

CONVENTION ON INTERNATIONAL TRADE IN ENDANGERED SPECIES
OF WILD FAUNA AND FLORA

Thirteenth meeting of the Conference of the Parties
Bangkok (Thailand), 2-14 October 2004

Interpretation and implementation of the Convention

Information paper on specimens to be exempted from the provisions of the Convention

This document has been prepared by the EU Presidency on behalf of the member states of the European Union.

Introduction

1. In its provisional assessment of the proposals to amend Appendices I and II at the 13th meeting of the Conference of Parties, the Secretariat raised a number of concerns regarding the EU's proposed amendment to the Interpretation section of the Appendices. These related mainly to a lack of clarity in certain parts of the draft text and concerns that the wording might inadvertently exempt certain parts or derivatives that should remain under control. It is recognised that there is some substance to these concerns and a detailed response has therefore been provided at Annex A below.

2. In addition some Parties have questioned whether such an exemption is necessary, while others have expressed concern that the proposed exemption for cell lines and vaccines will remove their powers to prevent the appropriation of their intellectual property rights in certain genetic materials and undermine the progress made towards securing agreement on access and benefit sharing arrangements under the Convention on Biological Diversity.

3. This paper therefore seeks to address these concerns and explain in more detail why this proposed amendment is necessary.

The Proposal

4. The proposal is based on the one submitted by Switzerland as Depositary Government's but seeks to use language that more accurately defines the type of specimens covered by the annotation. It also extends the annotation to cover synthetically produced cell lines, which are widely used by the pharmaceutical industry in the production of vaccines and other medicines.

5. The EU's proposal was designed to take account of the concerns raised by the World Health Organisation at the last Conference (COP12, Inf 19), regarding the need to ensure timely access by individuals and communities to life saving vaccines and other biological products. Also, having consulted with representatives from the pharmaceutical industry, the EU remains concerned that the text proposed by the Depositary Government does not adequately reflect the terminology currently in use within the industry. It fears that there may be scope for misinterpretation or misunderstanding as to the nature and extent of the derogation. It is also concerned that immunisation programmes worldwide may be put at risk if vaccines have to be made subject to the CITES permitting process. We therefore believe that the annotation should be amended to define terms such as in vitro DNA and clarify what the term pharmaceutical products means.

6. Although no one has actually managed to detect the presence of original genetic material in vaccines or other pharmaceutical products it is possible that trace elements of such material may be present – see Annex B for further details. It is for this reason that we would prefer to refer to specimens that theoretically at the molecular level do not contain any part of the original animal or plant genetic material from which they are derived. These proposed changes also make it clear that

the annotation only applies to specimens derived from a manufacturing process and will not utilise original genetic material.

Cell Lines and Vaccines

7. Cell lines are cells of uniform morphology that are capable of indefinite propagation in vitro - see Annex C for further details. These are widely used in medical research and the development of viral vaccines for use in health protection programmes against diseases such as poliomyelitis, rabies, influenza, yellow fever, Japanese encephalitis (and other encephalitic viral diseases) and smallpox. They are also increasingly being used as an alternative to using live animals in medical experiments – see Annex D for further details.

8. Millions of vaccines and tens of thousands of cultivated cell lines are traded worldwide every year see Annex E for further details. Issuing permits for these specimens would not only add greatly to existing workloads, it would also place an unnecessary financial burden on the pharmaceutical industry thereby putting vital medical research at risk. There is no conservation benefit to be gained from controlling these specimens and these products should therefore be exempt from the CITES controls.

Protection of Intellectual Property Rights

9. The draft annotation has been carefully worded to ensure that products mainly containing original genetic material are not included in the derogation. Parties therefore need not fear that this proposal would undermine their efforts to protect their intellectual property rights in genetic material derived from native species. In any case, there are mechanisms in place to safeguard such rights through the World Trade Organization (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPs) Agreement. These issues are also currently being discussed by the World Intellectual Property Organization (WIPO) at the Inter Governmental Committee (IGC) on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore. The relationship between the WTO TRIPs Agreement and the CBD is also currently under discussion at the TRIPs Council.

