Contents

Personal Perspectives
Harmonization of pharmaceutical regulation between CADREAC and the European Union 271

Vaccines and Biomedicines
Gene transfer medicinal products 275
Gene transfer methods 275
The regulatory situation 278
Nomenclature of gene transfer medicinal products 282

Safety Issues
Interactions with grapefruit juice 283
Miconazole oral gel: interaction with warfarin 283
Fluoroquinolones and tendon disorders 284
On-line reporting of adverse reactions 284
Behaviour changes with fluoxetine, paroxetine and sertraline 285
Hepatobiliary adverse reactions with the newer antidepressants? 286
Convulsions with newer-generation antihistamines 287

Regulatory and Safety Action
Gene therapy retroviral vector trials "on hold" 289
Contraceptives and nonoxinol-9: new warning 289
Fluoxetine approved for paediatric use 290
Anorectic agents: reinstatement of marketing authorization 290
Anakinra and combination therapy 291
Estrogen and estrogen/progestin therapies: new safety information 291
Diathermy and implanted leads 292

International Nonproprietary Names (INN)
Nomenclature for drug combinations 293
Naming of excipients: future challenges 296

ATC/DDD Classification
Final list 308
Temporary list 311
WHO Drug Information
is now available at:
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Personal Perspectives

Harmonization of pharmaceutical regulation between CADREAC and the European Union*

"Omnium graduum difficillimus est primus" — The first step is the most difficult (Roman saying)

By 1997, ten countries from Central and Eastern Europe (CEE) had acquired the status of European Union Associated Countries. In order to prepare for full European Union (EU) membership and in anticipation of future adoption of EU pharmaceutical legislation, drug regulatory authorities from Bulgaria, the Czech Republic, Estonia, Hungary, Poland, Romania, Slovak Republic and Slovenia held a round of discussions on the need for harmonization.

Objectives of the talks focused on improved collaboration with EU competent bodies and updating and reform of existing administrative structures in line with the pre-accession strategy of the EU. As a primary target, CEE countries set out to improve networking, both within their own countries and with the EU. Following a meeting of CEE regulators at the International Conference of Drug Regulatory Authorities (ICDRA) in Bahrain in 1996, inauguration of activities was launched in June 1997 at a meeting of CEE drug regulatory authorities and delegates from the European Agency for the Evaluation of Medicines (EMEA), the European Commission, WHO, and European regulatory and industrial organizations.

Participants discussed the scope of EU accession in relation to their own regulatory activities and looked for ways to establish dialogue and collaboration to enhance harmonization of legislation, boost administrative capacity and achieve practical integration into EU structures. The principal outcome of the meeting was a Memorandum of Understanding stating the following principles:

1. EU Associated Countries wish to undertake intensive collaboration and cooperation both within their own countries and with the EU. A working group of representatives from participating countries will be established for the purpose of unification and information sharing.

2. Representatives of the participating countries agree to meet on a regular basis.

3. In order to encourage more intensive collaboration and promote improved exchange of information, greater involvement of representatives and experts of the EU Associated Countries in EU working parties and committees is proposed as follows:

- Inclusion of one representative in the EU Pharmaceutical Committee with observer status. Observers from the Associated countries will rotate in a commonly agreed manner.

- Inclusion of one representative in the Committee on Proprietary Medicinal Products (CPMP)* Working Groups for safety, efficacy and quality, with observer status.

- An expression of willingness by Bulgaria, Czech Republic, Estonia, Hungary, Slovak Republic and Slovenia to become EMEA Dissemination Centres.

- Willingness to join the EMEA Telematic Network.

- Readiness to discuss with the European Commission mutual recognition of good manufacturing practices (GMP), good laboratory practice (GLP) good clinical practice (GCP) and good review practice including their assessment.

4. In recognition and preparation for integration of EU processes, representatives will prepare common standard operating procedures (SOP) for automatic registration of products already licensed under the EU centralized procedure.

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*The CPMP is a scientific advisory body of the European Agency for the Evaluation of Medicinal Products (EMEA) http://www.ema.eu.int
Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries – CADREAC

In 1998, as a result of the foregoing activities, drug regulatory authorities from Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovak Republic and Slovenia met to sign the Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries – CADREAC. The agreement lays down the following principles and common goals:

• to protect public health by ensuring the use of medicinal products that meet international standards of quality, efficacy and safety; and

• to ensure that relevant information is provided on these products.

A further aim of CADREAC was to intensify collaboration within the countries and with the European Commission, EMEA and drug regulatory authorities from EU member countries.

Cyprus and Turkey later joined CADREAC, thus extending the number of member countries to twelve. Other countries, including Croatia, Russia, Ukraine, Belarus, Moldova, Yugoslavia and Switzerland, have participated as observers in annual meetings.

The mission of CADREAC is to facilitate the smooth transition of regulatory conditions in EU associated countries to achieve regulatory standards and *acquis communautaire* by:

• Implementation of EU regulatory standards.

• Involvement in professional activities within EU.

• Introduction of mutually recognized procedures.

• Development of common strategies.

• Organization of regulatory meetings.

• Exchange of information.

The latest revision of the Collaboration agreement is available on the CADREAC homepage at http://www.cadreac.org. The website is designed and maintained by the Bulgarian Drug Agency on a voluntary basis. CADREAC has a yearly rotating presidency which also hosts the Secretariat. CADREAC observers to the EU Working Groups and committees are nominated on a two-year rotational basis and each member country may have up to two observers. Observers are expected to participate proactively in the work of the groups, disseminate materials and information within CADREAC, and provide feedback to the EU bodies on behalf of CADREAC members.

In line with progressive harmonization of the pre-accession strategy, CADREAC countries comply with the "Procedure on the Granting of Marketing Authorizations by CADREAC Drug Regulatory Authorities for Medicinal Products for Human Use Authorized in the European Union Following the Centralized Procedure and the Variation and Renewal of such Marketing Authorizations". This procedure was adopted on 17 December 1998 and the latest revision was made in 2001 which concerned retrospective inclusion of the centralized procedure (CRP) in the common CADREAC simplified system process. Until full accession to EU status, any new drug placed on CADREAC markets is considered a national procedure even if it has CRP status. CRP status within CADREAC is based on several conditions:

• The medicinal product has already been granted marketing authorization by the EMEA.

• The applicant provides parts I and II of the dossier as accepted by the EMEA and a detailed list of contents of parts III and IV. These parts are submitted on request, along with a declaration that the dossier is identical to that presented to the CRP. The applicant submits also the final CPMP Assessment Report including all annexes, the consolidated list of questions and answers and the final EU Commission Decision together with annexes. If any variations have been accepted at the time of submission, relevant details should be provided too. A periodic safety update report (PSUR) is subject to submission every 6 months for the first 2 years, annually for the next 3 years and then with each renewal. The summary of product characteristics (SPC), patient information leaflet (PIL) and the sample package text should be submitted in the national language.

* Acquis communautaire combines the European Community legal system with European Court of Justice jurisprudence. As a condition of membership, new EU member countries are expected to adopt this as national legislation.
The timeframe of the assessment is recommended to be shorter than the national one, defined at 90 days, excluding any clock-stops.

Many DRAs already had experience with CRP products. This new agreement and the common approach by agencies has helped create a predictable, sustainable regulatory environment, while allowing faster access to innovative drugs approved through the CRP. In the beginning, the procedure suffered growing pains, leaving regulators and industry with unresolved issues. The EMEA played an essential role in providing scientific and regulatory support, training and additional information to CADREAC colleagues.

In April 2001, CADREAC agencies adopted the Procedure on the Granting of Marketing Authorization by CADREAC Drug Regulatory Authorities for Human Medicinal Products already authorized in EU Member States following the Decentralized Procedure – the decentralized procedure (DP) is a mutual recognition procedure and differs from CRP mainly through submission of a full dossier along with the assessment report(s), a consolidated list of questions raised by the Concerned Member State(s) and the applicant's responses. The procedure requires:

- an updated assessment report from the Reference Member State agency;
- a periodic safety update report (PSUR) (if the dossier is submitted later than 9 months after authorization in the Reference Member State agency);
- a list of post-authorization commitments, if any; and
- a declaration from the applicant that the dossier is identical to the one submitted to the Concerned Member States for the purpose of the DP, including the variation, if applied or accepted. (The DP may be “parallel” or “repeat” depending on the time of application, and with reference to the time of application to the Reference Member State).

All CADREAC countries except Turkey have adopted the decentralized procedure. A considerable number of marketing authorizations of innovative medicinal products have already been granted through the DP within CADREAC and the procedure is, in principle, accessible for generics too.

CADREAC has forged a regulatory partnership with the EU through the accession process, transforming the challenges of negotiations into strengths and improving core competencies. CADREAC provides a forum for the identification of programming needs for on-line dialogue with the Commission, EMEA and EU member states, while implementing the *acquis communautaire* in the accession countries.

Overcoming logistic constraints is crucial for the successful implementation of EU legislation and practice. Firstly, a considerable amount of specific legal provisions are to be incorporated into national laws and, secondly, introducing a new regulatory philosophy in national parliaments is not always easy and often meets with conflicting industrial interests. At the time of CADREAC inauguration, EU legislation in pharmaceuticals consisted of seventeen EU Directives, along with Council Regulations and many related administrative acts, supplemented by case law decisions. This has now been consolidated into one European pharmaceutical legislation, and is currently under revision. The EU Review 2001 is available on http://pharmacos.eudra.org/F2/home.html.

Pan European Regulatory Forum

The experience and commitment already yielded by the CADREAC agencies was further developed and strengthened through the Pan European Regulatory Forum (PERF) project. PERF was an EU PHARE-funded project from 1999–2000, and provided technical support through EU member states to EU accession countries. PERF initially identified priority action areas such as good manufacturing practices (GMP), *Acquis communautaire*, pharmacovigilance, dossier assessment, and telematics. PERF, coordinated through the EMEA, consisted of a programme of working meetings, conferences, training, joint visits and inspections, and dissemination of information. The project was considered very useful and successful and was continued as PERF II for the 2000–2003 period.

Providing opportunities for networking and common initiatives with the EU member states authorities is one of the most important objectives of CADREAC. Sharing experiences and regulatory achievements, along with visions and values, and helping to develop one’s own regulatory authority have been the incentives and driving forces in CADREAC. In particular, there was a strong impact on staff motivation. This was achieved through training of as-
sensors and their exposure to different regulatory environments and structures. This was complemented by implementation of knowledge and approaches in the home country, and the power of interacting and working with many teams, provision of feedback to needs assessment and continuous focus on performance improvement.

CADREAC is a successful example of a non-political, technical and scientific initiative conceived to strengthen drug regulation. Under the political EU accession umbrella, it has integrated the efforts of CADREAC regulators toward complete harmonization of legislative modifications and administrative procedures necessary to guarantee compliance with current EU legislation on medicinal products. CADREAC objectives have been met through the dedication of staff, hard work and political commitment from health authorities.

The winner is the public by having medicines that comply with high scientific standards as laid down by EU legislation, and predictable, transparent pharmaceutical regulation integrated within EU legislation. For the founders and supporters of the CADREAC process, there remains the inspiration of actively building rather than simply witnessing truly historical events. After 2004, when the majority of CADREAC countries join EU as members, the model of that collaboration may be exhausted, but the achievements and successes will be available to future initiatives.

References


Gene transfer medicinal products*

Gene therapy as currently known began in the United States of America in 1989 when cancer patients were treated with tumour-infiltrating lymphocytes transduced with a marker gene to track in vivo distribution. The first therapeutic trial about a year later involved the treatment of children suffering from an inherited immunodeficiency disease called adenosine deaminase deficiency (ADA). Recently, the first cure by gene therapy was effected in newborns suffering from the rare Severe Combined Immunodeficiency type X-1 (SCID-X1) and at least four SCID-X1 babies have been reported to have reconstituted their immune systems. Gene transfer medicinal products have also been used for DNA vaccines.

The WHO Clinical Gene Transfer Monitoring Group is an international group of experts from France, Germany, Netherlands, Republic of Korea, United Kingdom, and United States of America convened under the auspices of WHO. The Group is working on development of a general definition of gene transfer medicinal products. Its objectives will be to monitor development in clinical gene transfer, consider nomenclature for gene therapy products, provide advice to the WHO INN Expert Group, and consider development of an appropriate WHO guideline. More information is available at: http://www.who.int/biologicals/

Gene transfer methods

Retroviral vectors

Murine leukaemia virus (MLV)-based retroviral vectors were the first gene delivery vehicles employed for use in humans. During the first three years of gene therapy trials, MLV-based retroviral vectors were more or less the only gene delivery vector used and they still represent more than 35% of clinical trials.

The recombinant retrovirus used in gene therapy is defective in that it cannot complete its full replication cycle and thus fails to produce any progeny virus. It is generated by introducing the vector into a packaging cell that produces all viral proteins needed to form infectious, but replication-deficient, virions.

In gene therapy, safety is the highest priority. With regard to retroviral vectors, two safety issues are apparent: insertional mutagenesis and the appearance of RCR (replication competent retrovirus). The possibility of insertional mutagenesis has recently been raised in gene therapy trials using retroviral vectors to insert genes into blood stem cells. Two patients have developed a leukaemia-like condition after successful retroviral gene therapy for X-linked severe combined immunodeficiency (X-SCID). Further studies are under way to determine the cause (1–3). However, the true effect of insertional mutagenesis in retroviral gene therapy can only be assessed over a substantial period of time with a significantly high number of patients.

