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TABU

LÄÄKEINFORMAATIOTA LÄÄKELAITOKSELTA
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Summary

Summary

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National Agency for Medicines launches product information on pharmaceuticals

The quality of on drug information is measured using objectivity, availability, validity and transparency as criteria. Managing drug information has become a decisive prerequisite for successful medical therapy. The need to make reliable information on medicines available to health care professionals and consumers has become an increasingly important feature of the policy on medicines in the European Union and its Member States. National Agency for Medicines wants to meet this demand in Finland with a new, even by international standards high-grade service.

On NAM's revised and improved web pages (www.nam.fi) opened in April, the contents of SPCs and PILs authorised in Finland are accessible to anyone interested in information on medicines. Corresponding details of medicinal products with the EU's centralised marketing authorisation can be accessed via links from the web pages (http://www.emea.eu.int/) of the European Agency for the Evaluation of Medicinal Products (EMEA).

NAM's service covers initially about half the medicinal products with marketing authorisation, i.e. roughly 2,000 products. The new service was preceded by a challenging project involving the conversion of all the printed product summaries and package inserts into electronic data prior to being published. The new service of the NAM also includes useful search functions. This work calls for close co-operation between the pharmaceutical industry and the National Agency for Medicines. The project has, understandably, prepared the way for more extensive electronic interaction between the authority and industry.

The SPC (Summary of Product Characteristics) is the most important published document with regard to the authorisation procedure. It summarises all relevant information on the quality, efficacy and safety of the medicinal product. Its subject matter is binding on the pharmaceutical industry in all dissemination of information on the medicinal product and in its marketing. Health care professionals in general, and physicians in particular, should be able access easily and reliable a current, approved summary of product characteristics. As the contents need to be amended and approved almost daily, updated information is in great demand. The SPCs contain clinical information on the product's approved indications, dosage, contraindications, adverse drug reactions and interactions.

The PIL (Patient Information Leaflet) is a written instruction for the user of the medicine. It is a collection of essential information promoting the correct and safe use of the medicine. It is common knowledge that PILs are easily lost, and it is hard to find necessary information on a specific medicine later on. Now anyone who needs or is interested in such data can make use of the service where the correct information can be found. It will be equally easy for physicians to check, what information about the prescribed medicine the patient will get anyway.

The contents of both the summary of product characteristics and the patient information leaflet will conform to the marketing authorisation decision or amendment. Summaries of product characteristics are stored in the database in a manner that enables multiple search functions in the Internet. Patient information leaflets are published as they come, in authentic-looking .pdf files, and may therefore vary in quality and readability.

NAM's objective is to publish information on all medicinal products on the market as soon as possible, and to ensure that the information published already can be updated fast and flexibly. For that to succeed, it is naturally important that the pharmaceutical industry supports this project by going over to using documents drawn up according to our instructions in electronic data form. I believe that the pharmaceutical industry is quite willing to co-operate in this matter. As the service involves products marketed by pharmaceutical companies, the publication of correct, error-free product information parallel to their competitors' products on the web pages of the National Agency for Medicines should be in the interests of all companies concerned.

The new, challenging service has already been a learning process in itself, as far as information technology and content production, 'substance', are concerned. National Agency for Medicines invites anyone making use of the new service to give constructive feedback and new ideas for the further improvement of our drug information services.

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Summary

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Categorically risky drugs to be avoided during pregnancy and lactation

A unique situation is created by drug use during pregnancy: the mother's illness has to be treated while the foetus ought not to be harmed by the drug(s) used in treatment. A good basic rule is to try to select a drug about which there are reports concerning experience of the use during pregnancy, and to try to avoid the combined use of several drugs. The smallest possible drug dose adequate for the mother from the point of view of treatment should be used, and, if possible, attempts should be made to divide the dose into several daily doses to avoid peak toxic concentrations.

Pregnancy

Since the foetal defects caused by thalidomide were reported the effects of drugs on pregnancy and the foetus have been widely studied. Nevertheless, the legitimate use of drugs during pregnancy is still associated with many problems. For many drugs, however, the information relating to humans is still too insignificant to enable the foetal risks to be assessed reliably. Furthermore, new drugs are continually being introduced on to the market, and the classification of the safety of their use during pregnancy is based solely on animal studies.

A normal pregnancy without specific factors of exposure is associated with a 3% risk of finding some defects in the newborn. However, only a couple of percent of all developmental disorders are thought to be associated with legitimate drug use. Nearly all drugs pass the placental barrier and so are delivered to the foetus. In addition to causing defects, the adverse drug effect may be manifested as miscarriage, growth retardation, foetal death or problems later in life (e.g. learning difficulties, increased risk of cancer). Drugs known to cause possible foetal defects in humans are listed in Table 1.

