TABU

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Editorial

An increased focus on the aims and responsibilities of drug marketing

From time to time drug marketing targeted at doctors – recently also at pharmacists – arouses criticism and public debate. There is a special feature in this type of marketing which applies to both target groups, i.e. doctors in their role as prescribers and pharmacy personnel as far as generic substitution is concerned. They both have an influence on the choice of drug and therefore also on the costs borne by the patient and society. In addition to the legal provisions governing marketing in general, drug marketing is also governed by detailed restrictions referred to in the Medicines Act and Decree and common to all EU countries. These provisions limit the content of the information distributed in marketing as well as the means by which marketing is targeted at various groups.

As regards drug marketing, Section 92 of the Medicines Act lays down the framework for contacts between pharmaceutical companies and health care personnel as follows: *Medicinal product sales promotion targeted at health care personnel and veterinarians, such as various benefits and gifts, must be modest in terms of economic value and must be related to their professional activities. In the case of sales promotion events, hospitality must be moderate and secondary in relation to the purpose of the event, and it must not extend beyond health care personnel. Sales promotion must not be inappropriate or of such a nature that it can be considered to endanger public trust in the impartiality of prescription, use or supply of medicinal products.*

Persons entitled to prescribe or supply medicinal products must not ask for or accept any inducement prohibited in subsection 1 or otherwise in violation of what is provided therein.

The main aim of the provision is to ensure independence: the patient must be able to be confident that there are professional grounds for the prescription and supply of the drugs independent of marketing. As regards benefits, gifts and hospitality, it is emphasised that they should be of minimal economic importance and moderate. The formulation of the provision states the guidelines in principle, but there are no precise restrictions for normal daily activities. What is "modest in terms of economic value" or "moderate" depends on the generally accepted perceptions in society at the time. Nor is the National Agency for Medicines in the Medicines Act and Decree given the authority to issue more precise guidelines. The limits in practice are therefore set by the operation of control measures.

The quotation from the Medicines Act above is followed by a second subsection which goes on to emphasise the responsibility of those who are the target persons of marketing and prohibits them from asking for or accepting any unlawful inducement, to which usually little attention is paid. The reform of the Medicines Act in 2004 laid down that the responsibility for control in this issue was in the hands of the provincial governments and the National Board of Medicolegal Affairs.

In addition to the control exercised by the authorities, drug marketing is also governed by effective internal control within the industry itself. A review of the code applicable in the industry, the Finnish Code for the Marketing of Medicinal Products, was carried out at the end of last year, and the restrictions contained in it are now more precise in practice, especially with regard to events, travel and hospitality, as well as other inducements organised and/or offered by the industry. These more precise restrictions also correspond to the authorities' perception of appropriate marketing restrictions, and there are good grounds for expecting that this will lead to reduced need for supervision by the authorities.

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Own observation of an ADR

Agranulocytosis caused by Iruxol ointment

Agranulocytosis caused by chloramphenicol is a generally well-known adverse drug reaction, on account of which chloramphenicol tablets have not been available for decades. Nevertheless, chloramphenicol is still used in eye ointments and, for example, in an ointment called Iruxol which is used in the treatment of necrotic lesions. One gram of the ointment contains 0.6 IU of clostridiopeptidase A and 10 mg of chloramphenicol.

I would like to describe a case of agranulocytosis caused by the ointment in a patient with a heel lesion.

My patient is a 90-year-old female. She has coronary artery disease and degenerative osteoarthritis and she is hard of hearing. Apart from that, she has been in good condition and self-supporting. She suffered a fracture in her left hip on 22.11.2004, which was repaired using a gamma nail. The postoperative treatment went well and the patient became mobile again. However, a pressure sore developed in the left heel, prolonging the hospital treatment. The sore was treated with Iruxol ointment during 28.12.2004–10.2.2005, followed by Normgel, a moisturising gel. Suddenly on 24.2.2005 the patient developed a high fever with no special focal symptoms present. B-CRP was 294 mg/l and the blood count revealed agranulocytosis with WBC count of 0.6 x 10^9/l. The patient was transferred in a septic state for treatment at a central hospital. The medical treatment at the transferral stage consisted of the following: Oftagel 2.5 mg/g one drop x 4 in the eyes, Nitrosid 5 mg x 3, Furesis 40 mg x 2, Seloken 50 mg x 2, Primaspan 100 mg x 1, Panadol Forte 1 g x 3, Viscotears 2 mg/g 1 drop x 3 in the eyes, Agiolax 5 ml x 1, Insomin 5 mg x 1.

