

# Biomedicines and Vaccines

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## Biomedicines: meeting the challenges

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Over the past two decades, the pace of development of biomedicines has accelerated. With concurrent political and socioeconomic changes, this has put a great strain on international systems of standardization and on the underpinning institutions. However, the public health importance of biomedicines and vaccines makes the continued operational viability and wellbeing of these systems a major international challenge. The commitment of governments, the public, industry and international institutions is pivotal to the successful resolution of the public policy issues concerning the production of biomedicines.

Because of current changes in the social and scientific framework, systems of standardization and control are subject to a powerful combination of forces. Privatization and reduced public spending have resulted in a squeeze on resources, targeting those laboratories on which the international system relies for the sustained operation of standard-setting, reference materials and expertise. This restructuring and streamlining requires that national institutions focus on immediate operational priorities rather than longer term scientific issues.

Conversely, it is evident that national authorities and the international systems they support are unable to keep up with the present upsurge in the number and complexity of biomedicines. Decisive action on priority setting and delegation of responsibilities within the stakeholder group will need to be taken. In order to resolve the disparity, industry may need to assume a greater share of responsibility through self regulation, and worksharing and harmonization will be a primary consideration. In addition, growing public scepticism over new scientific interventions and the social and ethical issues attached to use of diagnostics and treatments based on genetics and xenotransplants will require a broadening of the decision-making process to

involve more key players. As the developing world opens up to manufacture and marketing of biomedicines, the demand for international standards and quality control measures will increase even further.

## New partnerships

In reviewing the options, it is clear that new partnerships will play key roles. The advances in process control through the use of biotechnological methods provide sound justification for greater responsibility testing by the manufacturer. This, together with the availability of physicochemical methods of analysis, make more precise in-house monitoring feasible. This situation has already been endorsed through amendments to the regulatory mechanisms in the European Union and the United States. In addition, risk-assessment techniques can be used to relate regulatory requirements to potential hazards.

By adopting these mechanisms, the resources of national control authorities will be more effectively utilized. A survey conducted in 1996 by the National Biological Standards Board in the United Kingdom indicated that this change would be supported by industry and major control authorities. Making this happen in an orderly fashion will be a challenge for policy-makers within and outside the biomedicines community since it will be their responsibility to demonstrate that such changes are in the public interest. For the same reason, regulatory and advisory bodies must be careful in structuring a closer partnership with industry and issues such as conflict of interest will need to be addressed.

Another increasingly important partnership is with the public. Today's better-informed and more articulate public wants its views to be heard. New demands from society make biological products more accessible as witnessed by the availability of home tests kits for diagnosis and screening. One challenge here is to develop the right machinery for public input, and some national authorities have already set into motion impressive consultative systems. Evidence is now needed to evaluate how well these work and whether they are appropriate for other countries and regions. Finding the answers will be important for public confidence worldwide.

### Rethinking the process

A very relevant comment raised during the National Biologicals Standards Board (NBSB) survey was that governments and people in developing countries would not be able to afford some of the dramatic new advances that are likely to appear in the biologicals sector. It is therefore important to arrange for a more representative input to priority setting at international level before agreeing which products should take precedence for international standard-setting and guidelines. Debate may need to take place at national level on whether compromise or reconsideration of national priorities is called for to achieve equitable global policies.

Other aspects of process also demand attention. Spurred by growth in volume and the complexity of biomedicines, initiatives are already in progress for harmonization of regulation. The present national-based systems of biological standardization, coordinated centrally by WHO, mean that countries may enforce different requirements and that different bodies are duplicating each others' work. Neither is it a question of harmonization being advantageous only to industry, which bears the brunt of varying requirements. National control authorities have equally serious problems of workload. This increasing volume of work highlights the desperate need of both developed and developing countries to develop a system of mutual recognition and acceptance of marketing approvals worldwide.

There is, moreover, a public health interest in avoiding unnecessary delays in bringing safe and effective new drugs onto the market. We should not forget the success of AIDS activists in bringing about accelerated approval of HIV therapy.

However, as the European Union experience demonstrates, the difficulties of mutual recognition should not be underestimated. Although WHO is important as a coordinating agency, its guidance does not yet have comprehensive coverage nor global acceptance. Ideally, it could do more in bringing together national and international organizations for serious discussions — but does it have the resources? There is thus a need for government commitment which may need the same kind of approach as the problem of biodiversity.