Lactation

Nearly all drugs are secreted in the milk. The concentration in the milk usually remains very small, however, and the drug dose received by the infant through the milk is clinically insignificant. There are exceptions, however. Table 2 includes drugs which are known or suspected to cause problems when used during lactation. By no means all drugs have been studied specifically to find out how they are secreted in the milk. The planning of medication during lactation should follow the same general principles as those applied during pregnancy. Drugs which are only slightly bound to plasma proteins are also secreted in the milk. Regular exposure may allow drugs with a long half-life (or active metabolites) to accumulate in the child's body. Premature newborns with undeveloped drug metabolism and reduced rate of elimination form a special group. In many cases it may be necessary to arrange monitoring of the child.

Further information on harmful effects of drugs during pregnancy and lactation can be obtained from the teratological information centre attached to the Family Federation of Finland. Telephone enquiries (09) 641 716 are received on weekdays at 9–11 a.m.

Literature

Koren G, Pastuszak A, Ito S: Drug therapy: Drugs in pregnancy. N Engl J Med 1998;338:1128-1137

Ito S: Drug therapy: Drug therapy for breast-feeding women. N Engl J Med 2000;343:118-126

Briggs G, Freeman R, Yaffe S. In book: Drugs in Pregnancy and Lactation. Williams&Wilkins, 2002.

Table 2. Examples of drugs with problems during lactation.

Should not be used	*Not recommended*	*Care should be exercised*
Radioactive agents	*Lithium*	*Drugs with CNS effect*
Cytotoxic drugs/cytostatics	*Immunosuppressive agents*	*New antiepileptics and ethosuximide*
Dopamine-agonists	*(e.g. ciclosporin, azathioprine)*	*Antithyroids*
(prevention of secretion of milk)	*Barbiturates*	*Fluoroquinolone microbials*
Narcotics	*Benzodiazepine with long-term effect*	*Tetracyclines*
	Synthetic derivatives of vitamin A	*Chloramphenicol (systemic therapy)*
	Amiodarone (iodine)	*New drugs*
	Gold	

Table 1. Medicinal substances with explicit harmful effect on the foetus

MEDICINAL SUBSTANCE	*ADVERSE FOETAL EFFECT*	*NOTE*
Drugs affecting the renin-angiotensin system (ACE inhibitors, angiotensin II antagonists)	*Developmental disorders of the renal tubules, oligohydramnios and permanent renal damage and foetal deaths have been reported. Developmental disorders of the bones of the skull.*	*Risk associated with use during the 2nd and 3rd trimester. Medication should be changed on diagnosis of pregnancy at the latest.*
Vitamin A derivatives (anti-acne and psoriasis drugs, isotretinoin and acitretin)	*Frequency of severe multi-organ abnormalities (heart, CNS etc.) as high as 25% after exposure at the beginning of pregnancy. Delayed development.*	*Restriction of use, monitoring of use. Accurate information should be given to the patient. Reliable contraceptive measures should be used. Drugs remain in the body for a long time (acitretin even for many years)*
Aminoglycosides	*Potential ototoxicity.*	*Risk associated with parenteral use.*
Androgens	*Masculinisation of female foetus.*	*Risk involved if use continues beyond the 8th week of pregnancy.*
Diethylstilboestrol	*Increased risk of cancer in offspring (clear-cell carcinoma of the vagina)*	*No longer in use.*
Antiepileptics (valproate, phenytoin, carbamazepin)	*Increased risk of abnormalities; multi-organ abnormalities (valproate, carbamazepine: 1–2% risk of neural tube closure defect). Delayed development.*	*Planning of pregnancy. Untreated epilepsy a greater risk to the foetus than medication. Foetal damage possibly due to inherited predisposition. Folic acid supplements (0.4 mg) recommended while planning pregnancy and throughout the first trimester. Structural ultrasound, AFP measurement.*
Ethanol	*CNS injury, growth retardation, abnormalities, miscarriages.*	*Harmful throughout pregnancy.*
Fluconazole (?)	*Multi-organ abnormalities (skeletal development disorders, fissures, heart defects)?*	*Possible risk associated with high doses used in the treatment of systemic mycosis.*
Narcotics	*Prematurity, haemorrhages, infections, abnormalities, withdrawal symptoms of the newborn.*	*Harmful throughout pregnancy.*
Lithium	*Risk of cardiac development disorder, estimated to be 1-2% (risk of severe Ebstein's anomaly < 0.1%)*	*After exposure at the beginning of pregnancy, structural ultrasound of foetal heart during week 18–20.*
Misoprostol (used to treat gastric ulcers, also used in medical abortions)	*Causes miscarriages, can increase the risk of abnormalities (development disorders of limbs, damage to cranial nerve nuclei).*	*There is an anti-inflammatory analgesic available on the market containing misoprostol to prevent gastric symptoms. Harmful throughout pregnancy.*
Cytotoxic drugs/cytostatics	*Multi-organ abnormalities, miscarriages, growth retardation.*	*Following termination of medication a precautionary period should be observed before initiating pregnancy (including paternal exposure).*
Thalidomide	*Multi-organ abnormalities: partial or full absence of limbs, eye and ear anomalies, renal and urinary tract anomalies. 40% risk of miscarriage and 25% risk of severe abnormalities after exposure at the beginning of pregnancy.*	*New indications (leprosy, autoimmune diseases, metastatic carcinomas, secondary symptoms associated with AIDS). Mainly at trial stage, used with special indications in the USA. Close monitoring of use is necessary.*
Tetracyclines	*Developmental disorder of dental enamel, accumulates in the skeleton.*	*Risk from the 16th week of pregnancy onwards.*
Anti-inflammatory analgesics	*Harmful effect on the foetal renal function and blood circulation system (permanent renal damage reported with the use of nimesulide and indomethacin at the end of pregnancy, premature closure of shunt channel.*	*Harmful during the last trimester; paracetamol appropriate at all stages of pregnancy.*
Warfarin	*Bone and cartilage development disorders, foetal haemorrhages.*	*Medication should be changed immediately on diagnosis of pregnancy.*

