, including known potential contaminants such as simian virus 40 (SV40). Similarly, for measles vaccine produced in chicken cells, considerable testing is carried out to ensure the absence of adventitious

agents. In addition, the production process is based on eggs from chickens shown to be free from specific pathogens, such as avian leukosis virus. Although this retrovirus has never been shown to be pathogenic for humans, it is considered prudent to ensure its absence, as well as that of other retroviruses. The testing for retroviruses includes an assay for reverse transcriptase (5).

New developments in testing

Recently there has been a rapid development of techniques for the physicochemical analysis and characterization and purification of protein and polysaccharide antigens. Acellular pertussis vaccines, for example, consist of highly purified and highly characterized antigens. Tests are in place to ensure that each lot of vaccine antigen has properties consistent with lots shown to be protective in clinical trials. Toxicity is determined, where applicable, using highly sensitive and specific tests. This is in contrast to whole-cell vaccines, for which the fairly unspecific mouse weight-gain test is used — a test that is considered to be insufficiently sensitive to demonstrate residual pertussis toxin activity in acellular pertussis vaccines (6).

Procedures for testing for viral contaminants in vaccines produced in animal cell cultures have also evolved considerably in recent years. Use of polymerase chain reaction (PCR) amplification has revolutionized our ability to test for traces of particular virus contaminants. However, because the technique detects not only whole virions but also parts of viral genomes, great care must be exercised in drawing conclusions about the results and their implications for product safety. There is a need to ensure competence in molecular-based techniques, such as PCR, and their standardization as they become part of the universal armamentarium of routine testing laboratories.

Another recently developed highly sensitive technique is the product-enhanced reverse transcriptase (PERT) assay used to detect the presence of minimal amounts of reverse transcriptase in final vaccines or intermediates. This assay has increased the ability to detect reverse transcriptase by a factor of about 10^6 compared with traditional methods (7). However, this dramatic increase in sensitivity again raises the question of the biological significance of the findings. Use of PERT has resulted in the detection of very low levels of reverse transcriptase in attenuated vaccines of chicken-cell origin (8). This stimulated a lively debate about whether these vaccines were contaminated with a previously unknown retrovirus, and led to a number of studies to assess the risk of infection and disease in the vaccinated population.

Further investigation showed the reverse transcriptase detected was associated with particles identified as incomplete endogenous retroviruses of avian origin (EAV-0 and avian leukosis virus) (7–9).

These particles lack the envelope glycoprotein required for viral infectivity and are therefore non-infectious (9). Research is under way to determine whether the presence of vaccine virus itself, e.g. measles, rubella or yellow fever virus, in the chick cells could facilitate restoration of retroviral infectivity. The likelihood of this happening seems to be extremely low, but further studies are needed to resolve these theoretical concerns (9, 10).

Limitations of vaccine testing

Increased knowledge about certain diseases allows an understanding of the limitations of testing vaccines in the context of risk assessment. Currently, some potential hazards cannot easily be detected by laboratory tests. The agents of transmissible spongiform encephalopathies (TSEs), including that of bovine origin (BSE), which is involved in new variant Creutzfeldt–Jakob disease, provide a good example of the limitations of current testing procedures. Production of some vaccines requires the use of raw materials of bovine origin, for example, fetal bovine serum, which is added to cell culture media. The lack of practical laboratory tests to detect BSE-like agents necessitates use of a different approach to ensure the safety of the final vaccine, based on the following conditions: the avoidance whenever possible of starting materials of bovine origin; if use of such materials is unavoidable, use of low-risk tissues is to be preferred; and the sourcing of materials from countries that have not reported indigenous cases of BSE and have a compulsory BSE notification system, compulsory clinical and laboratory verification of suspected cases, and a BSE surveillance programme (11). Reliance on these procedures is not entirely satisfactory but there is nothing better available at present. However, much effort is being put into developing standardized assays and, once in place, these will no doubt be used (12).

In-process and final lot testing, although vital and necessary to ensure vaccine quality, are therefore not sufficient to ensure vaccine safety and efficacy in all cases.

Additional procedures to ensure safety and quality of vaccines

It has been recognized for some time that the quality of vaccines can be assured only through implementation of the following principles:
– the use of adequately characterized homogeneous starting materials of defined origin and acceptable quality (including cells and production seeds of virus or bacteria);
– adequate validation of the production process to demonstrate that the conditions are reproducible for different production lots;
– demonstration of consistency of production to the satisfaction of the national regulatory authority;

– independent lot release by a national regulatory authority as a check on the manufacturer's performance;
– pre-and post-marketing surveillance of the behaviour of the product in the target population to demonstrate safety and efficacy.