### A sustainable future

Although it is acknowledged that a strong scientific basis is needed to deal with unpredictable safety concerns such as that experienced in the United

Kingdom with bovine spongiform encephalitis, a current climate of financial stringency, public participation and a more consultative process could dilute the science of the biologicals world. Will this affect the long-term sustainability of scientific input to regulation? The national institutions which have nurtured this specialization and maintained research programmes may no longer be able to carry out this work. Some institutions have already reduced or abandoned their long-term research, such as the Statens Serum Institute in Denmark which has pulled out of reference standards manufacture. New institutions have been suggested as the solution. Given the daunting array of new scientific and technical products, the challenge of designing sustainable cross-sectoral and international research institutions may be one that policy makers cannot ignore.

Although WHO has the status to lead such an international programme, it does not control the required resources. This is not necessarily a bad arrangement since cooperative agreements based on local control of finances can be less bureaucratic and more effective. But the evolution of the present international system has led to imbalance. For example, almost 95% of new and the vast majority of existing international standards emanate from a single national establishment. This could lead to problems concerning continuity of supply. It would seem wise to bring in more partners and to agree on funding of an international system.

An essential part of the international programme for standardization and quality control of biologicals is the establishment and strengthening of national or regional authorities in developing countries. However, policy needs to be clear on how to provide funding and training. Can developed countries be persuaded to contribute and can they provide sufficient capacity in their agencies to provide training facilities.

### Facing the social issues

There are some areas where a separate advisory mechanism may be needed to explore ethical and social issues linked, for example, to gene therapy. Questions are thus raised concerning the legal status of research, and medical and public health issues including health insurance coverage and accessibility. In the future, the pace of progress of bringing some new biomedicines to market will almost certainly depend on these rather than scientific issues.

Another issue centres around the concept of "one worldwide standard". It is clear that reference standards must be developed for global application. However, where quality control is concerned a host of silent reservations are present. The notion that poorer countries should have lower standards of quality for biomedicines is offensive and tends to suppress discussion of whether the current developed country standards are appropriately pitched. These issues need to be addressed and now is the time to clarify the scope for flexibility within the system.

Already, national control authorities can gain acceptance for their own requirements as equivalent to those of WHO. A growing number of national control authorities rely on risk assessment to determine the stringency of quality control required for their particular circumstances. Thus, the single-standard principle is good, but still needs to be evaluated from time to time with regard to current practices and the appropriateness of quality control measures to specific environments.

A further issue is that the area of biomedicines, biologicals, vaccines and diagnostics is still ill-defined. Boundaries may need to be enlarged to include new kinds of product such as organs for transplant or cloning or even whole transgenic donor animals. Biotechnology enables modification of food and cosmetics to perform quasi-medical functions so these too could be candidates for regulation as biologicals. Thus, matters of what to regulate are likely to constitute some of the more difficult policy issues to be addressed.

The future public policy agenda thus includes many international challenges of this kind.

- Collaboration to meet new scientific, technical and public health demands.
- Harmonization which repairs the discrepancies or duplications of systems.
- A coordinated approach to redefine partnerships with industry and the public with a view to sharing experience and limit the confusion that results from decisions taken elsewhere.
- To engage and manage social and ethical concerns.
- To establish an international agreement on funding to cover such global concerns as international standards and guidelines.

- To support training for quality control strengthening in developing countries and the long-term maintenance of expertise and programmes for research.

I hope there will be those in the biologicals community who are committed to addressing these challenges and who may have the influence to create the conditions for international discussion.

## Progress in biological standardization

The WHO Expert Committee on Biological Standardization (ECBS)<sup>1</sup> held its 49th meeting in October 1998. The ECBS is responsible for setting global standards for biological substances used in medicine, including vaccines, blood products, biological therapeutics and diagnostic procedures.

Many of the items on the agenda of the meeting reflect the increasing complexity of biotechnology as well as the development of new approaches to in-process testing procedures using, for example, molecular based techniques in place of, or in addition to traditional testing in animals.