On the other hand, the possible presence of RCR has been considered a serious threat. Indeed, the presence of RCR has been reported in early gene therapy trials. A majority of RCR are thought to result from homologous recombination between the vector genome and the helper packaging constructs in the producer cell line. The recombination events can readily produce RCR. Therefore, it is essential

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to remove all overlapping sequences between the vector and the packaging constructs. Recently, a minimum size retroviral vector was developed which does not contain any viral coding sequences thus decreasing the probability of RCR production to very low levels.

As of September 2001, more than 200 gene therapy trials have used MLV-based vectors. Target diseases include cancer, genetic disease, HIV, and rheumatoid arthritis. Many trials reported partial response or acceptable safety of the procedure, but it should be noted that the majority of trials were carried out in patients with a limited life expectancy or in parallel with the use of other therapeutic modalities. This makes it difficult to evaluate the safety and efficacy of retroviral gene therapy.

MLV-based retroviral vectors have been instrumental in initiating gene therapy research and maintaining intense enthusiasm in this new therapeutic technology. Despite the development of many other alternative gene delivery vectors, they are still the most frequently used gene delivery vehicle and will continue to play a significant role.

Lentiviral vectors
Lentiviruses are known to infect a number of species including humans and monkeys. In their natural host, they generally cause no disease, whereas in the heterologous host they cause an acquired immunodeficiency disease termed AIDS in humans. As lentiviruses are able to infect a number of non-proliferating cells, lentiviral vectors have been derived and shown to possess a better gene transfer efficiency than retroviral vector, for example, derived from MLV.

Commercial biotechnology companies are known to be developing HIV-1, SIVagm, FIV and EIAIV vectors and it is anticipated that lentiviral vectors will one day be used, although no clinical gene transfer has yet been performed ex vivo or in vivo. Discussions with national regulatory agencies and ethics or expert committees on the foreseeable initiation of clinical trials using lentiviral vectors are ongoing.

As lentiviral vectors have improved gene transfer efficiencies compared to the currently used retroviral vectors, their use in the clinic is foreseeable and, it is generally believed, will lead to successful gene therapy approaches. These may include gene transfer into other non-proliferating cells, or where gene transfer into other non-proliferating cells seems desirable, such as in neuronal diseases.

Adenoviral vectors
Adenoviruses are non-enveloped DNA viruses of which there are many human- and animal-specific serotypes. Human adenoviral infections are associated with mild respiratory infections and rarely cause serious illness. Most of the adult population has some antibodies to adenoviruses. The use of adenoviruses in gene therapy is based on several favourable characteristics: (i) they have a safe vaccine history in humans; (ii) they generally grow well in culture and high yields are achievable; (iii) they infect a broad spectrum of cell types; (iv) the adenoviral genome has a low risk of integration into chromosomal DNA, can be readily manipulated and mutant or deleted viruses prepared; and (v) the virions are sufficiently robust.

The clinical use of adenoviral vectors (AdV) is associated with problems related to their inherent characteristics. The expression of transgene is often short-lived due to immune clearance of AdV infected cells. The main target organ is the liver, but receptors are poorly expressed elsewhere. Tropism for the liver is linked to inflammatory cytokine production and systemic toxicity. For first-generation AdV, there remains the risk of RCA generation and shedding to close patient contacts. Although, it remains unclear what dangers RCA pose to the population at large, regulatory authorities require manufacturers of AdV to reduce RCA generation to the absolute minimum. RCA may be detected by infectivity assays; RCA genomes can be quantified by quantitative polymerase chain reaction (QPCR). A reference material for wild type Ad5 has been prepared and characterized by the Adenovirus Reference Material Working Group to aid determination of particle counts and infectivity for both AdV and RCA.

Adeno-associated viral vectors
Adeno-associated viruses (AAV) are small single-stranded (ss) DNA viruses of the parvovirus family. There are 6 human serotypes of AAV, all of which appear non-pathogenic. The main advantage of AAV vectors for gene therapy applications is their long-term persistence in extrachromosomal sites and ability to insert, albeit inefficiently, the transgene in nuclear DNA. However, they are difficult to target as their receptors are widespread.
AAV vectors are indicated for the gene therapy of a number of inherited monogenic disorders and also for acquired chronic diseases such as Parkinson’s disease. A promising indication for AAV vector therapy is haemophilia B. Besides in vivo applications, AAV vectors may provide an alternative means to retroviral vectors for ex vivo transductions of haematopoietic stem cells. At present, there are no recognised AAV reference materials. The development and characterization of AAV and/or AAV vector reference reagents could be required if these vectors become more widely used.

Pox virus vectors
Following global eradication of smallpox, description of the engineering of vaccinia virus to express foreign genes has been increasingly reported from the beginning of the 1980s. Pox virus-based vectors can be considered as general delivery systems for immune induction and immunotherapy, particularly cancer immunotherapy.

Regarding their propagation, the structural and other abundant proteins produced by poxvirus-derived vectors are products of the late class genes, which are expressed only after viral DNA replication, and this could have implications for their design. In humans, canarypox virus-based recombinants expressing antigens from various viruses have been shown to be safe and antigenic with potential multiple applications in human (AIDS vaccine) and veterinary vaccinology.

Since the 1990s, several clinical trials have been conducted using vaccinia-derived vectors. Recombinant vaccinia viruses have mainly been used in Phase I clinical trials to induce specific immune response against generalized tumours. Fowlpox was also used in phase I testing for human papilloma cervical cancer. It is still being investigated whether vaccinia or canarypox-based recombinants expressing tumour antigen will have any therapeutic benefit.

Constraints in the construction and production of poxvirus vectors seem to be acceptable compared with the level of protein synthesis achieved with recombinant virus. The cytoplasmic replication cycle of poxvirus and the absence of genomic integration represent major advantages. Initial safety concerns of vaccinia virus vectors have been addressed by the use of highly attenuated replication-deficient strains as well as the engineering of host-range restricted poxviruses, such as canarypox virus. Until now, recombinant vaccinia viruses have been found not to cause significant hepatotoxicity. As for all viral vectors, careful bio-monitoring is required and the question of retaining patients in clinical trials is raised.

The large amount of protein synthesis during the replicative cycle of recombinant poxviruses causes a massive immune response that induces long lasting immunity. The high antigenicity of pox-vectors provides a potential safety benefit by virtually eliminating the likelihood of systemic infections with vaccinia virus in immunocompetent human hosts. However this may limit the potential clinical use in a drug or cytokine-sensitizing gene therapy approach since repeated applications of the same viral vector may lead to rapid immune clearance.

Herpes viral vectors
Herpes simplex(HS) type-1 virus can infect non-dividing cells, especially neurons. Various aspects of the basic biology of HSV-1 are attractive for viral vector development; HSV-1 has a broad host range cell range and is highly infectious. HSV has a large capacity for exogenous transgene insertion. Latent behaviour of the virus may be exploited for the stable long-term expression of therapeutic transgenes.

Conditionally replication competent HSV has been demonstrated to be an effective oncolytic agent in a wide variety of malignant tumours. Amplicons and defective vectors can be used for therapeutic intervention in chronic neurological and muscular disease, such as Duchenne muscular dystrophy, because vectors can transduce nondividing and dividing cells and also accommodate large cDNA, which cannot be inserted in smaller viral vectors. To date, only three HSV vectors have been entered into phase I clinical trials.

Even though human beings have antibody to HSV, the antibody has no ability to protect them against HSV infection. Antibody to HSV indicates a carrier of HSV. About 95% of the population in many countries have antibody to HSV, indicating a high rate of infection. Herpes simplex encephalitis is one of the most devastating of all HSV infections; mortality in untreated patients after HSV reactivation is in excess of 70%. Human subjects treated with herpesviral vectors should be monitored for the reactivation of HSV and virus shedding.

HSV-1 vectors are among the most efficient at gene delivery to the brain, with a predilection for many types of neurons. Gene therapy for nervous systems poses special issues related to damaging
responses to brain tissue due to injection injury, small volume to be injected and slow delivery times to avoid compression damage. Although experimental studies to date support the consensus that HSV vectors do not activate latent HSV-1, this may vary with different versions of HSV vectors and biological status of individual subjects. Even if there are some issues to be solved such as long-term expression and regulation of transgenes in brain, gene therapy of the nervous system has become an active research area with the pile-up of knowledge relating to mechanisms of neurological diseases and regulation of transgenes inserted in HSV vectors.

Naked plasmid DNA
It was not until around 1990 that free nucleic acid, which is not bound to any vector or transfection reagent, was shown to be spontaneously taken up by cells in vivo when delivered by several routes. Although some efforts are still ongoing to develop naked RNA, nowadays it is mostly naked DNA that is manufactured for use in clinical gene transfer. This method of gene delivery is distinct from those using non-viral vectors, and may include liposomes or other transfection reagents in combination with DNA. Naked DNA is mostly used as a prophylactic vaccine in clinical trials or for the therapy of peripheral artery disease. Naked DNA is currently used in about 10% of clinical trials worldwide. Plasmid DNA can easily and cost-effectively be produced by known and safe Escherichia coli strains.

Theoretical safety risks associated with the use of naked DNA have been described in the relevant European Note for Guidance (4) and the WHO guidance document on Nucleic Acid Vaccines (5). They include tolerance due to long-term or early presentation of antigens, adverse reactions and immunopathology, auto-immune reactions, adverse biological activities of the encoded antigens or proteins and induction of cancer as a consequence of chromosomal integration. No significant adverse sequelae attending these theoretical risks have been seen so far following naked DNA inoculation in humans or non-human primates.

Naked DNA in combination with vectored vaccines aimed at the development of prophylactic vaccines is currently used in a number of clinical trials. The main targets for prophylactic vaccination include HIV infection, malaria, tuberculosis, herpes virus infections and HBV infection. The main targets for the therapeutic use of naked DNA currently are tumours (immunotherapy) or peripheral artery occlusive disease. Due to its relatively easy production and use, naked DNA will play a role in such vaccination strategies.

The regulatory situation
United States of America
The US Food and Drug Administration (FDA) has taken a stepwise approach to the regulation of cellular and gene therapy products involving a progressive scale of requirements for product characterization and compliance with cGMP. Prior to the initiation of Phase I studies in humans, the generation of a certain level of information has to be in place. As development progresses, procedures and controls should become more specific because they are based upon a growing body of scientific data, documentation and experience that has been gained over time. The FDA recommends that, by Phase III, products should fully adhere to the requirements in the Code of Federal Regulations.

There are a number of documents that investigators can refer to for guidance on manufacturing a gene transfer vector for use in a clinical trial. Guidance for Human Somatic Cell Therapy and Gene Therapy (6) is a primary guidance for gene transfer clinical trials. It is important to recognize that all components used in the manufacturing process require regulatory considerations. In terms of product characterization, the FDA considers the general categories of safety, purity, identity, adventitious agents, potency, stability, and development of specifications for lot release. There are also additional considerations related to vector class. These procedures are outlined in the Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors (7).

FDA regulatory recommendations are discussed in open public meetings where FDA is advised by the Biologics Response Modifiers Advisory Committee (BRMAC). The consensus from committee discussions is that the likelihood of inadvertent germ-line transmission occurring in gene transfer clinical trials is low. These events will continue to be closely monitored.

European Union
The European Medicines Evaluation Agency (EMEA) approves new medicinal products derived by recombinant DNA or “high technology” for the...
The Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (1) drafted by the EMEA Biotechnology Working Party (BWP) came into force in October 2001. The Note for Guidance (NfG) defines gene transfer as the deliberate introduction of genetic material into somatic cells for therapeutic, prophylactic or diagnostic purposes. This definition excludes germ-line gene transfer although this is not explicitly stated. The NfG is not intended to apply to chemically synthesized oligonucleotides.

The purpose of the NfG is to provide recommendations on the quality, preclinical and clinical aspects of gene transfer medicinal products and assistance in generating data supporting marketing authorization applications within the European Community. In other words, the NfG is not a legally binding document for conducting gene transfer clinical trials nor for licensing in EU member countries.

The NfG refers to the following EU Directives:


The main purpose of both directives on genetically modified organisms (219 and 220) is the protection of the population and the environment from infectious genetically modified organisms.

The definition of a GMO within EU directives 219 and 220 covers micro-organisms including viruses, viroids, and cell cultures including those from animals, but does not cover naked recombinant DNA and naked recombinant plasmids.

After completion of the NfG, EU directive 2001/20/EC on Good Clinical Practice was accepted 4 April 2001. This directive will enter in force in all EU Member States in May 2004. It addresses also the dual review procedure of all clinical trials using medicinal products (including gene transfer trials), by the national competent authorities and the local medical ethics committees. The directive prohibits gene therapy trials that result in modifications to the subject’s germ-line genetic identity.

The NfG should be read in conjunction with other guidance notes adopted by the Committee on Proprietary Medicinal Products (CPMP). Guidance documents that are referred to in the NfG are:

- ICH-technical guidelines (e.g., ICH Q5B Note for Guidance on Quality of Biotechnological Products).
- CPMP Points-to-Consider on Human Somatic Cell Therapy.
- CPMP Note for Guidance on the preclinical pharmacological and toxicological testing of vaccines, CPMP/465/95.
- Note for Guidance on quality of biotechnological products: derivation and characterization of cell substrates used for production of biotechnological/biological product, CPMP/ICH/294/95.
- Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, CPMP/ICH/268/95.
- European Pharmacopoeia monographs.