The first three of these conditions can be met only by strict adherence to the principles of good manufacturing practices (13–16).

Characterization of starting materials

The characterization of starting materials relies heavily on testing, but also on supplier audits to ensure that the relevant characteristics remain unaltered (or differences are minimal) between lots. For the characterization of certain intermediate products (e.g. purified antigens), testing is also critical. However, validation of the process and demonstration that a product of consistent quality is obtained are also essential components of the quality assurance function.

The use of production systems based on cell banks of diploid cell lines or continuous cell lines allows adequate characterization of these starting materials. Furthermore, the adherence to a cell bank system (with master and working cell banks) ensures that the cost and effort invested in characterization is valid throughout the existence of the bank. When primary cell cultures from different species or embryonated eggs are used, the characterization of the cell substrate has to be repeated for every new production run. The trend in quality assurance of vaccines increasingly emphasizes production systems that are based, where possible, on well-characterized master and working cell bank systems (Table 1).

Characterization of a cell bank starts with an adequate description of the genealogy of the cell line. In addition, the cell line must be identified using, for example, genetic markers such as the histocompatibility leukocyte antigen (HLA) and DNA fingerprinting. If the cell line to be used is known to be tumorigenic, tumorigenicity assays are not required. However, if the cell line is to be licensed as non-tumorigenic, this characteristic has to be demonstrated and tumorigenicity tests become mandatory. These tests should include a comparison between the cell line under evaluation and a positive (tumorigenic) reference preparation. Several animal models are adequate for this purpose, such as athymic mice (genotype Nu/Nu), suckling mice, rats, or hamsters treated with antithymocyte serum, and/or irradiated and thymectomized mice reconstituted (T–B+) with bone marrow of healthy mice (17, 18).

The characterization of the cell bank includes evaluation of the potential decrease in cell viability during the storage period as well as the growth characteristics at different stages of its lifespan. For diploid cell lines, the maintenance of diploidy over time must be verified; however, it is not necessary to verify this diploid state for each production run (5, 17, 18).

Table 1. Characterization of cell substrates

- Genealogy
- Genetic markers (histocompatibility leukocyte antigen, DNA fingerprinting)
- Tumorigenicity
- Viability during storage
- Growth characteristics at passage levels
- Absence of contamination with other cell lines
- For diploid cells—demonstration of diploidy
- Absence of detectable contaminants

The potential presence of bacterial or fungal contaminants is investigated using conventional sterility tests (19). However, testing for mycoplasmas requires access to an independent laboratory where mycoplasmas used as positive controls can be safely handled without risk of contaminating cells to be used in production. Mycoplasmas are usually detected by using a combination of traditional culture and in-vitro methods (DNA fluorescent techniques) (19, 20).

The demonstration of freedom from viral contaminants is undoubtedly the most challenging of all tasks. There are basically four potential sources of viral contamination:
– infected animal tissues as a cell source;
– viruses used to establish the cell line (e.g. hybridomas);
– contaminated biological reagents;
– contamination during manipulation.

The amount and nature of the testing necessary to demonstrate freedom from viral contamination will vary to some extent, depending upon the source and nature of the cells to be used. In general, cell lines have to be tested for the presence of retroviruses, other endogenous viruses and adventitious viruses. A combination of assays is essential. These include electron microscopy, detection of reverse transcriptase, in-vivo and in-vitro infectivity tests, tests to induce the production of an antibody response in laboratory animals of different species, and other tests specific to the search for human, primate (SV40) or rodent viruses, depending on the origin of the cell line. Recent studies using very sensitive assays have shown that the screening process is satisfactory to ensure the absence of infectious SV40 (21).

Table 2 and Table 3 show the stages of the culture lifespan recommended for each of these tests by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (22). Screening for viruses must also be performed on any other relevant starting materials and if viral contamination is detected its nature must be established and the viral infectivity and potential human tropism determined. Adequate tests must then be developed to validate virus elimination or inactivation during the production process. In addition, appropriate tests for adventitious viruses must be performed at different stages of the production process (5, 22).