On arrival at the central hospital the patient's blood leukocytes were at their lowest 0.7 x 10^9/l and the patient was in agranulocytosis. B-CRP was at 417 mg/l on arrival. The patient had a slight temperature and her general condition was poor. The initial treatment consisted of tobramycin and ceftriaxone intravenously. She was also initially given filgrastim, a granulocyte colony-stimulating factor. The medication proved effective and B-CRP started to drop and the leukocyte values improved. There was no growth present in the blood cultures, but the urine sample showed a growth of *E. coli* bacteria in excess of 10^5. The pressure sore in the heel was initially very inflamed and painful. The situation has improved with topical treatment and debridements. The patient's general condition is distinctly improved. Treatment with acetylsalicylic acid has been stopped at the hospital, but otherwise the medical treatment continues unchanged at the time of transferral to a health centre.

The patient is recovering well at the health centre. She has regained her usual mobility and self-supporting lifestyle and moves about with a zimmer. Epithelialization of the extensive pressure sore in the heel is taking place gradually and plans have been made to discharge the patient within the following few weeks.

Discussion

There were immunological mechanisms involved in the agranulocytosis caused by chloramphenicol. Toxicity is associated with idiosyncrasy, which means that the patient's reaction to a small drug dose is often different and more intense than usual without its being a question of hypersensitivity to the drug.

The practice of naming the product, Iruxol, is unusual. It may be possible that the prescriber easily overlooks the fact that, in addition to clostridiopeptidase A, Iruxol ointment also contains chloramphenicol, whereas Iruxol Mono only contains the enzyme.

In addition to this case, seven other cases of suspected ADRs in association with the use of Iruxol have been recorded in the ADR database of the Finnish National Agency for Medicines. All reports were associated with skin reactions; in some cases the rash had also spread outside the treated area, and one patient had conjunctivitis in addition. This was exacerbated by the use of the eye ointment containing chloramphenicol. In two cases, an epicutaneous test was positive with chloramphenicol, in one case with Iruxol.

My own patient recovered from agranulocytosis. She could also just as easily have succumbed to it. In individual practice, cases such as this are extremely rare, but it may guide the use of antibiotics in future throughout the entire career of the prescriber. An eye ointment containing chloramphenicol is a conventional method of treatment following, for example, the removal of a foreign object in the cornea. There is no broad spectrum antibiotic ointment to replace it. There are several eye drops containing antibiotics which may be used. But they do not have the broad antibacterial spectrum of chloramphenicol.

In using of Iruxol, the allergising effect of the ointment is worth bearing in mind, together with the possibility of blood count changes especially with long-term use and in the treatment of extensive areas.

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The growing consumption of hypnotics and sedatives evens out

Temazepam and nitrazepam of the conventional benzodiazepines, and short-acting midazolam and triazolam, are classified as hypnotics and sedatives (ATC Code N05CD). The more recent hypnotics and sedatives include zopiclone and zolpidem (ATC Code N05CF) with a structure different from benzodiazepines but with similar properties.