Gene transfer medicinal products derived by recombinant DNA technology fall under the scope of Council Regulation EEC 2309/93. Marketing approval is granted by the European Commission via the centralized procedure initiated by sending an application to the Committee for Proprietary Medicinal Products (CPMP) at the European Agency for the Evaluation of Medicinal Products (EMEA). Notice for Applicants for medicinal products for human use is available on http://pharmacos.eudra.org/eudralex/index.htm. Scientific Advice with a view to marketing authorization is given by the CPMP at the EMEA. One of the relevant European guidelines is the Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products (4). Arrangements for conducting clinical trials vary among EU member states.

France
Since 1993, the French agency for the safety of health products (AFSSAPS) has developed an
approach to anticipate regulatory and quality issues of gene therapy. Within a working group environment, a report on gene therapy has been produced by an expert group drawn from regulators, quality control experts and academia.

Priorities were defined in terms of products to be controlled, control testing and methods to be developed. Four categories of products were listed: viral vectors, plasmids, synthetic vectors and genetically modified cells. Key in vitro tests to be performed were identity, purity, activity (potency) and safety. Efficacy should be assessed by measuring expression of the protein encoded by the transgene. Microbiological and viral safety and search for replicative competent particles in patients and environment should be considered.

The expert group pointed out the main issues to be addressed before regulation can be finalized and the validation studies that manufacturers should document before submission of a file to regulatory authorities – assessment of assay variability, specificity, quantification limit – which are of major importance in developing a routine “production” process. The need for standardization of methods and for internationally available reference preparations was also considered a major need if international harmonization of evaluation criteria was to be achieved.

**Germany**

Gene transfer medicinal products are medicinal products under German Drug Law and include DNA, viral or non-viral vectors and genetically modified autologous, allogeneic or xenogeneic cells. No official definition of gene transfer medicinal products is given: they are either vaccines, blood products or other drugs.

As for other medicinal products, regulations exist for the manufacture and clinical trial of gene transfer medicinal products. Application of genetically modified organisms (GMOs) and therefore of gene transfer medicinal products in humans is not regulated by the German Gene Technology Law (GenTG). Approval of deliberate release according to the GenTG is not required. In contrast to other medicinal products, an appraisal of the central Commission on Somatic Gene Therapy of the Scientific Board of the German Medical Association is required for clinical trials involving the use of gene transfer medicinal products. Experimental pre-clinical work in gene therapy including the construction, use, storage and inactivation of vectors, genetically modified bacterial or mammalian cells or animals has to be conducted according to German Gene Technology Law. Experiments involving the use of genetically modified organisms (GMOs) have to be performed in fully equipped laboratories or animal facilities having safety levels.

Other laws and regulations apply and are executed by different competent authorities where the laboratory or clinic is located. These include:

- Good Manufacturing Practice (GMP) is generally required for the manufacture of medicinal products for human use.
- Good Laboratory Practice (GLP) should be applied for pharmacological-toxicological tests, the results of which are to be used in an application for a marketing authorisation.
- Manufacturing authorization is necessary for manufacturers who intend to commercially or professionally manufacture the drug (and/or the active ingredient).
- Import authorization is required for parties wishing either commercially or professionally to bring finished (ready-prepared) medicinal products, test sera, test antigens, active ingredients which are of human or animal origin or which are gene-technologically manufactured into Germany from countries who are not member states of the European Union or Contracting States of the European Economic Area Agreement.

Prior to licensing, gene transfer medicinal products are only to be used in or on humans during clinical trials. Exceptions are considered separately. Guidelines specify the necessary ethical considerations and clinical trial applications. Clinical trials can only be conducted if certain requirements are met. Gene transfer medicinal products derived by recombinant DNA technology fall under the scope of EU Council Regulation (EEC) 2309/93.

Information about clinical trials in Germany is available at [http://www.pei.de/themen/themlink.htm](http://www.pei.de/themen/themlink.htm) (-> Gentherapie -> Tabelle zu klinischen Studien unter Anwendung von Gentransfer-Arzneimitteln in Deutschland). Additional information is currently being prepared by the German Register for Somatic Gene Transfer Studies and will also be available at [http://www.zks.uni-freiburg.de/dereg.html](http://www.zks.uni-freiburg.de/dereg.html). Unfortunately, the gene therapy websites of the European Society for Gene Therapy (http://www.wiley.co.uk/...
wileychi/genmed/clinical/) and of the Office of recombinant DNA Technology at the US National Institutes of Health (http://www4.od.nih.gov/oba/rac/clinicaltrial.htm) do not contain sufficient information about clinical trials involving the use of gene transfer medicinal products in Germany.

Following the transformation of European Directive 2001/20/EC (http://europa.eu.int/eur-lex/en/lif/dat/2001/en_301L0020.html), a positive opinion of the local ethics committee advised by the Commission on Somatic Gene Therapy and written approval from the competent authority will be necessary prior to initiation of clinical trials involving the use of gene transfer medicinal products in all European member states, including Germany. In Germany, this will require an adoption of the German Drug Law which is expected to be finalized in 2002 or 2003.

Netherlands

In December 1999, the Medical Research Involving Human Subjects Act came into force in the Netherlands. The Act describes the establishment of the Central Committee for Research Involving Human Subjects. This Central Committee has several tasks, including the review of clinical gene transfer protocols. Without their approval, a gene transfer trial cannot commence. Licensing is harmonized with the EU procedure.

The Central Committee has not produced guidelines on gene transfer but a statement on gene therapy in which the review procedure is described and the existing FDA/CBER and EMEA guidance documents adopted. In practice, the Central Committee follows the FDA/CBER-guidelines, with one exception concerning the requirements on safety studies on ex vivo transduced cells. Obviously the ‘dry run’ approach is not perfect and the number of 5 dry runs is arbitrary. Nevertheless, according to the Central Committee the ‘dry run’ approach gives a better assessment of possible RCRs in the pool of ex vivo transduced cells.

South Korea

In Korea, serious research into gene therapy began around 1994 with financial support from the Ministry of Science and Technology. Gene therapy guidelines were established in the year 2000, and Korea’s first government-approved gene therapy clinical trial was carried out the following year in ischemic diseases using naked DNA expressing VEGF165.

The Guidelines for the Approval and Clinical Trial of Gene Therapy Products are essentially a mix of the guidelines of three regulatory agencies, namely that of the USA FDA, EMEA, and Japan’s Ministry of Health, Labour and Welfare. The objective of the guidelines is to ensure the quality and safety of drugs used in gene therapy. In it, gene therapy products are defined as medicinal products of genetic material or genetically modified cells administered to the human body for the treatment of diseases. Diseases for gene therapy application include fatal or life-threatening hereditary diseases, cancer and AIDS. For a gene therapy clinical trial to take place, there should be no alternative effective therapeutic methods or gene therapy technology.

Laws and regulations related to gene therapy are set out in the Pharmaceutical Affairs Law, Enforcement Regulation of the Pharmaceutical Affairs Law, Evaluation of Specification and Test Methods of Drugs, and Evaluation of Safety and Efficacy of Drugs. The responsible government agency is the Korean Food and Drug Administration (KFDA) where three offices handle gene therapy matters. First, the Pharmaceutical Safety Bureau receives an investigational new drug (IND) submission, distributes papers to relevant offices, and finally clears or refuses the submission. Next, two other clearance offices are the Biologics Evaluation Department and the National Institute of Toxicological Research.

Licensing standards cover safety, purity, potency, effectiveness and consistency. An IND submission should contain (i) the information on chemistry, manufacturing and controls; (ii) pharmacology and toxicology; and (iii) clinical protocol. Detailed information required by the KFDA is not significantly different from that required by agencies in other countries.

Any investigators or industry that wants to perform gene therapy clinical trials should first obtain approval from the institutional review board (IRB) at the hospital in which the clinical trial is going to be performed. The KFDA strongly recommends having a pre-IND meeting, which takes place a maximum of 2 months after the request has been made. The KFDA will respond to an IND submission (previously processed through a pre-IND meeting) within 1 month. If it has not been through a pre-IND
meeting, there is no maximum time frame, so theoretically, it may take an indefinite amount of time. The actual review is done by KFDA scientists and other officials. However, the review must be evaluated once again by the Central Drug Evaluation Committee (which belongs to the Ministry of Health and Social Welfare). There are two advisory subcommittees on gene therapy, for ethics and safety.

Nomenclature of gene transfer medicinal products

The aim of the WHO Expert Group on International Nonproprietary Names is to designate one generic name for each pharmaceutical substance to avoid confusion of use among regulatory authorities, drug manufacturers, health professionals and patent authorities. The International Nonproprietary Names (INN) system was initiated in 1950 and, at present, over 7000 names have been designated for pharmaceutical substances.

Gene transfer is a complex and rapidly developing area leading to a variety of potential clinical products. More than 600 currently approved trials have been, or are being, carried out and it is expected that within a few years several gene transfer products will be commercially available. There is, therefore, a need to consider how gene transfer medicinal products will be named.

FDA recommendations for such a nomenclature focus on two points. Firstly, the name should indicate clearly that the product is a vector carrying a gene (as opposed to a protein) to be transferred for therapeutic purposes. Secondly, FDA recommends that certain items be omitted from the name such as the indication, the viral subtypes/plasmid backbone (if there is no significant difference in the tropism/action), and the promoter used to drive expression of the transgene. These items can be included in the package insert. It is FDA’s opinion that in terms of a nomenclature system for gene transfer medicinal products, the simpler the better, although this position is still under review.

The important aspects of gene transfer medicinal products are (i) the distinction between in-vivo gene transfer or clinical transfer of ex-vivo genetically modified cells, (ii) the nature of the gene often termed expression vector or expression construct used to modify the cells in vivo or ex vivo and (iii) the exact nature of the gene transfer reagent (non-viral vector or naked nucleic acid) or the viral particle used for the genetic modification.

Issues relating to nomenclature for gene transfer medicinal products using International Nonproprietary Names (INN) will be discussed at the next meeting of the WHO Clinical Gene Transfer Monitoring Group.

References

Safety Issues

Interactions with grapefruit juice

The serendipitous discovery in 1991 of the interaction of grapefruit juice with drugs occurred when grapefruit juice was used to mask the taste of ethanol in a study testing an interaction between the dihydropyridine calcium channel blocker felodipine and ethanol (1). It is now known that grapefruit juice can interact with a number of drugs, through local inhibition of one of the cytochrome P450 enzymes (CYP3A4) and P-glycoprotein (Pgp) in enterocytes in the intestinal wall (2). It has been shown that grapefruit juice does not affect hepatic CYP3A4.

Interactions with grapefruit juice have been most frequently studied with the dihydropyridine calcium channel blockers (CCBs) including felodipine and nifedipine. Significant interactions have also been found for some of the HMG-CoA reductase inhibitors (statins), particularly simvastatin but possibly also atorvastatin; the benzodiazepines midazolam and triazolam; as well as ciclosporin, saquinavir, and cisapride. This is not an exhaustive list and there are a number of other drugs with a potential for interaction which have not been studied. A recent article contains a more comprehensive list (3). The two most important characteristics of the "target" drugs are metabolism by gut wall CYP3A4 and/or Pgp and associated low oral bioavailability.

ADRAC has received 14 reports describing possible interactions with grapefruit juice. Most have involved either the dihydropyridine CCBs or statins. Three of the reports with CCBs have involved amlodipine, an interaction which is usually considered clinically insignificant. Grapefruit juice can inhibit the metabolism of target drugs and increase the amount of parent drug available for absorption, which may result in an increase in its pharmacological or toxic effects. For the CCBs, the reports usually describe hypotension and related symptoms, and for the statins, most reports describe myalgia and associated effects.

Prescribers should be aware that there are several groups of drugs that may interact with grapefruit juice and patients taking these drugs should be made aware of the possibility. It should also be noted that problems can arise from whole grapefruit (as in four of the ADRAC reports), and that the extent of the interaction can vary with different brands and strengths of juice. It is believed that with the exception of bitter Seville oranges, the interaction does not occur with other citrus fruits (4).

References


Miconazole oral gel:
interaction with warfarin

Attention has previously been drawn to the possibility of an interaction between miconazole oral gel (Daktarin Oral Gel®) and warfarin resulting in elevation of INR (1). The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has now received 18 reports describing this interaction, which is the most serious and important of the reactions described in the 32 reports to ADRAC involving oral miconazole.

In most cases there was a clinically significant increase in the INR of patients who had been stabilized on warfarin. This usually occurred within a week or two of commencing miconazole. In the 17 patients in whom the INR values were documented, the INR rose to between 7.5 and more than 18. In 9 cases, there were no symptoms but in the other 8 cases, the patients presented with bruising, haematuria or mucocutaneous bleeding. Most patients required the withdrawal of one or both drugs. At least 9 patients were given vitamin K and 5 of these required fresh frozen plasma. Miconazole oral gel is absorbed to a sufficient extent to affect warfarin metabolism and hence...
increase its blood concentration and activity. This may occur through inflamed oral mucosa or from the bowel after swallowing the gel. An interaction is probably less likely when miconazole is administered to the skin or vaginally but ADRAC has received one report of an interaction involving topical miconazole cream.

Prescribers should be aware that the possibility of an interaction with warfarin is the most important adverse effect of oral miconazole. It is mentioned in the product information and the consumer medicine information for both oral and vaginal miconazole products. It should also be noted that miconazole products are available without prescription and pharmacists as well as doctors need to be alert to a possible interaction (2).

References

Fluoroquinolones and tendon disorders
The association between fluoroquinolone antibiotics and tendon disorders (especially involving the Achilles tendon) has been reported by the Australian Adverse Drug Reactions Advisory Committee (ADRAC) and has recently been confirmed by an epidemiological study (1–3).