### Hib vaccine recommendations

At the meeting, revised recommendations (formerly requirements) for production and control of *Haemophilus influenzae* type b (Hib) conjugate vaccine were agreed. Prior to publication, these will be circulated for further comment to interested parties. *H. influenzae* type b causes several diseases in humans, the most common and serious being meningitis and pneumonia in children under 5 years of age. The capsular polysaccharide of *H. Influenzae* type b plays an important role in virulence, and conjugate vaccines derived from the type b polysaccharide covalently linked to a protein carrier are a safe and effective means of protecting against such infections. Requirements for *H. Influenzae* type b conjugate vaccine were first published in 1991 and, although valuable, needed updating to

<sup>1</sup> The Expert Committee included members from Belgium, Canada, China, Mexico, the Netherlands, Russia, United Kingdom and the USA. Temporary advisers were invited from Japan, the Netherlands, South Africa, Switzerland, the United Kingdom and USA, with representatives of the Council of Europe, European Association of the Plasma Products Industry, Pharmaceutical Manufacturers Associations, the International Society of Blood Transfusion, the International Society on Thrombosis and Haemostasis, and the International Association for Biologicals.

reflect recent vaccine control strategies. In particular, the biological assay of potency recommended in 1991 was shown not to correlate with the efficacy of the vaccine in infants nor to provide a sensitive indicator of vaccine quality. The ECBS therefore agreed that whilst immunogenicity testing in animals is necessary during vaccine development, an animal immunogenicity test need not be used for routine batch (lot) release. Instead, batch release testing should focus on physicochemical tests to monitor consistency of production of the polysaccharide, the protein carrier, and the bulk conjugate.

### **Acellular pertussis vaccine**

WHO Guidelines for the Production and Control of the Acellular Pertussis Component of Monovalent or Combined Vaccines are concerned with vaccines shown to be safe and effective in well-controlled clinical studies (1). However, the language of the Guidelines appears to exclude from the international market some vaccines in routine use in Japan. Acellular pertussis vaccines were introduced rapidly into the Japanese national vaccination programme as a result of concerns about the whole-cell pertussis vaccines, and without the benefit of a classical double-blind clinical efficacy study.

The ECBS emphasized that it was not its intention to exclude effective vaccines of this kind from use and agreed that in such cases the results of product-specific postmarketing surveillance and epidemiological data could be used to demonstrate efficacy. The Committee also confirmed the acceptance of the modified intracerebral assay as an alternative to an immunogenicity test for vaccine potency estimation to demonstrate immunogenic potential but not to reflect clinical efficacy.

However, the ECBS expressed concern that considerable confusion could occur if the potency of acellular pertussis vaccines estimated in the modified intracerebral challenge test is expressed in the International Units assigned to the International Standard for whole-cell pertussis vaccine. These International Units are accepted as indicative of protection by whole-cell pertussis vaccine but the ECBS recommended that they should not be used to reflect the protective immunity induced by acellular pertussis vaccines.

### **Oral poliovirus vaccine (OPV)**

An addendum containing several additions to the requirements for oral polio vaccine (OPV) was also adopted by the ECBS. Important progress has been

made towards the global eradication of poliomyelitis (2) and laboratory stocks may soon be the only source of wild poliovirus. The ECBS made additions to the existing requirements to ensure increased laboratory containment levels for wild polioviruses (3), which are used as controls in one test (the rct40 assay) of OPV.

Progress has also been made in understanding the molecular mechanisms and genetic determinants of virulence attenuation and reversion of the Sabin poliovirus strains used for manufacture of OPV (4). An addition to the requirements was made introducing the MAPREC (mutant analysis by polymerase chain reaction and restriction enzyme cleavage) assay (5) for quality control of OPV. This is the first of a new generation of tests of the molecular consistency of production of virus vaccines.

Additions to the requirements adopted by the ECBS concerned extra tests for adventitious agents. Tests on cell cultures have effectively excluded live simian virus 40 (SV40) from OPV for over 30 years (6). Newly developed gene amplification tests can additionally detect noninfectious SV40 sequences and although there is no evidence for SV40 sequences in OPV (6), the ECBS agreed to introduce a gene amplification test for SV40 in seed viruses to provide an additional level of security. The final addition to the requirements introduced antibody screening tests for foamy viruses in animals used for sourcing primary monkey kidney cells. This reflects modern quality control practices to thoroughly characterize starting materials to minimize any challenges to the manufacturing process.