Access and Benefit Sharing (ABS)

10. Some Parties also fear that this proposal might undermine the progress made towards securing agreement on access and benefit sharing arrangements under the Convention on Biological Diversity (CBD). We agree that CITES should not be used to circumvent such provisions. However, this exemption from CITES has no bearing on the rights of Parties to the CBD under Article 15, and in particular paragraph 5 of that Article, which provides that access to genetic resources shall be by prior informed consent unless otherwise determined by the party of origin. Pharmaceutical companies will still be subject to the provisions of the CBD and national implementing measures, in order to comply with any relevant ABS laws. In any case much of the original material used to produce cell lines and other pharmaceutical products were acquired long before either CITES or CBD came into force.

Recommendation

11. The Netherlands, on behalf of the EU member states, therefore recommends that the Parties adopt the amended proposal set out in the Appendix to Annex A.

Annex A

PROVISIONAL ASSESSMENT BY THE SECRETARIAT OF THE PROPOSALS TO AMEND APPENDICES I AND II AT THE 13TH MEETING OF CITES PARTIES –

PROPOSAL 1 – AMENDMENT TO THE ANNOTATION TO THE APPENDICES

In its provisional assessment, the CITES Secretariat raised a number of concerns regarding the proposed amendment to the annotation to the Appendices to the Convention put forward by Ireland on behalf of the member states of the European Union. This paper seeks to respond to the criticisms made.

Existence of Original Genetic Material

The Secretariat's principle concern is that the exemption cannot guarantee that small amounts of original genetic material may not be present in the samples concerned and that this could lead to the exemptions of products such as medicines that contain parts and derivatives of CITES listed species.

It is not our intention that any original genetic material should be covered by this proposed exemption. It is, however, theoretically possible that trace elements may be present at the molecular level – see Annexes B & C for further details. If so the quantities involved will infinitesimally small and unlikely to be detectable. These elements should therefore not in themselves be a sufficient justification for interfering in a trade which in all other respects has no impact on the conservation of species whatsoever. We nevertheless accept that the present wording of the proposal may cause some problems of interpretation and therefore propose a number of changes to the text, which will remove any ambiguity in this regard.

These changes have therefore been incorporated in the revised text provided in the attached Appendix, which we would ask the parties to adopt by way of clarification of the original proposal.

In Vitro Cultivated DNA

The Secretariat suggests that the words "in vitro cultivated DNA" be replaced by the term "synthetically derived DNA". However, we would prefer to retain the original wording as this more accurately reflects the process whereby secondary cells are cultivated from the original genetic material. Scientifically speaking, synthetically derived DNA refers to material reconstructed from the chemical elements to reproduce the original genetic code and as such is not subject to CITES control anyway.

However, by way of clarification, we have also amended the revised text in the attached Annex to make it clear that RNA (a product of DNA transcription) is also covered by the derogation.

Simplified Licensing Procedures

Finally the Secretariat refers to the simplified procedure under Conf Res 12.3 which provides a means for expediting trade in specimens of low conservation importance, including vaccines and cell lines. Certainly this expedited procedure does make the licensing process slightly less burdensome that might otherwise be the case but the hard fact is that even this concession is not sufficient to enable Parties to cope with the total volume of trade involved.

Thousands of cell lines and millions of vaccines and other medicines are traded every year. These shipments will require thousands of pre-issued permits to be provided by the management authority, which will also have to go through extensive registration procedures for the pharmaceutical companies concerned. All of this will require both management authorities and the companies themselves to expend a considerable amount in time and resources that they can ill afford and which would be much better spent on real conservation priorities.

For these reasons the Netherlands, on behalf of the EU member states, would therefore urge the CITES Parties to accept this proposed amendment, subject to the amendments as set out in the attached Appendix.