In a Netherlands review of data from a large UK general practice database, a cohort of 46,776 patients had used fluoroquinolones over a 6-year period and 704 cases of Achilles tendinitis were identified with 38 cases of Achilles tendon rupture. Current use of fluoroquinolones was associated with 46 of these cases. The adjusted relative risk of Achilles tendon disorders with current use of fluoroquinolones was 1.9 (95% confidence interval 1.3 to 2.6). This risk was increased to 3.2 (2.1 to 4.9) among patients aged 60 and over and was not significant in patients under 60. In patients aged 60 or over, concurrent use of corticosteroids and fluoroquinolones increased the relative risk to 6.2 (3.0 to 12.8).

There have been 112 Australian cases of tendon disorders with fluoroquinolones reported to ADRAC, including 30 cases of tendon rupture. Almost all have involved the Achilles tendon. Most occurred with ciprofloxacin (100) but there have also been cases with norfloxacin (9), gatifloxacin, enoxacin and moxifloxacin. It is not known why there have been so many more reports with ciprofloxacin, as it and norfloxacin have had a similar number of prescriptions (over 600,000) dispensed on the PBS over the past 5 years. The other three fluoroquinolones are not subsidised by the PBS.

In the Dutch study, ciprofloxacin and norfloxacin had a similar risk but there was an increased risk with ofloxacin, which is not available in Australia. Of the 106 reports where the age was specified, 73 patients were aged 60 or over, and 20 other patients were in their fifties. Although concomitant medication was not always documented, 47 patients were taking oral corticosteroids.

With the marketing of two new fluoroquinolones (gatifloxacin, moxifloxacin), ADRAC wishes to remind prescribers that tendon disorders are a class effect of fluoroquinolones and that age and concomitant corticosteroids are established risk factors. Patients should be advised to be alert for pain or discomfort in the Achilles tendon or calf and inform their doctors if this occurs (4).

References

On-line reporting of adverse reactions
The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has commissioned a new database and on-line reporting of suspected adverse reactions is now available. Potential reporters will be able to register and have access to past notifications as well as to information from the database. For people who use the service infe-
quently it will also be possible to lodge ADRs. On-
line reporting began on 1 January 2003. To access
this facility, click on “On-line Services” at the TGA
website (www.health.gov.au/tga) and follow the
links. There will also be a link from the adverse
drug reactions section of the website

In addition, ADRAC is working with the Collaborat-
ing Centre for e-Health at the University of Ballarat
and three developers of prescriber desktop soft-
ware to provide on-line reporting. The information
available from the software will be automatically
used to complete the fields in the on-line “blue card”
and the prescriber will need only to complete the
details of the ADR and a few other fields before the
software sends the on-line form to ADRAC. It is
anticipated that this facility will be available from
early 2003. Once this work is complete, on-line
reporting will be extended to the pharmaceutical
industry using ICH specifications. It is also hoped to
extend on-line reporting to hospitals and pharma-
cies.

Reference: Australian Adverse Drug Reactions Bulletin,

Behaviour changes with fluoxetine,
paroxetine and sertraline

There have been rare reports of fluoxetine and,
more recently, paroxetine and sertraline being
associated with aggressive or suicidal thoughts and
behaviour. Due to similar pharmacological profiles,
the same reactions may occur with other selective
serotonin reuptake inhibitors (SSRIs). It is possible
that these reactions can be attributed to akathisia
(involuntary severe motor restlessness). However,
the most common reason for self-harm behaviour
during treatment with any antidepressant is worsen-
ing depression. The development of severe agita-
tion or self-harm behaviour is an indication that the
patient and their antidepressant therapy require
prompt review. Patients should be advised to seek
medical attention as soon as possible if they de-
velop agitiation or restlessness, or if their depres-
sion worsens.

Soon after its introduction internationally, fluoxetine
was claimed to cause suicidal thinking and behav-
our (1). This allegation was investigated by a
number of regulatory agencies, including the Food
and Drug Administration in the United States in
1991, and was not substantiated. More recently,
there have been several further case reports, some
given media prominence, and some leading to legal
proceedings, not only in relation to fluoxetine (2, 3),
but also to paroxetine and sertraline (4). Systematic
reviews continue to support the view that selective
serotonin re-uptake inhibitors (SSRIs) are effective
and are not associated with increased suicidality or
increased violence (5). However, these reports (1–
6) raise questions about whether the small group of
patients experiencing the rare side effect of aka-
thisia are at increased risk of suicide.

Detailed case reports (1, 4) describe the emer-
gence of marked restlessness and agitation fol-
lowed by suicidal thinking or behaviour in patients
soon after commencing fluoxetine or other seroton-
ergic agents. This restlessness and agitation may
reflect akathisia (involuntary severe motor restless-
ness). Although more commonly associated with
antipsychotics — reflecting dopamine receptor
blockade — interactions between the serotonergic
dopaminergic systems may account for aka-
thisia also occurring with SSRIs (7–10). A putative
link between akathisia and suicidal behaviour is
less clear, and not all of the more recent case
reports describe preceding restlessness (1–4).
Older groups of antidepressants have also been
associated with increased suicidal thinking and
behaviour, although not related to increased rest-
lessness (11).

The key issues in treating depression are the
selection of an appropriate treatment in conjunction
with the depressed person, and the use of an
adequate dose for an adequate length of time,
along with attention to current stressors. The most
common reason for suicidal ideation or behaviour
during treatment with any antidepressant remains
worsening depression. The development of agita-
tion or self-harm behaviour (from any cause) indi-
cates the need to increase support to ensure the
patient’s safety, as well as a review of treatment to
check that it is optimized for that person.

As with many medicines, rare serious side effects
may emerge during treatment and patients should
be aware of these and what action to take. It is
recommended that all patients taking SSRIs should
be advised that if they become particularly agitated
or restless, they should seek medical advice and
stop their antidepressant in the interim. In addition,
any serious worsening of their symptoms, particu-
larly in relation to suicidal thoughts, should be
reported urgently to their treating doctor (or on-call
colleague).
References


Hepatobiliary adverse reactions with the newer antidepressants?

Suspected hepatobiliary adverse reactions (ARs) may be associated with the newer antidepressants that exert an effect on serotonin neurotransmission. These include citalopram (Celexa®), fluoxetine (Prozac®), fluvoxamine (Luvox®), mirtazapine (Remeron®), nefazodone (Serzone-5HT®, paroxetine (Paxil®), sertraline (Zoloft®), trazodone (Desyrel®) and venlafaxine (Effexor®).

Spontaneous reporting systems are suitable for detecting signals of potential drug safety issues. However, the data cannot be used to determine the incidence of adverse reactions (ARs) because ARs remain underreported and total patient exposure is unknown. From the data available, no fatal outcomes were reported for hepatobiliary ARs associated with these antidepressants. In 2 reports involving nefazodone, liver transplantation was required. In 3 other reports involving nefazodone, liver transplantation was considered, but the patients’ conditions eventually improved after prolonged hospital care. The time of onset of liver injury ranged from 1 to 4 months. None of these 5 patients had a prior history of liver disease.

Health Canada has been monitoring the safety profile of nefazodone since it was marketed in Canada in 1994 and has taken the following action:

- A summary of reported reactions associated with nefazodone was profiled in the April 1996 issue of the Canadian Adverse Reaction Newsletter (1).

- A summary of 9 Canadian case reports of suspected symptomatic hepatic dysfunction associated with nefazodone was outlined in the July 1999 issue of the Canadian Adverse Reaction Newsletter (2).

- Two Dear Healthcare Professional Letters issued by the manufacturers of Serzone-5HT®, and Lin-Nefazodone® (3) and of Apo-Nefazodone® (4) recommending that patients be counselled about the risk of hepatotoxic effects before the initiation of nefazodone therapy and that close monitoring is required should signs of hepatotoxicity or abnormal liver aminotransferase or bilirubin levels develop during treatment.

- Health Canada issued a public advisory on the safety profile of nefazodone on 9 July 2001, related to the risk of severe liver injury (5).

The current literature documents several cases of severe hepatic failure associated with nefazodone (6–8). The US Food and Drug Administration (FDA) recently included a black-box warning in the Serzone® package insert, stating that the reported rate in the United States of liver failure resulting in
death or liver transplantation is about 1 case per 250,000–300,000 patient-years of Serzone® treat-
ment. This rate is about 3-4 times the estimated background rate of liver failure. It is possibly an under-
estimate of true risk because of underreporting (9).

At present, there is no way to predict in which patient liver failure is likely to develop (9). Ordinar-
ily, treatment with nefazodone should not be initi-
ated in patients with active liver disease or with an elevated baseline serum transaminase level (9).
Although it is unclear whether periodic liver function tests can help prevent serious liver injury, it is generally believed that early detection of drug-induced hepatic injury along with immediate discontinu-
tion of the suspected drug enhances the likelihood of recovery (9). Patients should be ad-
vised to be alert for signs and symptoms of liver dysfunction (e.g., dark urine, jaundice [yellow discoloration of the skin or the eyes], loss of appetite and discoloured stools) and to report them to their physician immediately (9, 10).

Mano Murty, Iza Morawiecka, Suniti Sharma
Canadian Adverse Reaction Newsletter, 13: 1
(2003).

References

Convulsions with newer-generation antihistamines

Antagonists of histamine H1 receptors are commonly classified as first-generation or new-generation antihistamines based on their frequent sedating effect at therapeutic doses (1). The “newer-generation” antihistamines, also known as second- or third-generation antihistamines, include astemizole, cetirizine, desloratadine, fexofenadine, loratadine and terfenadine, and were developed as non-
seminating alternatives to the first-generation compounds. The sale of terfenadine and astemizole was stopped in Canada because of associated QT prolongation which could lead to torsades de pointes or ventricular fibrillation.

Loratadine, cetirizine, fexofenadine and deslor-
atadine have been marketed in Canada since 1988, 1991, 1997 and 2002, respectively. Loratadine, fexofenadine and desloratadine are available as nonprescription drugs. Cetirizine is available as both a nonprescription (5 and 10 mg) and prescrip-
tion (20 mg) drug.

Seizures or convulsions have been reported in the literature with some first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine and pyribenzamine) as well as with some newer-
genration antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine) (1–3). According to the US Food and Drug Administration Adverse Event Reporting System (July 1999), convulsions associated with cetirizine, fexofenadine and loratadine accounted for 2.5%, 3.1% and 2.1% respectively of the total adverse events reported with these drugs (1).
Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.
Gene therapy retroviral vector trials "on hold"

United States of America — The Food and Drug Administration (FDA) has placed on "clinical hold" all active gene therapy trials using retroviral vectors to insert genes into blood stem cells.

FDA took this action after it learned that a second child treated in a French gene therapy trial has developed a leukaemia-like condition. Both this child, and another who had developed a similar condition last August, had been successfully treated by gene therapy for X-linked severe combined immunodeficiency disease (X-SCID), also known as "bubble baby syndrome."

Infants with X-SCID have a gene defect that leads to a complete lack of white blood cells that can fight infection. Without treatment, they die from complications of infectious diseases during the first year of life. The only treatment for this condition is a bone marrow transplant. In early results of the French study in which a normal gene is inserted into blood stem cells of patients with X-SCID, nine of the 11 children had promising results and could leave the hospital and lead relatively normal lives.

After notification of the first case last year, FDA identified the three US gene therapy studies that most closely resembled the French trial and stopped enrolment of human subjects in those trials. They remain on clinical hold, a condition which FDA can impose when adverse events or other safety questions arise during a clinical study. FDA’s continuing review of adverse event reports from all US studies involving retroviral vectors has to date found no evidence of leukaemia caused by the gene therapy. Moreover, the agency has to consider the potential risks of any experimental therapy within the context of the disease it may treat — in this case a devastating disease in children.

FDA's action includes a temporary hold on the enrolment of new patients in a subset of gene therapy trials that involve the use of retroviruses to insert new genes in blood stem cells, irrespective of the disease condition.

The temporary hold reflects FDA’s appreciation that some of these trials involve patient populations and gene therapy products that may be appropriate to continue after they are updated to reflect this new risk information. FDA will consider and evaluate specific requests for clinical indications for fatal or life-threatening disorders for which there are no viable alternative treatments.

Reference: FDA Talk Paper, T03–04 2003

Contraceptives containing nonoxinol-9: new warning

United States of America — The Food and Drug Administration (FDA) is proposing new warnings for the labels of over-the-counter vaginal contraceptive drugs that contain the spermicide nonoxinol-9.

FDA is requesting public comment on the proposed labelling statements and on the most effective way to present this new warning which will state that vaginal contraceptives containing nonoxinol-9 do not protect against infection from HIV (human immunodeficiency virus, the AIDS virus) or other sexually transmitted diseases (STDs).

The proposed label warnings will also advise consumers that the use of vaginal contraceptives containing nonoxinol-9 can increase vaginal irritation, which may actually increase the possibility of transmitting the AIDS virus and other STDs from infected partners.

FDA’s proposed labelling statements are based on recent studies using nonoxinol-9, including data from a four-year World Health Organization study of 991 HIV-negative sex workers in Africa and Thailand. The study, whose final results were recently published, showed nonoxinol-9 to be ineffective in the prevention of HIV infection (2).

Nonoxinol-9, works as a vaginal contraceptive by damaging the cell membrane of sperm. It has been shown in laboratory studies to damage the cell walls of certain organisms that cause STDs and to be active against some STD-causing bacteria and viruses. On the basis of data that are described in the labelling proposal, FDA believes that this same
membrane-damaging effect can harm the cell lining of the vagina and cervix, thereby increasing the risk of STD transmission.