Table 2. Tests for retroviruses and other endogenous viruses recommended as part of the characterization of cell lines

Test	Master cell bank	Working cell bank	Cells at passage limit
Infectivity	+	−	+
Electron microscopy	+	−	+
Reverse transcriptase	+	−	+
Other virus-specific tests	As appropriate[a]		As appropriate[a]

[a] As appropriate for cell lines known to have been infected by such agents.

Table 3. Tests for adventitious viruses, recommended as part of the characterization of cell lines

Test	Master cell bank	Working cell bank	Cells at passage limit
In-vitro assays	+	−[a]	+
In-vivo assays	+	−[a]	+
Production of antibodies	+	−	−
Other	For human and primate lines	−	−

[a] For the first working cell bank, this test should be performed on cells at the limit of in-vitro cell age, generated from that working cell bank; for working cell banks subsequent to the first, a single in-vitro and in-vivo test can be done either on the working cell bank or on cells at the limit of in-vitro cell age.

Validation of the production process

As defined by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (23), validation is

> "The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes — including equipment, buildings, personnel and materials — are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do...
>
> "... it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved."

Adequate validation is beneficial to the manufacturer in several ways.
- It deepens the understanding of processes, decreasing the risk of processing problems.
- It decreases the risks of defect costs.
- It decreases the risk of regulatory non-compliance.
- It may result in less in-process control and end-product testing.

Validation can be prospective, concurrent or retrospective, depending on when it is performed in relation to production. To be considered validated, a process must consistently meet all specifications at all production steps, at least three times consecutively. Once the process has been validated, it is expected that it will remain under control. If modifications to the process are made, equipment or systems involved in the process are changed, or deviations occur, a re-validation of the process is required (16, 23).

An example of validation is the procedure used to demonstrate inactivation of a potential contaminant. The production process is reproduced in the presence of an added bolus of a known contaminant — this is known as "spiking". Validation then consists of showing that the purification and inactivation procedures in use remove the added contaminant to give a large margin of safety.

Demonstration of consistency of production

An appropriately validated production process, as defined above, will result in a consistent product. This means that the critical characteristics of the vaccine, usually measured by the in-process and final product specifications, are consistently met for different production runs. Product specifications are set to ensure, to the maximum possible extent, that the vaccine concerned will be safe and effective when administered to the target population.

Safety and efficacy of vaccines are evaluated through clinical trials in humans. Once safety and efficacy have been proven in the human population, consecutive production lots must be shown to be consistent with the vaccine lot(s) used to perform the clinical trials. Thus, final product testing becomes a demonstration of consistency of production to ensure that each lot possesses the characteristics of a lot shown to be safe and efficacious in clinical trials (24).

Independent lot release

Lot release by national regulatory authorities is the key to the control of vaccines, and provides a vital check on a manufacturer's performance in controlling a production process which is inherently variable owing to the biological nature of starting materials, the manufacturing process itself and the test methods. As a minimum, lot release should be based on review of the summary lot protocols, which contain details of that particular lot. In addition, some selected laboratory testing can be carried out. Lot release should be included in the regulations that cover biological products. The responsibility for lot release generally rests with the head of the national control laboratory.

Post-marketing surveillance

An additional important tool for monitoring vaccine safety and efficacy is post-marketing surveillance. Adverse events, although rare, occasionally follow immunization with vaccines. Some of these events are due to intrinsic characteristics of the vaccine. Special attention needs to be given to rare adverse events, which are usually not detectable in pre-licensure clinical trials owing to the size of the immunized population. Other events occur coincidentally with immunization but are due to other causes. Some serious events have been reported as a result of programmatic errors, mainly mishandling of vaccines and/or inadequate immunization practices (25).

Post-marketing surveillance may permit monitoring of vaccine efficacy, usually by measuring case reduction. Also, post-marketing surveillance data can provide definite information on the safety and effectiveness profiles of different vaccines. Hence, it is critical to implement strong surveillance systems in all countries. The responsibility for monitoring the safety and efficacy of vaccines already on the market rests with the national regulatory authority, but immunization programmes should also have a monitoring and case investigation system in place. Thus, investigation of reports and appropriate responses should be a collaborative and coordinated effort of the two groups (25).

Although the modern regulatory process includes consideration and evaluation of controlled clinical trials to demonstrate safety and efficacy, post-marketing surveillance can complement this information by providing results in larger populations under field conditions using a controlled surveillance system (phase IV trials). For newer vaccines it is becoming common practice to require manufacturers to perform post-marketing surveillance studies to further assure the safety and effectiveness profile of the vaccine. Spontaneous reporting systems can also signal potential problems that must then be confirmed by controlled studies.