### **Other matters**

The ECBS established eleven new or replacement International Standards and Reference Materials covering a wide range of products (Table I). Additionally, several International Standards and Reference Materials that are no longer required were discontinued following a recently introduced consultative process (Table I). The Committee also proposed to discontinue certain Requirements and International Reference Materials at its next meeting. These are listed in Table 2, on page 89 and are proposed for comment.

A fully revised and complete list of WHO International Standards and Reference Reagents will be published as an Annex to the report of the 49th ECBS and will soon be available on the internet. The Committee noted that transfer of International Reference Materials from the Statens Serum Institute in Copenhagen and the Central Veterinary

**Table 1**  
**International biological standards and reference reagents established**  
**by the 49th WHO Expert Committee on Biological Standardization**

<p><b>Antibodies</b>  anti-hepatitis A immunoglobulin, human  <i>Clostridium perfringens</i> beta antitoxin, equine</p> <p><b>Antigens</b>  pertussis vaccine</p> <p><b>Blood products</b>  factor VII, concentrate  factor VIII, concentrate  factor VIII and von Willebrand factor, plasma  haemoglobincyanide  heparin, unfractionated  plasmin</p> <p><b>Cytokines/endocrinological substance</b>  activin A, human, recombinant  sex-hormone binding globulin</p>	<p>Second International Standard  Second International Reference Preparation</p> <p>Third International Standard</p> <p>First International Standard  Sixth International Standard  Fourth International Standard  Sixth International Standard  Fifth International Standard  Third International Standard</p> <p>First Reference Reagent  First International Standard</p>
<p><b>DISCONTINUATIONS</b></p> <p><b>Antibiotics</b>  demeclocycline  doxycycline  hygromycin B  minocycline  oxytetracycline  tetracycline</p> <p><b>Antibodies</b>  histoplasmin antiserum, rabbit, for H  and M immunodiffusion test  <i>Mycoplasma pneumoniae</i> antiserum, equine  parainfluenza virus antiserum, equine</p> <p><b>Miscellaneous</b>  histoplasmin for H and M immuno-  diffusion test  hyaluronidase</p>	<p>First International Standard  First International Reference Preparation  First International Reference Preparation  First International Reference Preparation  First International Reference Preparation  First International Reference Preparation</p> <p>First Reference Reagent</p> <p>First Reference Reagent  First Reference Reagent</p> <p>First Reference Reagent  First International Standard</p>

Laboratory in Weybridge to the National Institute for Biological Standards and Control (NIBSC) had been accomplished in a safe and timely manner. This had been made necessary by changes in the function of the two former custodian laboratories. Neither the Statens Serum Institute nor the Central Veterinary Laboratory will any longer hold and distribute WHO International Reference Materials. The NIBSC and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam are WHO International Laboratories for Biological Standards.

It was noted that the Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, USA, has been established as a new WHO Collaborating Centre for Biological Standardization. The ECBS also endorsed several new projects including new international reference materials for blood group reagents, quality control of virus markers (HBsAg, anti-HCV and anti-HIV) in blood screening, and prion diagnostic tests.

The Committee also considered scientific issues that potentially affect the use of biological medi-

TABLE 2

**WHO Requirements and International Reference Materials  
proposed for discontinuation at the next meeting of the  
WHO Expert Committee on Biological Standardization**

**Requirements for Cholera Vaccine**

Revised 1968, WHO Technical Report Series, No. 413, (1969)  
Addendum 1973, WHO Technical Report Series, No. 530, (1973)

**Requirements for Smallpox Vaccine**

Adopted 1966, WHO Technical Report Series, No. 323, (1966)

**Antibiotics**

The First International Reference Preparation for candicidin (1978)  
The First International Reference Preparation for nisin (1969)  
The First International Reference Preparation for rolitetracycline (1968)