**Reference:** FDA Talk Paper, T03–05 2003.

**Fluoxetine approved for paediatric use**

**United States of America** — The Food and Drug Administration has approved new uses for the antidepressant fluoxetine (Prozac®) to treat children and adolescents seven to 17 years of age for major depressive disorder and obsessive compulsive disorder (OCD). This is the first approval of one of the newer types of antidepressants (selective serotonin re-uptake inhibitors or SSRIs) for treating depression in this population.

According to the National Institute of Mental Health (NIMH), depression affects up to 2.5% of children and about 8% of adolescents in the United States. OCD affects about 2% of the population, and typically begins during adolescence or early childhood. At least one-third of the cases of adult OCD began in childhood. The social and economic costs of OCD were estimated to be $8.4 billion in 1990.

Today’s approval of fluoxetine for use in children and adolescents was based on two placebo controlled clinical trials in depressed outpatients whose diagnoses corresponded to standard rating criteria under the American Psychiatric Association’s Diagnostic and Statistical Manual. Symptoms of depression include general emotional dejection, withdrawal and restlessness that usually interfere with daily functioning, and includes at least five of the following nine symptoms: depressed mood; loss of interest in usual activities; significant change in weight and/or appetite; insomnia or hypersomnia (abnormally excessive sleep); psychomotor agitation or retardation; increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; a suicide attempt or suicidal ideation. The studies of fluoxetine for depression produced a statistically significant effect for the drug compared to placebo on the “Childhood Depression Rating Scale R (revised).”

In children with OCD between the ages of seven and 13 and adolescents 13 to 18, fluoxetine produced a statistically significant result compared to placebo on a measurement called “The Children’s Yale Brown Obsessive Compulsive Scale.” Obsessive-compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are repetitive and purposeful, and intentional behaviours (compulsions) that are recognized by the person or their parent or guardian as excessive or unreasonable.

Common side effects associated with use of fluoxetine in children and adolescents were similar to those experienced by adults and include nausea, tiredness, nervousness, dizziness, and difficulty concentrating. In one clinical trial in children and adolescents eight to 17 years of age, after 19 weeks of treatment with fluoxetine, paediatric patients gained, on average, about 1.1 cm less in height (about a half an inch) and about one kg. less in weight (about two lbs.) compared to paediatric patients treated with placebo. The clinical significance of this observation on long-term growth is unknown. The manufacturer of Prozac® has agreed to conduct a Phase IV postmarketing study to further evaluate any potential impact of fluoxetine on long-term growth in children.

Fluoxetine is also approved for major depressive disorder in adults, bulimia, and panic disorder.


**Anorectic agents: reinstatement of marketing authorization**

**European Union** — The European Court of First Instance has, on 26 November 2002, annulled previous European Commission decisions taken in 2000 to withdraw the marketing authorizations for anorectic agents.

The Court ordered that “the Community cannot act beyond the powers conferred on it. The conditions for withdrawal of a marketing authorization must be interpreted in accordance with the general principle of protection of public health. A mere change in the consensus on the efficacy of those drugs in the treatment of obesity, which is not based on any new data, does not justify withdrawal of marketing authorization.”

The Court found, *inter alia*, that precedence must be given to the protection of public health and requires:

- the taking account exclusively of considerations relating to health protection;
• the re-evaluation of the benefit/risk balance of a medicinal product where new data give rise to doubts as to its efficacy or safety, and

• in cases of scientific uncertainty, the application of the rules of evidence in accordance with the precautionary principle

The Court of First Instance considered that mere changes in a scientific criterion for assessing the efficacy of a medicinal product, based on a consensus in the medical community, justify the withdrawal of a marketing authorisation of a medicinal product only if those changes are based on new data.

In those circumstances, the Court of First Instance found that the Commission decisions on anorectic agents should be annulled.

Reference: Judgment of the Court of First Instance in Joined Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00. Press Release No. 94/02 26 November 2002. Available at: http://www.curia.eu.int/en/cp/aff

Anakinra and combination therapy

Canada — The manufacturer of anakinra (Kineret®) has advised healthcare professionals of new information on use in combination with etanercept. Anakira is a recombinant nonglycosylated form of the human interleukin-I receptor antagonist indicated to reduce the signs and symptoms of active rheumatoid arthritis.

A recently completed clinical trial of 242 patients in the United States with rheumatoid arthritis who had not previously been treated with biological agents demonstrated that:

• patients receiving concurrent anakinra and etanercept had a higher incidence of serious infections than in patients receiving etanercept alone; and

• no therapeutic benefit of the combination treatment over etanercept alone was observed.

Physicians are reminded of the wording in the warnings section of the prescribing information "use of Kineret® with TNF blocking agents should only be done with extreme caution and when no satisfactory alternatives exist". The prescribing information will also include an amendment on lack of therapeutic effect with combination therapy.


Estrogen and estrogen/progestin therapies: new safety information

United States of America — The Food and Drug Administration (FDA) is advising women and health care professionals of important new safety changes to labelling of all estrogen and estrogen with progestin products for use by postmenopausal women. These changes reflect FDA’s analysis of data from the Women’s Health Initiative study (WHI), a landmark study sponsored by the National Institutes of Health that has raised concerns about risks of using these products.

The WHI study has several components, one of which was designed to assess the effects of Prempro®, a combination of estrogens plus a progestin, on the risk of developing heart disease. The Prempro® arm of the WHI was halted early in July 2002 because the overall health risks, particularly the risks of invasive breast cancer and cardiovascular disease, exceeded the benefits of the drug. Estrogen and progestin hormones have never been approved by FDA for prevention of heart disease, although physicians could prescribe them "off-label" for this use.

All other manufacturers of estrogen and estrogen with progestin drug products for use in postmenopausal women have been requested to make similar changes to the labelling for their products. It is estimated that about ten million postmenopausal women in the USA currently use estrogen and combination estrogen with progestin products for relief of menopausal symptoms and prevention of postmenopausal osteoporosis. Estrogen products are approved for use in relieving vasomotor symptoms of menopause such as "hot
flashes" and night sweats; symptoms of vulvar and vaginal atrophy such as dryness, itching, and burning; and prevention of postmenopausal osteoporosis. Because there are few alternatives for the relief of severe vasomotor symptoms and severe symptoms of vulvar vaginal atrophy, estrogens and estrogens with progestins have an important role in women’s health.

Health care providers are advised to prescribe estrogen and combined estrogen with progestin drug products at the lowest dose and for the shortest duration for the individual woman. After discussing treatment with their doctor, women should have yearly breast exams by a health care provider, perform monthly breast self-examinations, and receive periodic mammography examinations based on age and risk factors. Other ways to reduce risk factors for heart disease (e.g., high blood pressure, poor diet, tobacco use) and osteoporosis (e.g., an appropriate diet, use of Vitamin D and Calcium supplements, weight-bearing exercise) should be proposed.


Diathermy and implanted leads

United States of America — The Food and Drug Administration has advised of the risk of serious injury or death to patients with implanted electrical leads who are exposed to diathermy treatments.

Reports have been received in which patients with implanted deep brain stimulators (DBS) died after receiving diathermy therapy. One patient received diathermy following oral surgery, the other for treatment of chronic scoliosis. In both cases, the interaction of the diathermy with the implanted device caused severe brain damage in the area where the lead electrodes were implanted.

There are three types of diathermy equipment used by physicians, dentists, physical therapists, chiropractors, sports therapists, and others: radio frequency (shortwave) diathermy, microwave diathermy and ultrasound diathermy. Shortwave and microwave diathermy, in both heating and non-heating modes, can result in serious injury or death to patients with implanted devices with leads. This kind of interaction is not expected with ultrasound diathermy. Electrocautery devices are not included.

Laboratory testing has shown that patients with any implanted metallic lead are at risk of serious injury when exposed to shortwave or microwave diathermy therapy. This is true even if the implanted device is not turned on, and even if the lead is no longer connected to an implanted system. Interaction of the diathermy energy with the implanted lead causes excessive heating in the tissue surrounding the lead electrodes. Insufficient testing has been done to determine whether there is a safe distance between the diathermy applicator and the implant system that might allow patients to be treated with diathermy without risk of injury.

It is recommended that shortwave or microwave diathermy should not be used on patients who have any implanted metallic lead, or any implanted system that may contain a lead. Both the heating and non-heating modes of operation pose a risk of tissue destruction.

Physicians and health care professionals should:

- Explain to the patient what diathermy is, and stress that they should not receive shortwave or microwave diathermy therapy.
- Be sure to ask the patient about possible implants before deciding to administer shortwave or microwave diathermy therapy. If the patient has an implanted lead or an implant containing a lead, diathermy therapy should not be used, even if the implant has been turned off. Examples of implanted systems that may contain a lead include cardiac pacemakers and defibrillators, cochlear implants, bone growth stimulators, deep brain stimulators, spinal cord stimulators, and other nerve stimulators.
- Do not administer shortwave or microwave diathermy therapy to a patient who has had an implant in the past unless you are absolutely certain that the implant and all leads in their entirety have been removed. Note that leads are often left implanted after the implant is removed.

International Nonproprietary Names (INN)

The Programme on International Nonproprietary Names (INNs) was established by the World Health Organization in the 1950s. The main task of the Programme is to designate names for pharmaceutical substances to be used for medical purposes internationally. The advantages of such global unification of terminology are manifold. The use of INNs facilitates mutual understanding of pharmacotherapeutic procedures used in different countries, assists drug regulatory authorities in reviewing documentation submitted in the process of drug licensing or the licensing of generic equivalents, and improves exchange of information and prescribing practices among medical practitioners. In the course of its operations, the INN programme has created names for some 7000 pharmaceutical substances.

Topics highlighted at the meeting of the Expert Group on International Nonproprietary Names (INN) in Geneva in November 2002 included a discussion on fixed-dose combinations and excipients. Two papers were presented for information. The first, set out below, discusses the assignment of INNs to combinations of drug substances. It reviews those INNs which have been used so far and describes experiences in naming drug combinations at fixed doses. Some advantages and disadvantages are presented. Following discussion, the INN Experts identified a number of technical, legal and regulatory obstacles to naming combination products and agreed that the INN system cannot be used for this purpose. They suggested that a new system should be devised for fixed-dose combinations.

The second article, reproduced on page 295, is a technical overview of the selection process for naming of excipients. It was prepared in response to requests for an evaluation of the present situation, and includes a discussion of the various options and consequences for the INN process.

Nomenclature for drug combinations*

For the past fifty years, it has been the task of WHO to assign International Nonproprietary Names (INN) to pharmaceutical substances. Over this period, various policies have been adopted by the INN Programme, and one of these has included the decision not to assign INNs to combinations of drug substances (1). None the less, INNs have been given to some natural product mixtures where active substances of closely related structure and action are isolated together. Examples include antibiotics such as gentamicin, neomycin and polymyxin.

Combinations of drug substances can be prescribed under certain circumstances, such as when substances are required to act synergistically. The combination of trimethoprim and sulfamethoxazole in a fixed proportion 1:5 was developed as an antibacterial agent known in some countries as co-trimoxazole. The individual components were given INNs but not the combination. Recently, because of safety concerns about the sulfa component, use of this combination has declined and trimethoprim is usually prescribed on its own (2).

Because bacterial resistance has developed to penicillins through emergence of penicillinase-producing strains that degrade the antibiotics, inhibitors of penicillinase have been identified that do not themselves possess antibiotic activity but allow a penicillin to exert its full activity by blocking the action of the enzyme (3). The best known of the inhibitors is clavulanic acid which has an INN. It is used only in combination, usually with amoxicillin.

* Background paper prepared for discussion by the INN Expert Group by Professor D. H. Calam, Chair of the British Pharmacopoeia Commission, and former Chair of the European Pharmacopoeia Commission.
In other cases, a combination of drugs is desirable for medical reasons. A combination of levodopa (an amino-acid precursor of dopamine) with a dopa-decarboxylase inhibitor, is the treatment of choice for Parkinson disease. Combinations are available with carbidopa and benserazide and all three compounds have separate INNs. Drug combinations are also prescribed in the treatment of hypertension using a combination of an angiotensin converting enzyme (ACE) inhibitor, such as captopril, with a thiazide diuretic, such as hydrochlorothiazide. Again, the individual drugs each have an INN.

Related combinations of a beta-adrenoreceptor blocking agent, for example atenolol, with diuretics, including chlortalidone or bendroflumethiazide, are also available.

Further examples of combinations are:

• analgesics containing paracetamol or acetylsalicylic acid with a low-dose opioid analgesic, usually codeine;
• potassium-sparing diuretics, such as amiloride, with a thiazide such as hydrochlorothiazide or furosemide;
• antacid preparations with a combination of aluminium and magnesium hydroxides;
• stimulant laxatives containing danthon with a softening agent such as sodium docusate or poloxamer.

Other combinations, either alone or packaged together, are available in addition to the above combinations. Extensively used examples of these products are oral contraceptives and preparations for hormone replacement therapy. Many products are packaged to contain tablets containing only an estrogen with tablets containing both an estrogen and a progestogen. These products are usually prescribed by brand name.

Considerations on use of drug combinations

The value of drug combinations in medical practice is a matter of debate. A combination product is likely to achieve better patient compliance than two separate preparations and it is easier to prescribe using a single name. However, the benefit of some combinations is challenged. With regard to the examples already mentioned, the British National Formulary, an important handbook used in the United Kingdom to aid selection of suitable medicines, says that diuretic combinations may be justified if compliance is a problem, but that a potassium-sparing diuretic such as amiloride is not usually necessary for routine treatment of hypertension (4). Combinations of aspirin/paracetamol with codeine are described as less suitable for use and advantages of use have not been substantiated. Combination antacids are stated to have no clear advantage over single preparations. The benefits of combining antibacterial or antifungal agents with corticosteroids for topical use are also debatable unless there is an associated infection.