New vaccines: a scenario of increasing complexity

With the development of new production technologies and the concomitant availability of new vaccines, producers and regulatory agencies face new problems that further increase the complexity of assuring consistently the safety and efficacy of vaccine production lots. Some of these problems are indicated below.

- *Unknown mechanisms of protection in humans, e.g. acellular pertussis vaccine* (6, 26). No unequivocal immunological correlates of protection against pertussis have yet been demonstrated nor has a generally accepted animal model to predict clinical efficacy been validated. The approach is therefore to demonstrate, for release purposes, that the lot to be released shares characteristics with lots for which safety and efficacy have been demonstrated (27). The challenge, given a lack of complete understanding, is to select the appropriate characteristics that correlate with safety and efficacy of the product.

- *No tests available to discriminate effective from non-effective lots.* Some years ago, one lot of *Haemophilus influenzae* type b (Hib) vaccine with capsular polysaccharide conjugated to the meningococcal outer membrane complex, which met all release criteria, was found to produce lower than expected immune responses in infants (28). This finding led to a thorough investigation of the problem and ultimately to the establishment of a new testing programme, which better controls the characteristics of the product. For Hib, the most relevant tests for this purpose are physicochemical tests.

- *Vaccines against the same disease often differ and thus may need specific quality control approaches.* In many cases new vaccines directed against the same disease produced by different manufacturers must be considered as different and unique products, owing to differences in antigenic structures, composition and concentration, differences in production methods, and, in particular, their formulation in different combinations with other antigens (Hib–Hep B, DTP–Hib, DTP–Hep B, DTP–Hep B–Hib, etc.). These vaccines will require different quality control testing programmes. Table 4 shows the various licensed formulations of Hib vaccine available on the market. There are differences in the size and content of the polysaccharide used, the carrier proteins used, the amounts of carrier proteins and the adjuvants used and their degree of adsorption (29). Table 5 summarizes the different formulations of DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccines) tested in clinical trials in Germany, Italy, Senegal and Sweden (30, 31). These vaccines and others in the pipeline differ from each other and this has necessitated the development of product-specific tests and specifications.

Table 4. **Formulation of *Haemophilus influenzae* type b conjugated vaccines**

Polysaccharide (PS)	PS per single human dose (μg)	Nature of carrier	Protein per single human dose (μg)
PS (size-reduced)	25	Diphtheria toxoid	18
PS (low relative molecular mass)	10	Diphtheria protein CRM 197	25
PS (size-reduced)	15	Outer membrane protein complex of *Neisseria meningitidis* group B	250
PS	10	Tetanus toxoid	20

Table 5. **Formulation of diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP) evaluated in clinical trials**

Composition[a]	Antigenic content per single human dose (μg)	Inactivation method	Type of adjuvant and content per single human dose (mg)
PT	40	Hydrogen peroxide	Aluminium hydroxide, 0.5 mg
PT	25	Formaldehyde/ glutaraldehyde	Aluminium hydroxide, 0.5 mg
FHA	25	Formaldehyde	
PT	10–20	NA[b]	Aluminium phosphate, 1.5 mg
FHA	5–20		
Fimbriae 2–3	5		
Pertactin	3		
PT	25	Formaldehyde	Aluminium hydroxide, 0.5 mg
FHA	25	Formaldehyde	
Pertactin	8		
PT-9K/129 G	5	NA	Aluminium hydroxide, 0.35 mg
FHA	2.5		
Pertactin	2.5		
PT	3.2		Aluminium hydroxide/
FHA	34		Aluminium phosphate, 0.23 mg
Pertactin	1.6		
Fimbriae 2	0.8		
PT	25	Glutaraldehyde	Aluminium hydroxide, less than 0.85 mg
FHA	25	NA	
PT	23.4	Formaldehyde	Aluminium hydroxide/ Aluminium phosphate, 0.17 mg
FHA	23.4	Formaldehyde	

[a] FHA = filamentous haemagglutinin; PT = pertussis toxin.

[b] NA = not available.