Summary

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Reports received by the ADR register in 2001

A total of 748 reports of suspected adverse drug reactions were received by the adverse drug reaction register of the National Agency for Medicines in 2001. About half of them were serious. The reports were distributed fairly evenly among various drugs; only 13 medicinal substances received more than 10 reports. The enclosed table cannot be used for comparing safety among the different substances because there is a considerable variation in the number of users of various drugs: there may be more reports concerning a frequently used drug than concerning one which is used less frequently, even though the incidence of an adverse reaction may in fact be similar. The length of time the drug has been marketed also affects the reporting of adverse reactions. Reports of all adverse reactions are specifically requested where newly introduced drugs are concerned, and there are consequently more reports on them than on many old familiar drugs.

The majority of reports (50) of adverse reactions last year were associated with the use of nimesulide, an anti-inflammatory analgesic. Nearly 70% of the reports (34) were associated with liver reactions. Up until mid-March 2002 the National Agency for Medicines had received a total of 109 reports on suspected adverse reactions associated with the use of nimesulide. Liver reactions accounted for 66 of them. The majority of the reports were of symptom-free elevation of liver enzymes either alone or together with hyperbilirubinaemia; serious liver reaction was reported in 25 of the cases. Two of the cases necessitated liver transplant, and one was fatal. Due to the serious liver reactions, the sale of the tablets and granules of nimesulide has been suspended. The National Agency for Medicines is at present reviewing the situation with the marketing authorisation holder (Aventis Pharma).

The use of the recent COX-2 selective anti-inflammatory drugs, celecoxib and rofecoxib, prompted a total of 36 reports about suspected adverse reactions last year (20 with celecoxib, and 16 with rofecoxib). More than half the reports on celecoxib were principally allergic reactions and skin rashes (10 cases). Celecoxib is a derivative of sulphonamide, and should not be prescribed for patients with hypersensitivity to sulphonamides. One patient on celecoxib therapy was reported as having elevated hepatic enzymes. The adverse reactions reported for rofecoxib were fairly evenly distributed among the various organ systems. Among these reactions can be mentioned the case of an elderly patient (a 79-year-old woman) who died as a result of perforated duodenal ulcer. The patient was concurrently using several other drugs, one of which was acetylsalisylic acid in small dosage (100 mg/day). Skin rash or pruritus was reported in only two patients who received treatment with rofecoxib. Rofecoxib was introduced on to the market in Finland at the end of 1999 and celecoxib in May 2000.

Leflunomide is indicated for use in adult active rheumatoid arthritis and introduced into Finland at the end of 1999. Last year the number of adverse reactions reported as associated with its use was 18, seven of which were related to elevated hepatic enzymes. Leflunomide may also cause serious liver reactions, and consequently, S-ALAT should be monitored prior to the commencement of leflunomide and at least once monthly during the first six months of therapy, and at intervals of 8 weeks thereafter. If the liver enzyme values are rising the dose should be reduced or the therapy discontinued (see SPC). Due to the increased risk of liver reactions concurrent treatment with methotrexate and/or other hepatotoxic medicinal substances is not recommended.