An important application of combinations involves oral contraceptives containing both an estrogen and a progestogen. A bewildering array of products is available of different strengths and combinations as well as packs containing combinations of combinations (different types of tablet each with the same active substances but in different doses). In the case of hormone replacement therapy products, tablets containing an estrogen alone and estrogen plus progestogen are packaged together.

Another doubt surrounding fixed combination products is whether the approach of "one size for everyone" is appropriate for optimal treatment of each patient (5). In fact, for many of the combinations mentioned above, different strength combinations are marketed varying from two to six depending on the particular combination. Sometimes, both components are factored — i.e. the ratio remains the same but the amounts differ. In others, only one component changes so that the ratio between the two components is not maintained.

Polyparmacy is now generally discouraged and many licensing authorities are reluctant to approve combinations, especially when more than two components are present. However, older preparations (many of which are available without prescription) do contain complex mixtures. These are mainly marketed for self-medication, and it would be useful to assess their value using current efficacy criteria.

Experience with naming combination products

About 15 years ago, in the hope of increasing generic prescribing to reduce the cost of medicines, the UK nomenclature authorities were asked to develop names for combination products. After vigorous debate, a system was introduced of "co-
names”. The initial list consisted of less than 20 names and has increased to 26 (6). Names were assigned only to combinations of two drug substances. Of these named combinations, pharmacopoeial monographs have been prepared for only 15 because, despite the existence of co-names for almost 15 years, the other combinations have not been considered sufficiently important or widely used to justify development of a monograph.

The initiative described above has met with mixed reactions. Products with the co-prefix caused confusion since some names used similar indicators (for example, -amol for paracetamol combinations and -zide for hydrochlorothiazide). This might be less important for products having similar indications. However, this initiative did not achieve the objective of introducing easily remembered names to be used instead of brand names. It also became clear that a system for indicating dose was required as almost half the combinations were available in different strengths. The method devised was to give an x/y number of the amounts of the two components respectively in any particular combination.

There are other sources of confusion surrounding co-names. Co-dergocrine mesilate (a British Approved Name or BAN), has been assigned to a mixture of four ergot alkaloids containing equal mass proportions of two compounds and a 2:1 ratio of isomers of the third (6). Other approved names for single compounds are potentially confusing with co-names for mixtures, for example codactide and the co-polymer names copovidone and copovithane. Use of a co-prefix as a useful indicator of a combination product has not escaped the notice of devisers of trade names. The names Co-Betaloc® and Co-Plus® are in use and other trade names could be considered as similar to co-names, for example Cosalgesic®, Coracten® and Colazide®.

Attempts to prevent further co-names being registered as trade names for pharmaceutical products have not always been successful.

In the United States of America, a similar system of Pharmacy Equivalent Names (PEN) has been developed (7). Unlike the UK system, these names have no official status and so do not have to appear on the label of the product. They are intended to provide a convenient short name that a prescriber may use in place of a long official title, to be informative and to discourage the use of different trivial names and abbreviations. Fourteen PEN have been issued, of which 8 are identical to the British co-names — in 2 cases using an abbreviation for the United States approved name (USAN). However, no provision is made for the availability of different strengths or ratios of the components. One PEN, co-bucafAPAP, applies to a combination of three active substances: butalbital, acetaminophen and caffeine. USP monographs exist for all the PEN combinations.

Conclusion

It appears that provision of drug combinations may offer benefit, particularly in broader public health interventions, by improving compliance or in cases where resistance is a problem. Nomenclature for drug combinations used in these circumstances will therefore be needed. However, given the limited experience available so far, further studies should be undertaken to determine the best approach and methods to be used.

References:

Naming of excipients: future challenges

Activities of the INN Programme have focused on selecting names for active pharmaceutical substances used in human and veterinary medicine while expanding only incidentally to other types of substances and products used directly or indirectly for health purposes. The rules governing the allocation of INNs are specifically adapted to indicate the therapeutic activity of a single substance and these rules may not be appropriate for naming of other types of products. However, over the years, the success of the Programme has led to requests for expansion into other areas, especially in cases where divergence in naming practices creates difficulties for international cooperation. One possible area highlighted for expansion is the naming of excipients.

At present, the naming of excipients is carried out with regard to chemical composition. Existing approaches to assigning names may include trivial (traditional) names, systematic chemical (IUPAC) names, or International Nonproprietary Names (INNs). Options available for the selection of excipient names include one-word names with syllables indicating specific properties of the substance, or an alphanumeric system.

The International Pharmaceutical Excipients Council (IPEC) has defined pharmaceutical excipients as any substance, other than the pharmacologically active ingredient, that has been appropriately evaluated for safety and is included in a drug delivery system to:

(i) facilitate the process of manufacturing of the medicinal product;

(ii) protect, support or enhance the stability and bioavailability of the active ingredient;

(iii) aid in the identification of the finished product;

(iv) enhance any other attribute of the overall safety and efficacy of the medicinal product during storage or use.

The INN Programme has already named those pharmaceutical substances that may serve a dual purpose as excipients or as pharmacologically active ingredients. INNs have also been assigned to a few specific groups of polymeric excipients such as cellulose derivatives, macrogols, macrogol esters, sorbitan esters, macrogol-sorbitan-fatty acid polymers, polysiloxanes, and poloxamers.

A considerable number of inorganic or simple organic substances are used as excipients. They are usually designated by short systematic names established according to the rules of the International Union of Pure and Applied Chemistry (IUPAC) or by traditional (trivial) names. The same applies to many excipients of plant or mineral origin designated by traditional names. In the case of active substances, the INN Programme avoids a formal recognition of such names, especially if they were in use before the INN Programme came into being. The adoption of such names (or their modified versions) occurs only when there are compelling reasons for such an action. This is done, for example, when the systematic name is considered too long or requires the use of locants or stereodesignators for proper identification of the substance. A comparable situation exists in the case of excipients. If the INN Programme is expanded to include this group of products, it will be necessary to decide whether to adopt a similar policy.

Groups of excipients

The repertoire of excipients available for the manufacture of different dosage forms may be broadly divided into either inorganic or organic substances. The table set out on pages 298–307 gives a brief description of each excipient category and use.

When considering the establishment of a system for naming excipients several approaches may be taken into account. Until now, the INN programme has used the same approach for excipients as that used for selecting INNs for active pharmaceutical substances, i.e. a single word to designate a substance or a group of substances. When a group name is given, the word is usually followed by an Arabic number to describe a distinguishing property of the individual member of the group. This requires the establishment of specific rules for individual groups of substances.

INNs for active substances are selected with regard to their use by physicians in prescribing. For that...
reason, they cannot be cumbersome and the one-word approach is preferred whenever possible. Names have to be distinctive in spelling and sound and to differ from each other to avoid confusion. They also have to differ from existing trademarks, to avoid infringement of intellectual property rights.

The INN programme avoids selecting names for old substances that have well established traditional (trivial) names or names devised according to the rules of chemical nomenclature.

Some of these considerations may also apply to excipients but will need to be modified. Names of excipients are not used by physicians or by the general public but mainly by pharmacy technologists and drug regulatory authorities. For that reason, INNs for excipients use the numbers as part of an excipients name, an approach that is not in use for active substances. A unique system for naming excipients will therefore be needed if the programme is faced with the daunting task of uniformly naming the several hundreds of substances and products currently in use.

One possible system is to retain one-word names composed of syllables each with a specific meaning. A similar system exists at present for naming monoclonal antibodies. This permits the description, in one or two words, of several properties of the product. The drawbacks of the system are that names are polysyllabic, difficult to pronounce, and sometimes quite similar.

Another possible system would be a straightforward alphanumeric code system. Such systems exist in related areas, such as the Colour Index numbering system. For example, CI 16255 for Ponceau 4R; CI 45430 for erythrosine or the European Union food additives nomenclature E 124 for Ponceau 4R; E127 for erythrosine. Similar types of designations (type name, plus a number) are used for excipients by some large-scale manufacturers of these materials. Depending on the number of digits in the numerical part, the system would permit any type of classification to be included, the description (definition) of the substance could contain any desired type of information.

The majority of excipients are mixtures, even if some of them (like inorganic salts and sugars) are essentially homogeneous substances. This creates a specific difficulty as any substance (or a product) designated by a name has to be properly characterized (defined). Whereas the definition of a homogeneous chemical substance is usually straightforward (even if sometimes rather cumbersome for substances of a complex structure), a definition of a mixture is more complicated. It has to include either the designation of the components and of their amounts (e.g. percentage), or provide information on its other properties which will distinguish it in an unequivocal manner.

Various situations exist among non-homogenous excipients. Natural products are usually heterogeneous (e.g. vegetable oils contain mixtures of fatty acids), synthetic polymeric materials may consist of mixtures of homologues with differing molecular mass distribution, some polymer constructs are also mixtures of individual products which may differ in the amounts of components each contains. In all such cases, it is necessary to decide on the type of elements that have to be included in the definition, so that the product can be described properly.

An additional difficulty in defining a product (or a member of a group of substances) is related to the existence of different grades of purity of excipients, usually depending on intended use. There is also the question of whether functionality related properties of excipients should be included in definitions and to what extent.
Excipient nomenclature: some examples

Inorganic Substances

MINERAL ACIDS, BASES AND SALTS
Mineral acids are widely used in diluted form as an acidifying agent in a variety of pharmaceutical and food preparations. A commonly used mineral acid is hydrochloric acid.

Mineral salts are water-soluble and may be used as excipients for various reasons. Many of the salts used in pharmacy are calcium salt, sodium salt or potassium salt. Mineral salts may be added to a pharmaceutical preparation to:

(a) serve as a buffer solution to maintain stability of the active ingredient
(b) provide an ideal ionic strength for stabilisation of the active ingredient
(c) provide an ideal isotonicity for ophthalmic and parenteral preparations
(d) act as an effervescent

Some examples of salts that are used as excipients in pharmaceutical preparations include sodium carbonate, sodium phosphate, sodium chloride, sodium bisulphite, calcium carbonate, calcium bisulphate, calcium sulphate, potassium bicarbonate and potassium phosphate.

Current Nomenclature Approach
Either the chemical names or trivial names are used for this group of substances. In some cases, there are different names assigned to the same substance by different pharmacopeias.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous Disodium Hydrogen Phosphate, Disodium Hydrogen Phosphate Dihydrate, Disodium Hydrogen Phosphate Dodecahydrate (Lat.)</td>
<td>Dibasic sodium phosphate (anhydrous, dihydrate, heptahydrate, dodecahydrate)</td>
<td>Disodium Phosphate, Anhydrous, Disodium Phosphate Dihydrate, Disodium Phosphate Dodecahydrate (Eng.), Dinatrii phosphas anhydricus, dihydricus, dodecahydricus</td>
</tr>
<tr>
<td>Heavy Magnesium Carbonate, Light Magnesium Carbonate</td>
<td>Magnesium carbonate (anhydrous, hydrate)</td>
<td>Magnesium Carbonate Heavy, Magnesium Carbonate Light (Eng.), Magnesii subcarbonas ponderous, Magnesii subcarbonas levis (Lat.)</td>
</tr>
<tr>
<td>Anhydrous Calcium Hydrogen Phosphate, Calcium Hydrogen Phosphate (═ dihydrate)</td>
<td>Dibasic calcium phosphate (anhydrous, dihydrate)</td>
<td>Calcium hydrogen phosphate, anhydrous, Calcium hydrogen phosphate, dihydrate (Eng.), Calcii hydrogenophosphas anhydricus, Calcii hydrogenophosphas dihydricus (Lat.)</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Calcium carbonate</td>
<td>Calcium Carbonate (Eng.) Calcii carbonas (Lat.)</td>
</tr>
</tbody>
</table>
SILICAS
Silicon dioxide ($SiO_2$) is widely used in the manufacture of pharmaceuticals, cosmetics and food products. It is used as an adsorbent, anticaking agent, glidant, suspending agent, tablet disintegrant and viscosity-increasing agent.

Current Nomenclature Approach
Trivial names or chemical names have been adopted by different pharmacopeias.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloidal Anhydrous Silica</td>
<td>Colloidal silicon dioxide</td>
<td>Colloidal anhydrous silica (Eng.), Silica colloidalis anhydrica (Lat.)</td>
</tr>
</tbody>
</table>

SILICATES (NATURAL, SYNTHETIC)
Silicates are complexes or salts of silicic acid. They may be naturally occurring or synthetic. Silicates are commonly employed as excipients in the production of pharmaceuticals as an adsorbent, stabilising agent, suspending agent or viscosity-increasing agent.

Bentonite ($Al_2O_3.4SiO_2.H_2O$) is a naturally occurring hydrated aluminium silicate used primarily in the formulation of suspensions, gels and sols.

Kaolin ($Al_2O_3.2SiO_2.2H_2O$) also a naturally occurring native hydrated aluminium silicate is used in the preparation of both oral and topical preparations.

Magnesium Aluminium Silicate is a complex that is made up of a three-lattice layer of octahedral alumina and two tetrahedral silica sheets. It is used in the formulation of tablets, ointment and creams.

Magnesium trisilicate ($Mg_2Si_3O_8.xH_2O$) is mainly used as a glidant in the manufacture of solid oral dosage forms.