Among the Nordic countries only Iceland has a higher consumption of hypnotics and sedatives than Finland. There has been a rapid increase in the consumption of hypnotics of the benzodiazepine type, especially zopiclone, in all the Nordic countries. In the rest of the Nordic countries, along with their increase, the consumption of the common benzodiazepines has dropped (Fig. 1). In Finland, in addition to zopiclone, the consumption of the most commonly used benzodiazepine, temazepam, was on the increase up to the year 2003 (Fig. 2). In 2004, for the

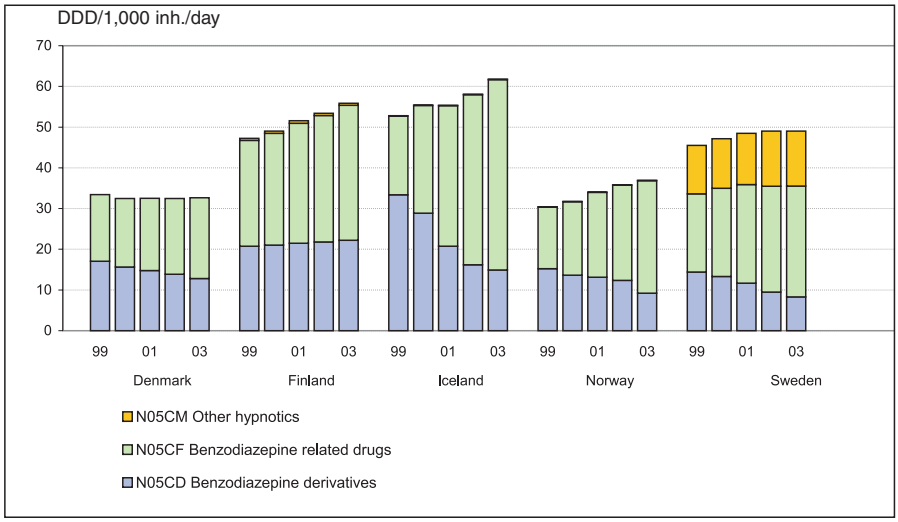

Fig. 1. The consumption of hypnotics and sedatives in Nordic countries 1999–2003

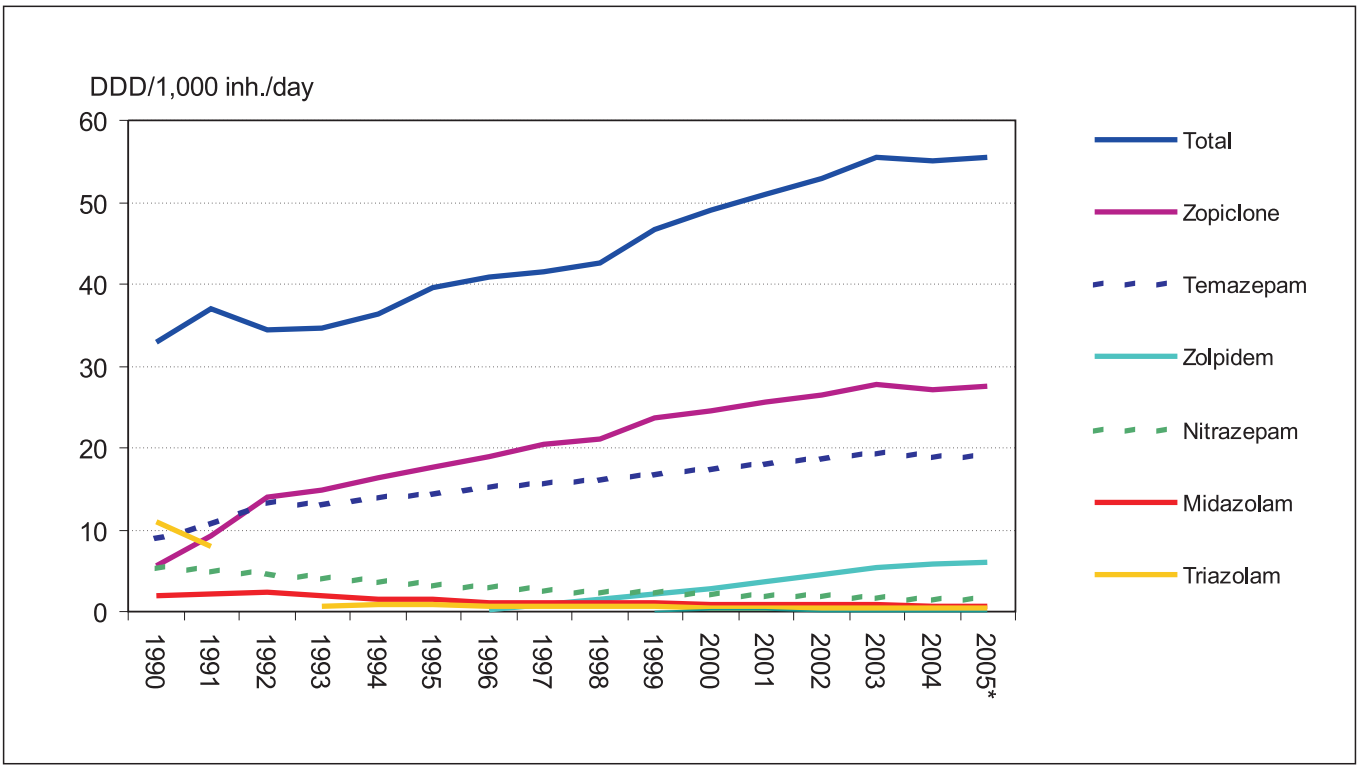

Fig. 2. The consumption of hypnotics and sedatives in Finland 1990–2005 (I–IV)*

first time in a decade, the consumption of hypnotics and sedatives remained at a slightly lower level compared with the previous year. Only the sales of zolpidem, with minor sales compared with other hypnotics, increased by 9%.

In the treatment of sleep disturbances, it is emphasised that the use of drugs should be as short-term as possible. The possibility of adverse effects and development of tolerance is reduced by temporary and occasional use. However, the majority of total sales of sleeping tablets in primary care consists of packets containing 100 tablets. The proportion of packets intended for the recommended treatment period of 7–14 days is only 3% of the sales (Fig. 3). Only zolpidem is sold almost exclusively in packets of 20 tablets (Fig. 4).