The following medicinal substances were those most frequently reported to the ADR register of NAM in 2001.

Substance	*Number of reports*
nimesulide (Nimed)	*50*
clozapine (Leponex, Froidir)	*26*
atorvastatin (Lipitor)	*20*
celecoxib (Celebra)	*20*
leflunomide (Arava)	*18*
mirtazapine (Remeron)	*17*
levofloxacin (Tavanic)	*16*
infliximab (Remicade)	*16*
rofecoxib (Vioxx)	*16*
iopromide (Ultravist)	*14*
terbinafine (Lamisil)	*13*
carbamazepine (several preparations, e.g. Tegretol, Neurotol)	*12*
esomeprazole (Nexium)	*11*

Infliximab is a monoclonal antibody which inhibits the biological activity of tumour necrosis factor alpha (TNF-α). It is indicated in severe active rheumatoid arthritis or Crohn's disease when the response achieved with other drugs has been inadequate. The drug was introduced on to Finnish market in September 1999. Last year 16 reports on adverse reactions associated with its use were received, five of which were related to an allergic reaction. Three patients were reported as having tuberculosis and one had a cytomegalovirus infection. Infliximab is known to increase susceptibility to infection and is consequently contraindicated in patients with tuberculosis or other severe infection. Patients should in addition be carefully monitored prior to, during and for six months following infliximab therapy in order to exclude tubercu-

losis and other infections.

The majority of reports on psychotherapeutic drugs concerned clozapine, a second generation antipsychotic. As in previous years, the great majority of reports (73%) were related to cases of granulocytopenia or agranulocytosis, one of which was fatal. An alteration in the white blood cell count occurs in about one percent of patients on clozapine therapy, and a leukocyte count should consequently be carried out prior to commencement of therapy and regularly during the medication. Cardiomyopathy was reported in one patient on clozapine therapy. Myocarditis, pericarditis and cardiomyopathy have been reported as very rare adverse reactions associated with clozapine therapy. The possibility of these reactions should be considered in patients who develop persistent tachycardia which continues at rest and is associated with arrhythmias, dyspnea and symptoms of cardiac failure.

The second largest group of reports received on psychotherapeutic drugs were those associated with mirtazapine, an antidepressant (17 cases). Six patients were reported as having CNS symptoms such as hyperkinesis, anxiety, hallucinations, dizziness and headache. Convulsions were also reported in one patient. Skin symptoms occasioned the reporting in four of the cases and granulocytopenia/agranulocytosis in two. Mirtazapine has been in use in Finland since 1996. Reduction in the white blood cell count has been reported in previous years in seven patients in all. Due to potential bone marrow suppression a warning is included in the SPC that mirtazapine therapy should be discontinued and a blood count ought to be control if the patient should develop fever or sore throat or exhibit other symptoms indicative of infection. Mirtazapine is a mianserin derivative. Granulocytopenia and agranulocytosis are adverse reactions known also to be associated with the use of mianserin. In the case of both substances these reactions usually occur following 4–6 weeks' use of the therapy and they usually disappear on its discontinuation.

Among statins, the majority of the reports to the ADR register last year were related to atorvastatin (20 cases). The second largest number of reports were related to simvastatin (9 cases). Liver reaction was the most typically reported adverse reaction in the use of atorvastatin; seven patients were reported as exhibiting elevated liver enzymes, and one patient had hepatitis. Myopathy was reported in two patients. Rhabdomyolysis was reported in four patients on simvastatin therapy. Two of the patients were concurrently receiving either gemfibrozil or ciclosporin, which are known to increase the risk of myopathy if used concurrently with statins. Myopathy and/or elevated creatinine phosphokinase were also reported in two patients on simvastatin therapy. The use of statins has increased significantly during recent years in Finland. Both atorvastatin and simvastatin are at present among the three most frequently used statins, which is probably also reflected in the number of reports received by the ADR register.

Among the antibacterials the majority of ADR reports received concerned levofloxacin of the fluoroquinolone group (16 cases), which has been on sale in Finland since mid-1998. Most of the reports (9) referred to adverse reactions on the Achilles tendon (tendinitis or tendon rupture). Nearly all the patients were elderly (over 65 years) and over half of them were on concurrent systemic corticosteroid therapy. Injury to the tendon can be seen within two days of the start of medication and it may be bilateral (affecting the tendons of both ankles). These rare adverse reactions on the tendon can be considered as a class effect of all fluoroquinolones. As with other fluoroquinolones, levofloxacin is contraindicated in patients with previous adverse reactions on the tendon associated with the use of fluoroquinolones. Elderly patients are especially at risk. Concurrent corticosteroid therapy increases the risk of tendon rupture. If tendinitis is suspected, the administration of fluoroquinolones should be discontinued immediately.