Appendix to Annex A

PROPOSALS FOR AMENDMENT OF APPENDICES I AND II PROPOSAL 1 – AMENDMENT TO THE ANNOTATION TO THE APPENDICES

Inclusion of a new paragraph after paragraph 4 in the Interpretation section of the Appendices, to read as follows (with the following paragraphs being renumbered):

“5. The following are not subject to the provisions of the Convention:

- a) *in vitro* cultivated DNA or RNA * that **theoretically at a molecular level** does not contain any part of the original **plant or animal** from which they are derived;
- b) cells or cell lines ~~** cultivated~~ **adapted to continuous cultivation** *in vitro* that theoretically at a molecular level do not contain any part of the original animal or plant from which they are derived;
- b) urine and faeces;
- c) medicines and other pharmaceutical products such as vaccines, including those in development and in process materials, ** + that theoretically at a molecular level do not contain any part of the original animal or plant from which they are derived; and
- d) fossils.”

* That is DNA or RNA that is ~~assembled from its constituent materials~~, not solely extracted directly from plants and animals.

~~** That is cultures of plant or animal cells that are maintained and/or propagated in artificial conditions and do not contain any significant amount of the original plant or animal from which they are derived.~~

~~+** That is products subject to a research or manufacturing process such as medicines, potential medicines and other pharmaceuticals such as vaccines that are produced under conditions of research, diagnostic laboratory or pharmaceutical production and do not depend for their production in bulk solely on material extracted from plants or animals and do not contain any significant part of the original plant or animal from which they are derived.~~

Annex B

NATURE OF CONTINUOUS PRIMATE CELL LINES USED

It is recognised that the original Vero cells were recovered from the kidney of an African Green Monkey (*Cercopithecus aethiops*) in Japan in the 1960's and the Rhesus Monkey cells were recovered from the foetal kidney of a *Macaca mulatta* during the 1970's. However, they have both been grown in artificial synthetic medium since then. Since that time the cells have been maintained continuously on artificial media and no materials of primate origin are used during the continuous culture of the cells. Therefore, the probability that there is a single molecule of original primate origin in the cells is extremely low.

If it is assumed that 100% of the molecules within the cells are of primate origin at tissue harvest, and at each subculture/passage the amount of original material is reduced by half. Then it is estimated that $2.35 \times 10^{-38}\%$ of the original primate molecules remain after approximately passage 125 or greater (the normal passage number for vaccine and other biopharmaceutical production systems).

As primate cells were the original cell substrates used in the production of these vaccines, all of these vaccines will contain DNA identical in nucleotide sequence to the original primate DNA. The internationally accepted limit is 10ng per human dose for residual DNA from a continuous cell line present in a biopharmaceutical product including live vaccines. However, the DNA molecules in the cells will not be composed of original primate DNA molecules, these will be sourced from the artificial synthetic molecules added to the culture system.

From these calculations we would conclude that theoretically the materials used today in the production of biopharmaceuticals contain very little, if any, amounts of original primate material.

Annex C

DEFINITIONS OF CELL LINES AND ASSOCIATED TERMINOLOGY

Primary Cultures

Primary cultures are derived directly from excised, normal animal tissue and cultured either as an explant culture or following dissociation into a single cell suspension by enzyme digestion. Such cultures are initially heterogeneous but later become dominated by fibroblasts. They can be maintained *in vitro* only for a limited period of time and die after a number of cell divisions, this process is called senescence (Neither invertebrate or plant cells exhibit the property of senescence). During their relatively limited life span primary cells usually retain many of the differentiated characteristics of the cell *in vivo*. A primary culture may be regarded as such until it is successfully subcultured for the first time, when it becomes a cell line.

Cell line

A heterogeneous population of cells arising from a primary cell culture at the time of the first subculture or from subsequent serial passaging of the cells (continuous/established cell line).

Serial Passage

Passage refers to the transfer of an inoculum of cells from an existing cell culture to fresh growth medium in another vessel (i.e. subculture); serial passage refers to repeated subculture.

After a certain number of serial passages, (primary) cells may die out (senescence) or may develop into a continuous cell line.

Continuous Cultures

Continuous cultures are comprised of a single cell type of uniform morphology that can be serially passaged in culture either for a limited number of cell divisions (approximately thirty to fifty) or otherwise indefinitely. Cell lines of a finite life are usually diploid and maintain their karyotype and some degree of differentiation. All normal cells are finite.