Conclusions

As discussed in this article, tests for evaluating vaccines are now available that are highly specific and sensitive. Their use as an integral part of the regulatory process can help ensure that vaccines are safer than ever. Experience in the field has shown this to be true. There is, however, a need to learn how to handle the data produced by some of the more novel and highly sensitive technologies. It must be recognized that data will become available that may be misleading or meaningless in the public health context. Recent scares precipitated by the possibility of obtaining sensitive test results (*7, 10, 21*) have shown that the risk–benefit assessment must consider the known characteristics of a vaccine in use for many years against the unknown threat caused by the detection of a potential contaminant that may or may not have public health relevance.

During the process of vaccine development, it is essential to establish vaccine characteristics, a vaccine safety profile, and key test parameters that correlate with clinical performance. This work is vital in defining criteria for lot release of products. It is important to note that the demonstration that a product consistently possesses the desired characteristics of safety and efficacy will depend on a multifaceted approach on the part of the manufacturer and the regulatory authority, drawing on thorough characterization of starting materials, demonstration of consistency of production, and appropriate selection of lot release tests — all under the strict and documented controls imposed by good manufacturing practices — as well as rigorous post-marketing surveillance activities. ■

Résumé

Nouveaux problèmes posés par l'assurance de la qualité des vaccins

Le contrôle de la qualité des vaccins s'articule depuis toujours en trois volets : contrôle des matières premières ; contrôle du procédé de production ; et contrôle du produit final. Cette approche a toujours été couronnée de succès, comme l'atteste la grande expérience que l'on a des vaccins traditionnels. Les efforts pour assurer l'innocuité des substrats cellulaires, animaux et humains, en sont un bon exemple. Avec les années, les méthodes servant à tester les vaccins ont évolué, gagnant en sensibilité et en spécificité. De fait, les nouveaux tests ont confirmé l'innocuité des vaccins qui avaient été administrés pendant de nombreuses années. Avec les nouvelles techniques dont on dispose aujourd'hui grâce à la biologie moléculaire, il est possible de pratiquer encore plus de tests sur les substrats cellulaires. L'amplification enzymatique a révolutionné les méthodes de recherche et nous permet aujourd'hui de retrouver des traces de contaminants viraux particuliers. Cependant, certains contaminants (comme les agents des encéphalopathies spongiformes transmissibles) restent encore difficiles à dépister avec des tests de laboratoire. Par conséquent, il faut faire intervenir d'autres méthodes pour assurer la permanence de la qualité : l'utilisation de matières premières homogènes, suffisamment bien caractérisées, ayant une origine précise et une qualité acceptable (y compris les cellules et virus ou bactéries des semences servant à la production) ; une validation suffisante des procédés de fabrication faisant la preuve que les conditions sont reproductibles pour les différents lots de production ; la mise en évidence d'une uniformité de la production conforme à ce qu'exige l'autorité nationale de réglementation ; la mise en circulation des lots opérée de façon indépendante par une autorité nationale de réglementation et servant à vérifier les résultats obtenus par le fabricant ; enfin, la surveillance du comportement du produit dans la population cible avant et après mise sur le marché afin de mettre en évidence son innocuité et son efficacité. Pour les nouveaux vaccins, de nouveaux problèmes viennent accroître la complexité des opéra-

tions permettant d'assurer une innocuité et une efficacité constantes du produit. Il s'agit de ceux posés par les vaccins dont on ignore quel est le mécanisme d'induction de la protection chez l'homme ; par l'absence de tests permettant de distinguer les lots efficaces des autres ; et par le fait que les vaccins fabriqués contre une même maladie diffèrent souvent et nécessitent peut-être des approches réglementaires spécifiques. Si l'utilisation des nouveaux tests applicables aux vaccins fait partie intégrante du processus de réglementation et peut aider à les rendre plus sûrs que jamais, il faut apprendre à utiliser les données issues de certaines des technologies les plus récentes et les plus sensibles. Les craintes suscitées récemment et aggravées par la détection de faibles concentrations de contaminants grâce aux tests extrêmement sensibles dont on dispose aujourd'hui, ont montré que l'évaluation du rapport avantages/risques dans le cas des vaccins doit tenir compte des caractéristiques connues d'un vaccin utilisé depuis de

nombreuses années et les peser en regard de la menace inconnue que fait planer la détection d'un contaminant potentiel – qui aura ou non une importance en santé publique. Au cours de la mise au point d'un vaccin, il est indispensable de déterminer ses caractéristiques, son profil d'innocuité et les paramètres essentiels corrélés aux données cliniques, indispensables pour définir les critères de mise en circulation des lots de produits. Le fait d'attester qu'un produit possède les caractéristiques d'innocuité et d'efficacité désirées va dépendre de l'approche adoptée par le fabricant et l'autorité de réglementation, approche qui doit comporter de multiples facettes et qui s'appuiera sur la caractérisation complète des matières premières, la mise en évidence de l'uniformité de la production, le choix de tests de mise en circulation des lots appropriés (répondant tous aux exigences strictes et documentées qu'imposent les bonnes pratiques de fabrication), ainsi que sur une pharmacovigilance rigoureuse.