**Antibodies**

The First International Reference Reagent for subtype specific antisera to hepatitis B surface antigens (1980); anti-HBs/ay(goat), anti-HBs/ad(goat), anti-HBs/ay(guinea pig), anti-HBs/ad(guinea pig), anti-HBs/ar(rabbit)  
The First International Standard fluorescein isothiocyanate (FITC)-conjugated sheep anti-human IgG (1976)  
The First International Standard FITC-conjugated sheep anti-human IgG (anti- $\gamma$  chain) (1981)  
The First International Standard FITC-conjugated sheep anti-human IgM (1977)

**Blood Products**

The First International Standard for anti-A, B blood typing serum, human (1981)

**Endocrinological Substances**

The First International Reference Preparation for desmopressin (1980)  
The First International Reference Preparation for gonadorelin (1980)  
The First International Reference Preparation for parathyroid hormone, bovine, for bioassay (1974)

Comments on proposals should be received before 30 September 1999.  
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cines including an update on the presence of low levels of reverse transcriptase in vaccines derived from chicken cells (7,8). The ECBS endorsed the proposed establishment of a Task Force to coordinate collaborative research on characterization, quality control and safety assessment of all cell substrates intended for vaccine production. The Committee emphasized that a valuable activity of WHO was to provide an international forum for discussion of important scientific issues that had potential to affect the use of biological medicines.

**References**

1. Guidelines for the production and control of the acellular pertussis component of monovalent or combined vaccines, *WHO Technical Report Series*, No. 878, 57-76 (1998).
2. *Polio: the beginning of the end*. World Health Organization, Geneva, 1997.
3. Global action plan for laboratory containment of wild polioviruses. World Health Organization, Geneva, (in press).

4. Wood, D.J. Important breakthrough for neurovirulence testing of oral poliovirus vaccine. *WHO Drug Information*, **12**(2): 78–79 (1998).

5. Chumakov, K.M., Powers, L.B., Noonan, L.P. et al. Correlation between amount of virus with altered nucleotide sequence and the monkey test for acceptability of oral poliovirus vaccine. *Proceedings of the National Academy of Sciences (USA)*, **88**: 199–293 (1991).

6. Sangar, D.V. et al. Examination of poliovirus vaccines for the presence of SV40 sequences. *Developments in Biological Standardization*, (in press).

7. Reverse transcriptase activity in chicken-cell derived vaccines. *Weekly Epidemiological Record*, **73**: 209–216 (1998).

8. Reverse transcriptase activity in vaccines. *WHO Drug Information*, **12**(3): 140–141 (1998).

## **Pertussis vaccines:**

### **WHO position**

Pertussis (whooping cough) is a bacterial disease of the respiratory tract caused by *Bordetella pertussis*. Worldwide, 90% of the 20–40 million annual cases occur in developing countries, with 200 000 fatalities. Before the worldwide introduction of pertussis vaccine into routine childhood vaccination programmes, pertussis was of considerable public health concern due to its highly contagious nature.

Concern about safety of the whole-cell pertussis (wP) vaccine has made routine pertussis vaccination of infants quite controversial in some countries and has led to the development of a new generation of pertussis vaccines based on selected bacterial components rather than on inactivated whole

cells. There are major differences in the content, mode of preparation and efficacy of whole-cell pertussis (wP) and acellular pertussis (aP) vaccines.

However, comprehensive clinical trials have demonstrated that the most efficacious vaccines of either category will protect more than 80% of the recipients from clinical disease. Provided that high and sustained vaccination coverage is achieved, such vaccines will eliminate pertussis as a public health problem. At the same time, recent experience illustrates the importance of ensuring documented high quality of wP vaccines used in national immunization programmes.

No causal link has been identified between wP and aP vaccination and permanent brain damage or death. In terms of redness and swelling at the site of injection, fever, agitation, prolonged crying, febrile seizures and hypotonic-hyporesponsive episodes, aP vaccines show some improvement compared with wP vaccines. Better information on the frequency (if any) of rare, serious reactions will be obtained with widespread aP use and postmarketing surveillance studies.

There is no indication of clinically significant immunological interference between aP and other vaccines simultaneously administered at different sites. However, the reduced immunogenicity of *Haemophilus influenzae* type b vaccine when combined with some aP vaccines is of concern and needs further elucidation. It is recommended that HIV-infected infants should receive the vaccine.

**Reference:** Pertussis vaccines. *Weekly Epidemiological Record*, **74**: 137–142 (1999).