The consumption of all hypnotics and sedatives is in hospital care 8%. The proportion has slightly diminished in recent years: it was 11% in 1999 (Fig. 5). The relatively small proportion of institutional consumption may be associated with the fact that the consumption of antipsychotics in Finland is almost double that in the other Nordic countries. (In 2003, their consumption in Sweden totalled 8.7 DDD/1,000 inhabitants/day, whereas the corresponding figure in Finland was 16.1). A proportion of this medication is probably associated with unspecific sedation more than with actual treatment of psychosis.

Among benzodiazepines, those most commonly sold, diazepam, oxazepam and lorazepam, are included in the group of anxiolytics in the statistics (N05BA), even though a proportion of their use is at least in part due to sleeping difficulties. Their consumption has not varied in any significant way in recent years.

The consumption of medicines is presented in daily doses, in proportion to the population and time. The figure represents, in promilles, the proportion of the population that has used the defined daily dose of the medicinal substance every day.

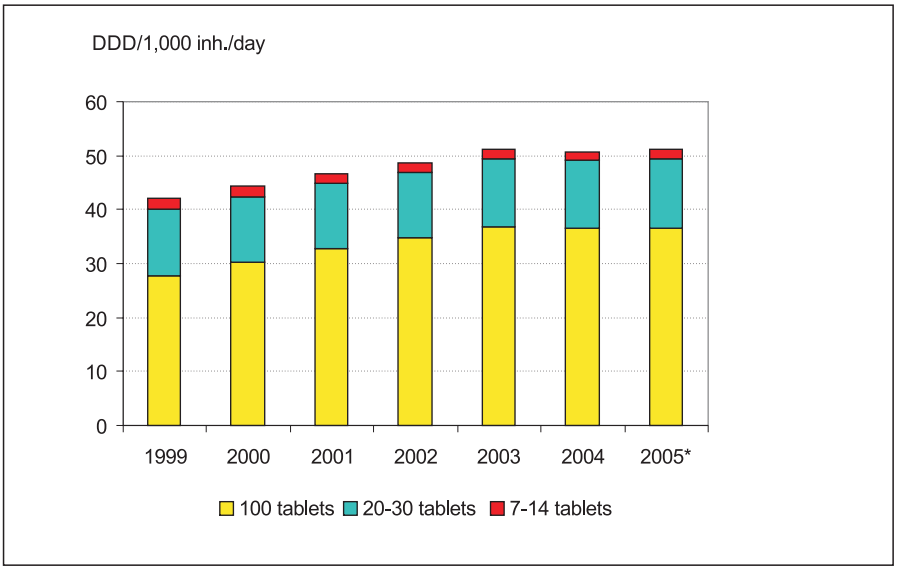

Fig. 3. The consumption of hypnotics and sedatives in the package sizes in Finland 1999–2005 (I–IV)*