Continuous cell lines that can be propagated indefinitely generally have this ability because they have been transformed into tumour cells. Tumour cell lines are often derived from actual clinical tumours, but transformation may also be induced using viral oncogenes or by chemical treatments. Transformed cell lines present the advantage of almost limitless availability, but the disadvantage of having retained very little of the original *in vivo* characteristics. The cells undergo certain alterations such that they exhibit some or all of the properties characteristic of tumour cells; an apparent capacity for unlimited *in vitro* growth and division; the ability to grow in soft agar; the development of new surface antigens; the ability to form tumours when injected into animals; an increase in the rate of nutrient uptake; a loss of contact inhibition (i.e. inhibition of movement and cell division due to contact with neighbouring cells).

Commonly used cell lines of each culture type

Attached Cell Lines		
Name	Species and tissue of origin	Morphology
MRC-5	Human lung	Fibroblast
HELA	Human cervix	Epithelial
VERO	African Green Monkey Kidney	Epithelial
NIH 3T3	Mouse embryo	Fibroblast
L929	Mouse connective tissue	Fibroblast
CHO	Chinese Hamster Ovary	Fibroblast
BHK-21	Syrian Hamster Kidney	Fibroblast
HEK 293	Human Kidney	Epithelial

Attached Cell Lines		
Name	<i>Species and tissue of origin</i>	<i>Morphology</i>
HEPG2	Human Liver	Epithelial
BAE-1	Bovine aorta	Endothelial
Suspension Cell Lines		
<i>Name</i>	<i>Species and tissue of origin</i>	<i>Morphology</i>
NSO	Mouse myeloma	Lymphoblastoid-like
U937	Human Histiocytic Lymphoma	Lymphoblastoid
Namalwa	Human Lymphoma	Lymphoblastoid
HL60	Human Leukaemia	Lymphoblastoid-like
WEHI 231	Mouse B-cell Lymphoma	Lymphoblastoid
YAC 1	Mouse Lymphoma	Lymphoblastoid
U 266B1	Human Myeloma	Lymphoblastoid
SH-SY5Y	Human neuroblastoma	Neuroblast

Definitions from:

- Dictionary of Microbiology and Molecular Biology 2nd edition, Paul Singleton and Diana Sainsbury, John Wiley and Sons, 1987
- A Dictionary of Virology, 3rd Edition, Brain W J Mahy, Academic Press, 2001
- ECACC website
- [Sigma Aldrich website](#)

Annex D

USES OF PRIMATE CELLS IN THE PHARMACEUTICAL INDUSTRIES

1. As substrates for viral vaccines, e.g. Vero cells are used for the production of Polio (Polio vaccine is also a component of many combined vaccines), JEV, Influenza, Smallpox vaccines and rhesus monkey cells for Smallpox, Rabies. A SARS vaccine is also being developed in primate cells. In some cases their use is prescribed by the WHO and European Pharmacopoeia (EP) Monographs and the US Food and Drug Administration (FDA). Traditionally viral vaccines such as these would have been produced in primary monkey cells.
2. Vero cells are used in assay methods for safety of vaccines as a replacement for animal methods e.g. neurovirulence assays in live monkeys.
3. Vero cells are used extensively to screen human and veterinary biological products and processes for viral contamination, as they are susceptible to a variety of viruses. The International Conference for Harmonization (ICH) Guidelines on viral safety (ICH Q5A), the EP and the WHO vaccine requirements specifically request the use of monkey kidney cells to screen for viral contamination in biological products and vaccines. Commonly Vero cells are used for this purpose.
4. Vero cells are part of the EP monograph and US FDA PTC method for the detection of mycoplasmas, which is an assay used to detect many different products for contamination.

Annex E

TRADE IN VACCINES

Summary of World-Wide Scale of Vaccine Production Using Continuous Primate Derived Cell Lines

A number of the WHO recommended vaccines are developed and manufactured using continuous cell lines of primate origin. Some examples are given below:

Polio Virus vaccine (PVV) that contains three poliovirus strains. The vaccine viruses are normally grown on Vero cells (derived originally from African Green Monkey (*Cercopithecus aethiops*) kidney cells) and then concentrated, purified and inactivated with formaldehyde or used as a live virus vaccine preparation. Approximately 18 manufacturers, located around the world, produce PVV using Sabin vaccine seeds provided by the WHO. The Vero cells used as the substrate for PVV production are provided by the WHO and are available through the American Tissue Culture Collection (ATCC) in the United States of America or the European Cell Collection (ECACC). Cells are provided at minimum charge for the production of vaccines.