Resumen

Nuevos retos para asegurar la calidad de las vacunas

El control de la calidad de las vacunas siempre se ha basado en tres componentes: el control de las materias primas, el control del proceso de producción, y el control del producto final. Este enfoque ha tenido éxito, según demuestra la vasta experiencia adquirida con las vacunas tradicionales. Los esfuerzos desplegados para garantizar la seguridad de los sustratos celulares, tanto animales como humanos, son un ejemplo de ello. Con el tiempo los procedimientos de análisis de vacunas han ganado en sensibilidad y especificidad. Han aparecido nuevas pruebas que han confirmado de hecho la seguridad de las vacunas administradas durante muchos años. Con las nuevas técnicas hoy disponibles basadas en la biología molecular, es posible realizar aún más pruebas con sustratos celulares. La técnica de amplificación mediante la reacción en cadena de la polimerasa (RCP) ha revolucionado nuestra capacidad para detectar trazas de contaminantes víricos específicos. Sin embargo, algunos contaminantes (como los que median las encefalopatías espongiformes transmisibles) no pueden detectarse hoy fácilmente mediante pruebas de laboratorio. En consecuencia, es necesario implantar procedimientos adicionales para asegurar la calidad: el uso de materias primas homogéneas adecuadamente caracterizadas, de origen definido y calidad aceptable (incluidas células y virus o bacterias simientes para producción); la validación adecuada del proceso de producción para demostrar la reproducibilidad de las condiciones de fabricación de los diferentes lotes; la demostración de la uniformidad de la producción conforme a lo dispuesto por los órganos nacionales de reglamentación; la autorización independiente de los lotes por un organismo nacional de reglamentación como validación del funcionamiento del fabricante, y la vigilancia, antes y después de la comercialización, del comportamiento del producto en la población destinataria a fin de demostrar su seguridad y eficacia. En el caso de las vacunas nuevas, aparecerán

nuevos problemas que aumentarán aún más la complejidad de los mecanismos necesarios para asegurar sistemáticamente la inocuidad y la eficacia de los productos. Entre esas dificultades cabe citar las vacunas para las que se desconoce el mecanismo de inducción de protección en el ser humano; la falta de pruebas disponibles para distinguir los lotes eficaces de los no eficaces; y el hecho de que a menudo para una misma enfermedad se emplean vacunas que presentan diferencias y pueden requerir enfoques normativos específicos. Aunque el uso de nuevas pruebas de análisis de vacunas como parte integrante del proceso reglamentario puede contribuir a garantizar que las vacunas sean más seguras que nunca, es necesario aprender a manejar los datos generados por algunas de la más recientes tecnologías de alta sensibilidad. Algunas alarmas recientes, provocadas por el hecho de que al aplicar las pruebas sumamente sensibles ahora disponibles se han podido detectar pequeñas concentraciones de contaminantes, han demostrado que al evaluar la razón riesgo-beneficio de las vacunas hay que comparar las características ya conocidas de la vacuna usada durante muchos años y la amenaza de riesgos desconocidos asociada a la detección de un contaminante potencial — que puede tener o no trascendencia para la salud pública. Durante el proceso de desarrollo de vacunas, es indispensable establecer las características de la vacuna, un perfil de inocuidad de la misma, y parámetros analíticos clave que estén correlacionados con datos clínicos. Esta información es fundamental para definir los criterios que habrán de regir la autorización de los lotes de los productos. Para demostrar que un producto presenta sistemáticamente las características deseadas de seguridad y eficacia, el fabricante y el órgano de reglamentación deberán actuar en múltiples frentes, apoyándose en una caracterización exhaustiva de las materias primas, en la demostración de la uniformidad

de la producción y en una selección idónea de las pruebas de autorización de lotes (todo ello con arreglo a los controles estrictos y documentados que imponen las

prácticas adecuadas de fabricación), así como en unas actividades rigurosas de vigilancia poscomercialización.

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