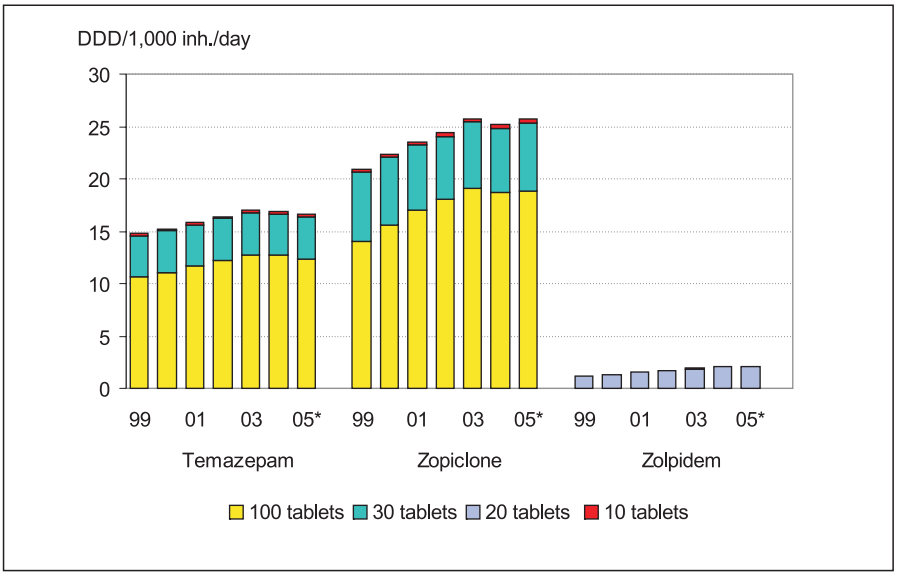

Fig. 4. The consumption of most common hypnotics and sedatives in the package sizes in Finland 1999–2005 (I–IV)*

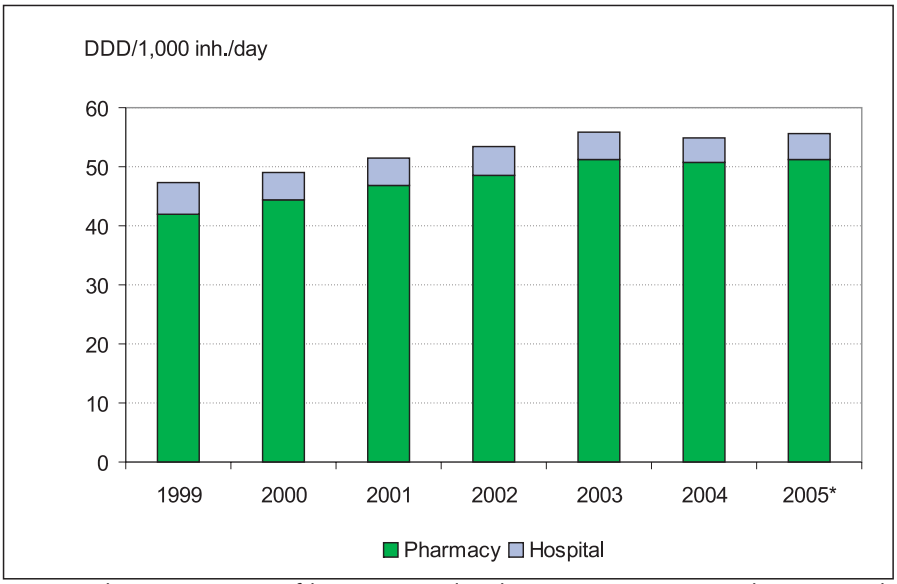

Fig. 5. The consumption of hypnotics and sedatives in outpatient and institutional care in Finland 1999–2005 (I–IV)*