Routine coverage with three doses of oral PPV worldwide has remained above 80% since 1990. In 1997, more than 450 million children were immunised during NIDs (National Immunisation Days) in 80 countries worldwide (source: CDC, USA). With 130 million children born each year (Source: WHO Immunisation profiles), conservative estimates of annual doses required are over 500 million.

Purified Vero Rabies vaccine (PVRV) is also grown on Vero cells, inactivated by propiolactone and purified by ultracentrifugation; licensed in France in 1984. Rabies vaccine adsorbed vaccine (RVA) uses a Kissling strain of rabies virus adapted to a diploid cell of foetal rhesus monkey lung fibroblast, inactivated by propiolactone, and containing alum phosphate.

Two rotavirus vaccines: rhesus rotavirus tetravalent vaccine (RRV-TV), prepared on primate cells, and bovine strain WC3x Human Reassortant Rotavirus vaccine also uses primate cells.

The worldwide scale of vaccine production using primate cells is difficult to quantify, however, considering only the WHO poliovirus eradication programme, there have been 1.6 billion doses of this vaccine administered since 1996. The future expected use of the vaccine is likely to remain at the same rate. The use of other vaccine types is also on the increase due to the increase rate of travel.

The use of Vero cells by only one vaccine company for the production of their vaccines has involved the administration of about 100 million doses over 15 years world-wide in approximately 60 countries. The Vero cell line is also a platform for the production of a variety of different viruses such as Influenza virus, tick borne encephalitis, Hepatitis A virus, (recombinant) vaccinia virus, Ross River virus, Japanese encephalitis virus, St. Louis encephalitis virus and West Nile virus, as well as those traditionally produced in Vero cells. In the future it is conceivable that these continuous cell lines be used for the production of other non-vaccine biopharmaceuticals such as therapeutic proteins or gene therapy vectors.

Vaccine industry overview

For all vaccines including viral vaccines:

- By 2001 global vaccines grew to a value of \$5.4 billion.
- Global revenues are set to reach nearly \$10 billion in 2006.

Human Viral Vaccines currently available or under development

- Adenovirus vaccine
- Hepatitis A Vaccine
- Hepatitis B Vaccine
- Influenza Vaccine

- Japanese Encephalitis Virus Vaccine
- Measles Vaccine
- Mumps Vaccine
- Polio Vaccine (inactivated; live & attenuated)
- Rabies Vaccine
- Rubella (or German Measles) Vaccine
- Smallpox Vaccine
- Varicella (or Chickenpox) Vaccine
- West Nile Vaccine
- Yellow Fever Vaccine

Of which most can be produced on cell substrates, some of which are simian/primate.

COMPANIES

Some of the key companies producing vaccines: -

- Aastrom Biosciences
- Acambis
- Avant Immunotherapeutics

- **Aventis Pasteur**

Aventis Pasteur is a significant global player in the vaccine field, offering a broad range of vaccine products. Currently, the company supplies in excess of one billion vaccine doses to immunise 400 million people each year. AP currently has the broadest range of vaccines and combination vaccines, with a strong emphasis on childhood vaccines. The company also produces the world's most popular influenza vaccine, Fluzone.

In Europe the following paediatric vaccines are available: Inactivated polio vaccine (IPV), Measles, Mumps, Oral polio vaccine (OPV), Rubella, Varicella. Adult vaccines: Influenza vaccine, Rubella. Travel vaccines: Inactivated polio vaccine (IPV), Japanese B encephalitis, Oral polio vaccine (OPV), Rabies, Yellow fever

- **Baxter Healthcare**

Baxter Healthcare is a major global healthcare corporation with BioScience, Medication Delivery, Renal and Transfusion Medicine divisions as well as Vaccines.