Current Nomenclature Approach
Trivial names have been adopted by pharmacopeias.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium Magnesium Silicate</td>
<td>Magnesium aluminum silicate</td>
<td>Aluminium Magnesium silicate (Eng.) Aluminii magnesii silicas (Lat.)</td>
</tr>
</tbody>
</table>

Organic Substances

Homogenous Substances

MONOALCOHOLS, ETHERS, CARBOXYLIC ACIDS AND PHENOLS (INCLUDING ANTIOXIDANTS AND PRESERVATIVES)
Monoalcohols are short chain aliphatic alcohols that possess only one hydroxyl group. Ethanol is commonly used as a solvent; in addition, it is also employed for its antimicrobial preservative property and its ability to enhance penetration of drugs through the skin. Isopropyl alcohol is used both as a disinfectant and solvent.
Dimethyl ether is a liquefied gas which, when exposed to atmospheric pressure, will undergo vaporisation, hence it is commonly employed as an aerosol propellant.

Organic acids such as ascorbic acid, benzoic acid, citric acid, fumaric acid, lactic acid, malic acid and tartaric acid are widely used as antioxidants or preservatives to prevent degradation of the active ingredient.

**Current Nomenclature Approach**
Trivial names and chemical names have been adopted as non-proprietary names in some pharmacopeias.

**Examples:**

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol (96%)</td>
<td>Alcohol</td>
<td>Ethanol (96 per cent) (Eng.) Ethanolum (96 per centum) (Lat.)</td>
</tr>
<tr>
<td>Chlorobutanol, Anhydrous Chlorobutanol, Anhydrous Chlorobutol</td>
<td>Chlorobutanol (anhdyrous, hemihydrate)</td>
<td>Chlorobutanol anhdyrous, Chlorobutanol hemihydrate (Eng.) Chlorobutanolium anhdyricum, Chlorobutanolium hemihydricum (Lat.)</td>
</tr>
<tr>
<td>Racemethol</td>
<td>Menthol</td>
<td>Menthol, racemic (Eng.) Mentholum racemicum (Lat.)</td>
</tr>
<tr>
<td>Ethyl hydroxybenzoate</td>
<td>Ethylparaben</td>
<td>Ethyl paraphydroxybenzoate (Eng.) Ethylis paraphydroxybenzoas (Lat.)</td>
</tr>
<tr>
<td>Phenoxyethanol</td>
<td></td>
<td>Phenoxyethanol (Eng.) Phenoxyethanolum (Lat.)</td>
</tr>
<tr>
<td>Benzyl Alcohol</td>
<td>Phenylethyl alcohol</td>
<td>Benzyl alcohol (Eng.) Alcohol benzylicus (Lat.)</td>
</tr>
</tbody>
</table>

**MONOSACCHARIDES AND DISACCHARIDES**
Monosaccharide, like dextrose, is used as a tablet and capsule diluent, a sweetening agent as well as a tonicity agent. Glucose is often used as a coating agent, a sweetening agent or a tablet binder. Disaccharide like lactose is commonly used as a tablet or capsule filler. Sucrose is a good sweetening agent, a filler, a viscosity-increasing agent and a sugar-coating agent.

**Current Nomenclature Approach**
Trivial names or chemical names are used.

**Examples:**

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous Glucose Glucose (= mono-hydrate) anhydricum, Gluco-</td>
<td>Dextrose (anhydrous, monohydrate)</td>
<td>Glucose anhdyrous, Glucose monohydrate (Eng.) Glucosum sum monohydricum (Lat.)</td>
</tr>
</tbody>
</table>
DIOLS AND POLYOLS
Hydrocarbons that consist of two or more hydroxyl groups are called diols and polyols respectively. Glyc-
erol, for example, is used as an emollient, a humectant or a plasticizer. Sometimes the hydroxyl groups
are sourced to give a range of esters that are commonly used as non-ionic emulsifying agents (eg.
glyceryl monooleate, glyceryl palmitostearate). Some diols and polyols are used as sweetening agents

Current Nomenclature Approach
Both trivial names and chemical names have been used.

Example:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol</td>
<td>Glycerin</td>
<td>Glycerol</td>
</tr>
</tbody>
</table>

SWEETENING AGENTS
Sweetening agents are added to a formulation to mask the unpalatable taste of some medicine. There
are a few sweetening agents that are commonly used in pharmaceuticals. These include mannitol, xylitol,
saccharin, sucrose, sorbitol and aspartame.

Current Nomenclature Approach
The trivial names of these sweetening agents are used.

Natural Substances

VEGETABLE OILS
Vegetable oils are natural oils that are usually obtained directly from the seeds of a plant. Pharma-
ceutically, appropriately processed vegetable oils are used as vehicle or solvent for drugs. Some of the
widely used vegetable oils are peanut oil, soybean oil, corn oil, canola oil, cottonseed oil and sesame oil.
Sometimes, oil can be hydrogenated to give special quality, e.g. hydrogenated castor oil that is used
either as an extended release agent, a stiffening agent or a tablet or capsule lubricant.

Current Nomenclature Approach
Trivial names are commonly used.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachis oil</td>
<td>Peanut oil</td>
<td>Arachidis oleum</td>
</tr>
</tbody>
</table>

FATS
Fats are solid or semi-solid fatty substances. They are usually obtained from animal sources. The most
commonly used fat in the manufacture of ointment or cream is lanolin.

Current Nomenclature Approach
The trivial name is used. Different names are used for lanolin depending on the literature.

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wool fat</td>
<td>Lanolin</td>
<td>Adeps lanae</td>
</tr>
</tbody>
</table>
FATTY ACIDS AND THEIR SALTS AND ESTERS
Fatty acids are long chain aliphatic carboxylic acids. They can be converted into salts and esters chemically and are used as emulsifying agents or tablet/capsule lubricants. Some of the commonly used fatty acids and derivatives are stearic acid and its sodium, magnesium, calcium and zinc salts; oleic acid; palmitic acid; sodium stearyl fumarate; ethyl oleate, glyceryl monooleate, isopropyl palmitate etc. This group also includes products obtained by partial esterification of a fatty acid with sorbitol and its mono and di-anhydrides, known as Spans®.

Current Nomenclature Approach
Trivial names are used for aliphatic fatty acids and their derivatives. INN names are given to sorbitan esters.

Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan laurate</td>
<td>Sorbitan monolaurate</td>
<td>Sorbitan laurate</td>
</tr>
<tr>
<td>Sorbitan palmitate</td>
<td>Sorbitan monopalmitate</td>
<td>Sorbitan palmitate</td>
</tr>
<tr>
<td>Sorbitan trioleate</td>
<td>Sorbitan trioleate</td>
<td>Sorbitan trioleate</td>
</tr>
</tbody>
</table>

Polymeric Materials

NATURAL HOMOPOLYMERS

STARCHES
Starches are obtained from different sources and can be modified differently to give a range of different physicochemical properties and usages. There are starch, sterilizable starch, pregelatinised starch and sodium starch glycolate. Starch is often used as a disintegrant in tablets or capsules. It is also a main ingredient in dusting powder.

Current Nomenclature Approach
Trivial names are given to describe starch variety.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maize Starch, Potato Starch, Rice Starch, Tapioca Starch, Wheat Starch</td>
<td>Starch (corn, potato, tapioca, wheat)</td>
<td>Corn starch, Potato starch, Rice starch, Wheat starch (Eng.) Maydis amylum, Solani amylum, Oryzae amylum, Tritici amylum (Lat.)</td>
</tr>
<tr>
<td>Pregelatinised starch - (Pregelatinised Maize Starch)</td>
<td>Pregelatinised starch</td>
<td>Pregelatinised starch (Eng.) Amylum pregellificatum (Lat.)</td>
</tr>
</tbody>
</table>

DEXTRINS
Dextrin is starch that is partially hydrolysed. Cyclodextrins are cyclic oligosaccharide with at least 6 D-(+)-glucopyranose units attached by a (1-> 4) glucoside bonds. There are 3 types of cyclodextrins, namely α, β, and γ-cyclodextrins. β-cyclo-dextrin yields cyclodextrin of different physicochemical properties. Examples of the sourced β-cyclodextrins are dimethyl-β-cyclodextrin, trimethyl-β -cyclodextrin, 2-hydroxyethyl-β -cyclodextrin, 2-hydroxypropyl-β -cyclodextrin and 3-hydroxypropyl-β -cyclodextrin.
Current Nomenclature Approach

<table>
<thead>
<tr>
<th>INN</th>
<th>Systematic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfadex</td>
<td>α-cyclodextrin</td>
</tr>
<tr>
<td>betadex</td>
<td>β-cyclodextrin</td>
</tr>
</tbody>
</table>

**CELLULOSES**

Cellulose is obtained from plant materials and has been sourced and processed into various forms for a wide range of applications. These include powdered cellulose, microcrystalline cellulose (obtained by partial depolimerization of cellulose), carboxymethylcellulose calcium/sodium, cellulose acetate phthalate, ethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc. These different types of cellulosic derivatives are used as stabilising agent, suspending agent, disintegrating agent for tablets and capsules, viscosity increasing agent.

**CELLULOSE ESTERS**

Current Nomenclature Approach

The present INN approach for naming cellulose esters is the following:

(i) esters with one acidic residue: a two-word name (= INNM approach)

(ii) esters with several different acidic residues: a one word name with a cell- prefix and -ate suffix.

Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate</td>
<td>(INNM) cellulose acetate phthalate</td>
</tr>
<tr>
<td>Cellacetate</td>
<td></td>
</tr>
</tbody>
</table>

**CELLULOSE ETHERS**

Current Nomenclature Approach

Present INN approach for naming cellulose ethers is to create a one word name with an -ellose suffix.

For esters of cellulose ethers with one acidic residue - a two-word name (= INNM approach), e.g. hypromellose phthalate.

Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>USP</th>
<th>Systematic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyprolose</td>
<td></td>
<td>Hydroxypropylcellulose</td>
</tr>
<tr>
<td>Hypromellose</td>
<td></td>
<td>Hydroxypropylcellulose</td>
</tr>
<tr>
<td>Carmellose</td>
<td></td>
<td>Carboxymethylcellulose</td>
</tr>
<tr>
<td>Hyetellose</td>
<td>Carboxymethylcellulose</td>
<td>Hydroxypropylcellulose as USP</td>
</tr>
<tr>
<td>Methylcellulose *</td>
<td></td>
<td>Hydroxyethylcellulose</td>
</tr>
<tr>
<td>* retained as well-established name</td>
<td></td>
<td>Cellulose methyl ether</td>
</tr>
</tbody>
</table>

**MODIFIED CELLULOSE ETHERS**

Current Nomenclature Approach

Present INN approach for naming modified cellulose ethers is to create a one word name with an -ellose suffix.
PROTEINS
Proteins are macromolecules of polypeptides and are often derived from animal or human sources. Albumin is the smallest plasma protein that is used commonly as a stabilising agent in injectables. Gelatin is a mixture of purified protein fraction obtained either by partial acid hydrolysis or alkaline partial hydrolysis of animal collagen. Gelatin is used as coating agent, film former and gelling agent.

Current Nomenclature Approach
Trivial names are used.

Example:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin - types A, B</td>
<td>Gelatin - types A, B</td>
<td>Gelatin (Eng.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gelatinum (Lat.) - types A, B</td>
</tr>
</tbody>
</table>

Synthetic homopolymers

POLYETHYLENE GLYCOLS
Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations.

Current Nomenclature Approach
The nomenclature adopted indicates the molecular mass of the polymer.

Example:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrogol</td>
<td>polyethylene glycol of general formula H-(OCH2CH2)n-OH, where n varies from 3 to 225 appropriately. Each macrogol name is followed by a number corresponding approximately to its average molecular mass</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrogol</td>
<td>Polyethylene glycol</td>
<td>Macrogol (Eng.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrogolum (Lat.)</td>
</tr>
</tbody>
</table>

POLYETHYLENE GLYCOL ESTERS
Polyethylene glycol esters are used as surfactants (emulsifying agents).

Current Nomenclature Approach
The nomenclature adopted indicates the molecular mass of the polymer.
Example:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrogol esters</td>
<td>monoester derived from a polyethylene glycol and a fatty acid of general formula H-(OCH₂CH₂)n-OOCR. Each macrogol ester name is followed by a number corresponding approximately to the average molecular mass of the polyethylene glycol portion, e.g. macrogol laurate 600, macrogol oleate 600, macrogol stearate 400, 600, 1000 and 2000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INN</th>
<th>USAN NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrogol Stearate 400</td>
<td>Polyoxyl 8 Stearate</td>
</tr>
<tr>
<td>Macrogol Stearate 2000</td>
<td>Polyoxyl 40 Stearate</td>
</tr>
</tbody>
</table>

POLYMETHYLACRYLATES
Poly(meth)acrylates are methacrylic acid copolymers. This group includes a fully polymerised copolymer of methacrylic and acrylates of acrylic or methyl-acrylic esters. There are 3 types of polymethylacrylates (type A, B and C) that are defined according to the methacrylic acid content and solution viscosity. Polyacrylates are primarily used in oral capsule and tablet formulations as film coating agents.

Current Nomenclature Approach
Trivial names are used.