New functional guidance for generic applications

The EU-wide regulatory framework within mutual recognition procedures (MRP) is based on the co-operation and sharing of the regulatory workload between 25 EU Member States and 3 EEA countries. The National Agency for Medicines (NAM) in Finland is willing to handle its share of the common regulatory workload. However, every national competent authority, as NAM, has limitations to accommodate large and unexpected fluctuations in the number of Marketing Authorisation Applications (MAAs).

During 2003 and 2004 NAM has granted app. 500 national marketing authorisations per year. In 2004, the number of MRP procedures with Finland as reference member state (RMS) has been expanded to over 150 procedures (30 % of all MRP procedures in the EU). Due to the large number of MAAs for generic products during recent months the NAM has currently over 800 pending applications for marketing authorisation. Most applicants are planning a Mutual Recognition Procedure after national authorisation in Finland. A considerable amount of these products are not planned to be marketed in Finland.

There is a serious concern that this extremely heavy workload will definitely lead to delays and longer processing times for all marketing authorisation procedures in Finland. Therefore, NAM is obliged to adjust its functions to cope with the unexpected workload due to MAAs of generic products intended for other markets. According to NAM's opinion the applicants should submit their future MAAs for generic products primarily to those Member States to which their products are *de facto* targeted.

As a part of these new functional measures and guidance:

- The applicants are asked to provide a list of planned national or decentralised submissions during 2005 to the national marketing authorisation procedure in Finland. The following information should be included to the list if possible:
  - Drug substance, strengths and pharmaceutical forms
  - Number of trade names (duplicates)
  - Plans for MRP or decentralised procedures (DCP) incl. concerned member states (CMSs) and draft time schedule.

  When the NAM is planned to act as the RMS, the applicant should contact prior to the national or decentralised submission in order to draw up a time plan.

- The applicants are asked to provide information concerning the schedule for marketing introduction in Finland for each individual MA (pending MAAs as well as planned submissions). The information is extremely important for NAM to prioritize assessment duties. This information will be also taken account to analyse the consequences of the new so-called *Sunset Clause*[1] coming to operation since 30 October 2005. In the future this may risk the validity of Finnish marketing authorisations and consequently the grounds for Finland to act as RMS for those medicinal products.

- The NAM will concentrate to keep the processing time of each individual national authorisation in 210 days. To get more resources for processing of applications in the order of submission, so-called clones or duplexes are not any more processed by fast track. The applicants are asked to take account the chance in the procedure of the NAM in the future submissions.

- The applicant can help to cut processing times by submitting complete and well-compiled applications. However, to make the discussions more efficient between the NAM and the applicant, especially in clinical and pharmaceutical issues concerning SPC and PIL, the applicants are asked to provide a contact point of the Finnish/Swedish speaking person authorised for communication with the NAM.

The National Agency for Medicines is committed to contribute and to co-operate in the national and European marketing authorisation procedures in the best possible ways and according to the legislative frameworks. However, the new functional and practical measures and guidance above are regarded necessary for the purpose of keeping the regulatory processes in control and in rational management.

[1] *Marketing authorisation ceased to be valid if product is not marketed within three years or for three consecutive years.*

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Safety of products containing materials of human origin

There is intensive development of products containing materials of human origin, and the products are commercially available worldwide. They are expected to offer completely novel opportunities in the treatment of several diseases.

The use as transplants for various purposes of organs and tissues, both fresh and stored in tissue banks, including blood and its derivatives, is well established. The same applies to various bio-prostheses originating from human tissue. New technologies offer a fast-growing selection of different techniques for the utilisation of materials of human origin. It is likely that clinical practices will in the near future be dominated by three different categories of technology.