- Berna Biotech
- Biomira

- **Chiron Vaccines**

Chiron Vaccines, the fifth largest vaccine business in the world, currently offers more than 30 novel and conventional vaccines for adults and children.

- Corixa
- Dendreon
- Dynport Vaccines

- **GlaxoSmithKline (GSK)**

GSK has a wide variety of vaccines, including vaccines against hepatitis A and B, diphtheria, tetanus and whooping cough, polio and influenza. GSK is the world's leading vaccines manufacturer with 25% of the world vaccine market. In 2001, GSK Biologicals distributed over 900 million doses of vaccines to 171 countries.

The company is one of the primary suppliers of vaccines to major international organisations such as the WHO, UNICEF and PAHO. GSK is also one of the principal donors of vaccines - in conjunction with two major polio manufacturers, it has donated 100 million doses of polio vaccines to developing countries.

GSK Biologicals has confirmed that their vaccines produced in Simian cells (not only Oral and inactivated Polio Vaccine, but also possible vaccine components) contain residual traces of genetic material of simian origin. This is also applicable to any other company producing vaccines in simian/primate cells.

- Immune Response

- **Merck**

Merck has a comparatively broad vaccine portfolio, currently consisting of 11 marketed vaccines. The company focuses on 2 key areas: MMR and hepatitis.

- Nabi

- **Powderject/Evans Vaccines** (acquired by Chiron, 2003)

PowderJect / Evans Vaccines is a rapidly growing international pharmaceutical company. With a range of products sold under its Evans Vaccines brand, PowderJect is one of the world's largest vaccines companies. Evans Vaccines' products include influenza, tuberculosis, yellow fever and tetanus vaccines. PowderJect is developing a broad range of next generation vaccines, based on the use of its proprietary powder injection and DNA vaccination technologies.

SBL Vaccines' injectable polio vaccine is sold in Sweden.

Evans Vaccines, a wholly-owned subsidiary of PowderJect Pharmaceuticals, is the only significant vaccine producer in the UK and is the 6th largest vaccine manufacturer in the world. The company manufactures and markets a range of products, which in addition to vaccines includes the analgesic diamorphine.

Fluvirin® - Flu Vaccine

Fluvirin® is a triple antigen flu vaccine. Fluvirin® is approved for sale in 30 countries including the US, UK, Belgium, France, Ireland, Spain, the Netherlands, Germany, Sweden, Norway, Australia

Arilvax® - Yellow Fever vaccine

Evans Vaccines produces and markets the yellow fever vaccine Arilvax®. Arilvax® is approved for sale in 17 countries including the UK.

- Progenics
- Solvay
- Therion Biologics
- Vaxgen
- Vical
- **Wyeth**

The company sells products in more than 140 countries, and has a comprehensive product portfolio including treatments across a wide range of therapeutic areas – including pharmaceuticals, vaccines and biotechnology.

Wyeth's comprehensive vaccine range includes conjugate vaccines against meningococcal group C, Haemophilus influenzae Type b (Hib) and Streptococcus pneumoniae (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) together with polysaccharide pneumococcal and influenza vaccines. Future developments include multivalent vaccine preparations and new vaccine delivery presentations.

Trade in Cell lines - Source of Continuous Primate Cell Lines Used

The source of the continuous cell lines for many, if not all, vaccine manufacturers is the ATCC (American Tissue Culture Collection), ECACC (European Collection of Cell Cultures) or the WHO (World Health Organisation) cell banks. These were created to provide vaccine manufacturers with cells of a known quality and allow the use of primate material without the need to source fresh tissue from primates today.

For instance, the ECACC collections currently hold over 40,000 cell lines representing 45 different species (including primates), 50 tissue types, 300 HLA types, 400 monoclonal antibodies and at least 800 genetic disorders. ECACC currently distributes over 6,000 cell cultures each year to scientists for research purposes spanning all areas of life science research e.g. cancer, genetics, biotechnology and basic science.

The trade in cell lines covers areas such as: purchase of vials from appropriate repositories and shipping to point of manufacture of the vaccines or other pharmaceutical products; shipping of material to test the quality and safety of the of the cell population, prior to large scale manufacture; and shipping of banked materials to other manufacturing facilities.