Examples:

<table>
<thead>
<tr>
<th>BP</th>
<th>USP/USPNF</th>
<th>PhEur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonio methacrylate</td>
<td>Methacrylic acid</td>
<td>Methacrylic Acid</td>
</tr>
<tr>
<td>-</td>
<td>copolymer</td>
<td>-</td>
</tr>
<tr>
<td>Methacrylic Acid - Methyl</td>
<td>Methacrylic acid</td>
<td>Methacrylic Acid</td>
</tr>
<tr>
<td>Methacrylate Copolymer (1:1)</td>
<td>- type A</td>
<td>-</td>
</tr>
<tr>
<td>Methacrylic Acid - Methyl</td>
<td>Methacrylic acid</td>
<td>Methacrylic Acid</td>
</tr>
<tr>
<td>Methacrylate Copolymer (1:2)</td>
<td>- type B</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>Methacrylic acid</td>
<td>Methacrylic Acid</td>
</tr>
<tr>
<td>Methacrylate Copolymer (1:2)</td>
<td>- type C</td>
<td>-</td>
</tr>
</tbody>
</table>

POLYVINYL ALCOHOL
Polyvinyl alcohol is a polymer that can be represented by the empirical formula of (C₂H₄O)n, in which the average value of n lies between 500–5000. Various grades with different viscosities and molecular weights are commercially. It is used primarily in topical pharmaceutical formulations, particularly in ophthalmic products.

Current Nomenclature Approach
Trivial names are adopted.

SILICONES
Silicones are used in barrier creams and as lubricants.
Current Nomenclature Approach

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimeticone</td>
<td>poly(dimethylsiloxane) – each name is followed by a number referring to the viscosity of the substance</td>
</tr>
<tr>
<td>Dimeticone 20</td>
<td>viscosity of 17.0 to 23.0 centistokes</td>
</tr>
<tr>
<td>Dimeticone 350</td>
<td>viscosity of 330 to 370 centistokes</td>
</tr>
</tbody>
</table>

Heteropolymers and mixtures

Natural heteropolymers

**GUMS AND RESINS**
Gums are formed upon injury of the plant or as a result of unfavourable conditions, such as drought, by the breakdown of cell walls. Gums upon hydrolysis will yield a mixture of sugars and uronic acids. Resins are complex mixtures of resin acids, resin alcohols, resin phenols and esters. Gums and resins are used pharmaceutically as emulsifying agents, stabilizing agents and suspending agents. Some examples include: guar gum, acacia and xantha gum.

Current Nomenclature Approach
Trivial names, frequently indicating botanical origin, are used.

**WAXES**
Waxes are natural mixtures containing appreciable quantities of esters derived from higher monohydric alcohols of methyl alcohol series combined with fatty acids. Waxes include products such as carnauba wax, microcrystalline wax, white wax, yellow wax and spermaceti wax.

Current Nomenclature Approach
Trivial names are used.

Synthetic and semisynthetic heteropolymers

**POLYETHYLENEGLYCOL-POLYPOLYPROPYLENEGLYCOL COPOLIMERS**
Polyethylenglycol-polypropylenglycol copolimers are used as ointment bases, suppository bases, tablet binders, emulsifying agents, tablet coating agents, may be also used as solubilizers and stabilizers.

Current Nomenclature Approach
Example:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloxamer</td>
<td>(\alpha)-hydro-(\omega)- hydroxypoly(oxyethylene) poly (oxypropylene)poly(oxyethylene) block copolymer; Each poloxamer name is followed by a number, e.g. poloxamer 188, 331, 407, etc. The first two digits multiplied by 100 correspond to the approximate average molecular mass of the poly(oxypropylene) portion; the third digit multiplied by 10 corresponds to the percentage by weight of the poly(oxyethylene) portion</td>
</tr>
</tbody>
</table>

**POLYETHYLENEGLYCOL-SORBAN-FATTY ACID POLYMERS**
Heteropolymers of polyoxyethylene, cyclic sorbitol anhydrides and fatty acids, known as Tweens®, are used as surfactants.
Current Nomenclature Approach

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate</td>
<td>poly(oxyethylene) derivative of cyclic sorbitol anhydrides with a fatty acid</td>
</tr>
</tbody>
</table>

Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>polyethylene 20 sorbitan* monolaurate</td>
</tr>
<tr>
<td>Polysorbate 55</td>
<td>polyethylene 20 sorbitan* tristearate</td>
</tr>
<tr>
<td>Polysorbate 85</td>
<td>polyethylene 20 sorbitan* trioleate</td>
</tr>
</tbody>
</table>

*polyoxyethylene 20 sorbitan corresponds to tris(polyethylene glycol 300) sorbitan ethers

CROSS-LINKED STARCHES
Microspheres produced by reaction of partially hydrolysed starch with epichlorhydrin are degradable by amylase. They are used as carriers in modified release dosage forms.

Current Nomenclature Approach
Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amilomer</td>
<td>Microspheres produced by reaction of partially hydrolysed starch with epichlorhydrin; half-life &lt; 120 min. The name is followed by a hyphenated numerical code in which the number preceding the hyphen indicated the half-life in minutes and that following the hyphen indicates the mean diameter of the microspheres in µm; e.g. amilomer 25-45 has a half life of 25 min. and a mean diameter of 45 µm</td>
</tr>
<tr>
<td>Cadexomer</td>
<td>Microspheres produced by reaction of partially hydrolysed starch with epichlorhydrin; half-life &gt; 120 min. The name is followed by a number referring to the mean diameter in µm of the microspheres; e.g. cadexomer 110</td>
</tr>
<tr>
<td>Eldexomer</td>
<td>Microspheres produced by reaction of partially hydrolysed starch with epichlorhydrin; half-life &gt; 120 min. The name is followed by a number referring to the mean diameter in µm of the microspheres; e.g. eldexomer 60</td>
</tr>
</tbody>
</table>

CROSS-LINKED POLYMERS OF ACRYLIC ACID AND CARBOHYDRATES
Polymers of acrylic acid cross-linked with allyl ethers of sucrose are used as emulsifying and thickening agents.

Current Nomenclature Approach
Examples:

<table>
<thead>
<tr>
<th>INN</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbomer</td>
<td>Polymer of acrylic acid cross-linked with allyl sucrose</td>
</tr>
</tbody>
</table>
### ATC/DDD Classification (final)

The following final anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 14–15 March 2002. They came into force on 1 September 2002 and are included in the January 2003 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whoccm@nmnd.no.

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/Common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>New ATC level codes (other than 5th level):</td>
<td></td>
<td>L01CX</td>
</tr>
<tr>
<td>Other plant alkaloids and natural products</td>
<td></td>
<td>C10AC04</td>
</tr>
<tr>
<td>New ATC 5th level codes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alemtuzumab</td>
<td>L01XC04</td>
<td></td>
</tr>
<tr>
<td>colesevelam</td>
<td>C10AC04</td>
<td></td>
</tr>
<tr>
<td>diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B</td>
<td>J07CA09</td>
<td></td>
</tr>
<tr>
<td>dodeclonium bromide, combinations</td>
<td>D08AJ59</td>
<td></td>
</tr>
<tr>
<td>escitalopram</td>
<td>N06AB10</td>
<td></td>
</tr>
<tr>
<td>estriol</td>
<td>G03CC06</td>
<td></td>
</tr>
<tr>
<td>ezetimibe</td>
<td>C10AX09</td>
<td></td>
</tr>
<tr>
<td>gefitinib</td>
<td>L01XX31</td>
<td></td>
</tr>
<tr>
<td>iodine (¹³¹I) human albumin</td>
<td>V09XA03</td>
<td></td>
</tr>
<tr>
<td>laronidase</td>
<td>A16AB05</td>
<td></td>
</tr>
<tr>
<td>nitric oxide</td>
<td>R07AX01</td>
<td></td>
</tr>
<tr>
<td>parecoxib</td>
<td>M01AH04</td>
<td></td>
</tr>
<tr>
<td>pleconaril</td>
<td>J05AX06</td>
<td></td>
</tr>
<tr>
<td>povidone-iodine</td>
<td>S01AX18</td>
<td></td>
</tr>
<tr>
<td>protein C</td>
<td>B01AD12</td>
<td></td>
</tr>
<tr>
<td>rosvavastatin</td>
<td>C10AA07</td>
<td></td>
</tr>
<tr>
<td>telithromycin</td>
<td>J01FA15</td>
<td></td>
</tr>
<tr>
<td>tenofovir disoproxil</td>
<td>J05AF07</td>
<td></td>
</tr>
<tr>
<td>trabectedin</td>
<td>L01CX01</td>
<td></td>
</tr>
<tr>
<td>valdecoxib</td>
<td>M01AH03</td>
<td></td>
</tr>
<tr>
<td>valganciclovir</td>
<td>J05AB14</td>
<td></td>
</tr>
<tr>
<td>vardenafil</td>
<td>G04BE09</td>
<td></td>
</tr>
<tr>
<td>zonisamide</td>
<td>N03AX15</td>
<td></td>
</tr>
</tbody>
</table>

**Change of ATC codes:**

**Previous:**
chondroitin sulfate

**New:**
chondroitin sulfate

M09AX02
M01AX25
### ATC name changes

Previous: Nucleoside reverse transcriptase inhibitors  
New: Nucleoside and nucleotide reverse transcriptase inhibitors  

### New DDDs:

<table>
<thead>
<tr>
<th>INN/common name</th>
<th>DDD</th>
<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>amisulpride</td>
<td>0.4</td>
<td>mg</td>
<td>O</td>
<td>N05AL05</td>
</tr>
<tr>
<td>caspofungin</td>
<td>50</td>
<td>mg</td>
<td>P</td>
<td>J02AX04</td>
</tr>
<tr>
<td>choriogonadotropin alfa</td>
<td>0.25</td>
<td>mg</td>
<td>P</td>
<td>G03GA08</td>
</tr>
<tr>
<td>colesevelam</td>
<td>3.75</td>
<td>g</td>
<td>O</td>
<td>C10AC04</td>
</tr>
<tr>
<td>escitalopram</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N06AB10</td>
</tr>
<tr>
<td>nitisinone</td>
<td>20</td>
<td>mg</td>
<td>O</td>
<td>A16AX04</td>
</tr>
<tr>
<td>olanzapine</td>
<td>10</td>
<td>mg</td>
<td>P</td>
<td>N05AH03</td>
</tr>
<tr>
<td>telithromycin</td>
<td>0.8</td>
<td>g</td>
<td>O</td>
<td>J01FA15</td>
</tr>
<tr>
<td>valganciclovir</td>
<td>0.9</td>
<td>g</td>
<td>O</td>
<td>J05AB14</td>
</tr>
</tbody>
</table>

### DDD changes:

**Previous:** folic acid  
0.3* mg O  
10** mg O  

**New:** folic acid  
0.4 mg O  

* Prophylactic dose  
** Therapeutic dose. Parenteral therapeutic dose unchanged
The following temporary anatomical therapeutic chemical (ATC) classifications, defined daily doses (DDDs) and alterations were agreed at a meeting of the WHO International Working Group for Drug Statistics Methodology which took place on 23–24 October 2002. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology, e-mail: whocc@nmd.no, before 1 February 2003. If no objections are received before this date, the new ATC codes and DDDs will be considered final and be included in the January 2004 issue of the ATC Index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

**ATC/DDD Classification (temporary)**

<table>
<thead>
<tr>
<th>ATC level</th>
<th>INN/Common name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New ATC level codes (other than 5th levels):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>adalimumab</td>
<td>L04AA17</td>
</tr>
<tr>
<td>Other anterior pituitary hormones and analogues</td>
<td>adefovir dipivoxil</td>
<td>J05AF08</td>
</tr>
<tr>
<td>Prostaglandin analogues</td>
<td>afelimomab</td>
<td>L04AA16</td>
</tr>
<tr>
<td></td>
<td>aleecept</td>
<td>L04AA15</td>
</tr>
<tr>
<td></td>
<td>aluminium diacetate</td>
<td>D10AX05</td>
</tr>
<tr>
<td></td>
<td>argatroban</td>
<td>B01AE03</td>
</tr>
<tr>
<td></td>
<td>benidipine</td>
<td>C08CA15</td>
</tr>
<tr>
<td></td>
<td>beraprost</td>
<td>B01AC19</td>
</tr>
<tr>
<td></td>
<td>bimatoprost</td>
<td>S01EE03</td>
</tr>
<tr>
<td></td>
<td>carbon dioxide</td>
<td>V03AN02</td>
</tr>
<tr>
<td></td>
<td>ciclesonide</td>
<td>R03BA08</td>
</tr>
<tr>
<td></td>
<td>combinations</td>
<td>D06AX30</td>
</tr>
<tr>
<td></td>
<td>docosanol</td>
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<tr>
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<td>etilevodopa and decarboxylase inhibitor</td>
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<td>helium</td>
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### New ATC 5th level codes (continued)

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<td>lanthanum carbonate</td>
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<tr>
<td>N04BA03</td>
<td>levodopa, decarboxylase inhibitor and COMT inhibitor</td>
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<td>S01AX19</td>
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<tr>
<td>N07BC04</td>
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<td>rifampicin, pyrazinamide, ethambutol and isoniazid</td>
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#### ATC code changes:

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<td>lepirudin</td>
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#### ATC name changes:

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
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</thead>
<tbody>
<tr>
<td>ethambutol, combinations</td>
<td>ethambutol and isoniazid</td>
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<tr>
<td>rifampicin, combinations</td>
<td>rifampicin and isoniazid</td>
</tr>
<tr>
<td>somatropin and analogues</td>
<td>somatropin and somatropin agonists</td>
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<tr>
<td>streptomycin, combinations</td>
<td>streptomycin and isoniazid</td>
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<tr>
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### New DDDs:

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<th>DDD</th>
<th>Unit</th>
<th>Adm.R</th>
<th>ATC code</th>
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* Temporary ATC code

### Change of DDDs:

- Previous: levofloxacin 0.25 g O,P
- New:        levofloxacin 0.5 g O,P J01MA12