One of these is cell therapy, which means the placing of live cells in a human body to produce natural substances, in which the patient is lacking due to various clinical situations and injuries. Another form of technology is gene therapy, which implies the transfer of genes to live cells either in order to produce a gene product missing in the cell, or a product previously unknown to the cell, with the aim of producing some totally new function. The third form of treatment of the future is tissue engineering, in which cultured cells are used to replace the activity of cell masses which normally act in a co-ordinated fashion. The borderline between these technologies is artificial. It would appear at present that all three are developing hand in hand – which is also supported by the fact that researchers are often using all three at the same time depending on the type of function they aim to produce.

The selection of products based on materials of human origin is growing on the markets. The growth is guaranteed by the ongoing intensive international research and product development in the field. A number of surveys of several applications have been published recently (1, 2, 3). A review commissioned by the European Commission well reflects the market situation and future prospects of the sector well (4).

Risks involved with new technologies

Assessment of the risks involved with products containing materials of human origin requires familiarity with the whole manufacturing process including the intermediate stages and the operators responsible for them. Some of the risks involved are of a type where experience already exists, e.g. the use of transplants, but where additional investigation is necessary in order to make the routines associated with therapies using tissue engineering technology safe. This group includes, for example, risks of rejection and infection. The risk of infection is the most important individual risk factor associated with tissue engineering technology products. Control of infection should be very strict during the entire handling process of cells, all the way from cell recovery and screening of materials. The biggest risk of infection in the use of human cells is cell contamination and the transfer of prions, viruses and mycoplasmata from the donor to the recipient. The products are considered to be associated with several risks, of which previous health care products have offered no experience. Unknown risks include, for example, the effects of cell modification, the use of scaffolding in the body, the cancer risk associated with stem cells and the risk of transfer of xenogenic infections (zoonoses) when using materials of animal origin. The safety of products is, of course, very much dependent on the procurement of materials of human origin and on a well controlled manufacturing process.

Directives to ensure safety

The increased therapeutic use of the materials discussed above, concern about the quality and safety of the products, including ethical viewpoints associated with the issues, has alerted the European Commission (5). There is a pressing demand to harmonise the requirements and measures of control among the EU member states.

The Directive 2004/23/EC issued in March 2004 by the European Parliament and Council sets out the standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (6). The provisions of the Directive should be incorporated in the national legislation by the 7th of April 2006. The provisions will set out the selection criteria for tissue and/or cell donors, for example, and the obligatory laboratory tests for donors, as well as the procedures to be followed in the procurement of cells

and/or tissues and in their reception at tissue establish-ments. Standards will apply and will be issued for the operation of tissue establishments and their control procedures. In practical terms, the provisions above will set the minimum standards for tissue bank services (tissue establish-ments) including requirements that apply for source materials of products engineered from human tissue and for cell therapy products with regard to donation, procurement and testing.

In 2000 the European Commission started the preparation of an EU regulation on products engineered from human tissue with the aim of setting up provisions for products lying in the area between medical devices and medicines. The industry in that area has already for a decade tried to achieve harmonised European requirements to supplant the varying national requirements. The Commission has published its most recent proposals for regulating the intermediate area (7). There is strong evidence that the provisions will be based on the control procedures governing medicines. The aim is to group all the cell and gene therapy products already classified as medicinal products and the unregulated products engineered from human tissue into a single entity (Advanced Therapies). The interest groups are requested to express their views about the Commission's proposal before the 20th of June 2005.

It is the legislator's duty to ensure that the national legislation provides flawless protection for patient safety. It is necessary to have a forward-looking approach, to identify the entities and to ensure that the necessary co-ordination is in place for the preparation of EC legislation. In Finland, the Ministry of Social Affairs and Health prepares the statutes and provisions. According to the performance target agreement between the Ministry of Social Affairs and Health and the National Agency for Medicines (NAM) in 2004, NAM has prepared a report on the safety of products containing materials of human origin. The report is based on literature studies and is a compilation of material produced by different sources in recent years (8). As a supervisory authority of medicines and medical devices and within the limits of its own expertise NAM assists the Ministry in the preparation of statutes. Biological medicinal products, especially biotechnology products, cell therapy products and gene therapy products, are the areas on which NAM will focus in its presence within the EU.

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