The majority of adverse reactions reported on antifungals were associated with the use of terbinafine tablets (13 cases). Six of the ADR reports concerned various skin reactions; one of the reports described a bullous rash similar to that manifested in toxic epidermal necrolysis, i.e. Lyell's syndrome. This serious skin reaction is included as a very rare adverse reaction in the SPC of terbinafine. Liver reactions associated with terbinafine therapy were also reported (2 reports of elevated liver enzymes, 1 of hepatitis).

Iopromide is a low-osmolar, iodine-containing contrast medium used in angiography, urography and contrast-enhanced computerised tomography. In 2001, the NAM received a total of 14 reports on adverse reactions caused by it, the majority of which were allergic reactions (urticaria, anaphylaxis). Special care must be exercised in the use of this preparation in patients who are hypersensitive to iodine. Hypersensitivity occurs most often in patients susceptible to allergies. Prevention of hypersensitivity reactions may be tried; for instance, by giving the patient antihistamines and/or corticosteroids before the examination.

The majority of reports about antiepileptics were associated with carbamazepine (12 cases). The adverse reactions were typical of those occurring during carbamazepine therapy, mostly related to elevated liver enzymes (4) and changes in the blood cells (4). One of the patients, a 47-year-old woman practically confined to bed at an institution for mentally retarded patients since birth, died of liver damage suspected to have been caused primarily by phenytoin and secondarily by carbamazepine. The patient had also been receiving several other drugs.

The majority of ADR reports last year concerning drugs intended for gastrointestinal diseases were associated with the use of a new proton pump inhibitor, esomeprazole (11 cases). Six of these reports were about various skin reactions or allergic reactions. One patient (a 72-year-old man) was reported as having had a fatal myocardial infarction, but the causal effect of the drug was considered unlikely. Esomeprazole is an S-isomer of omeprazole. The drug was introduced on to the Finnish market in January 2001.

Summary

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Information on product defects

Despite all necessary quality assurance measures product defects are still possible, and advance preparedness for their management should be in place. Even though the responsibility for the management of a product defect lies with the marketing authorisation holder, all pharmaceutical entrepreneurs are for their part obliged to take any measures made necessary by a product defect and to ensure that the measures taken are appropriate. Good operational preparedness for managing product defects is maintained by plans and guidelines for such management and by regular training of staff in regard to future situations where product defects may occur.

Despite the quality assurance measures a drug may be released on for consumption, which does not fulfil the quality criteria required or which is supplied with package labelling not complying with the marketing authorisation or with the type of labelling which is required, and we are dealing with a product defect. The marketing authorisation holder is responsible for managing any product defects. Handling defects occurring in drugs manufactured at pharmacies, hospital pharmacies, medicine centres, is the responsibility of the person in charge of the respective unit of manufacturing. According to the regulation of the National Agency for Medicines on product defects (1/1999) all pharmaceutical entrepreneurs are responsible, on their part and in accordance with the Medicines Act, for the measures required by product defects detected and for ensuring that the measures are appropriate.

To ensure effective and rapid prevention of any harm to the user arising from the product defect, or to reduce the harm to the minimum, pharmaceutical entrepreneurs should be well prepared to handle product defects. Such preparedness requires guidelines for operation and staff training in respect to any occurrence of product defects.

The National Agency for Medicines is the supervisory authority in Finland controlling appropriate handling of product defects. If defects are not appropriately handled by the parties responsible, the National Agency can ban the distribution, sale and supply for consumption of a batch of a defective product. Nonetheless, the operations of the marketing authorisation holders and drug manufacturers have been carried out responsibly, and the National Agency has had no need to interfere with product defects by means of the bans referred to in Section 101 of the Medicines Act.

Assessing the risks arising from product defects ...

To control that the measures taken in the management of product defects are effective and correctly balanced with regard to any danger or damage faced by the user, a classification system based on the severity of the defect is employed. Based on risk assessment, the product defects are classified as dangerous (Class 1), harmful (Class 2) or minor (Class 3). Any risk to which the drug user is exposed by a product defect should always be assessed individually. Risk assessment requires expertise. For instance, the National Agency for Medicines may in certain cases request from the marketing authorisation holder a statement by a medical expert with regard to any undesirable effects the drug may have on its user. The choice of measures is governed by the product defect classification system. Nevertheless, measures cannot always be taken categorically in respect, for instance, of products of which there are no batches free from defects and for which no replacement preparation exists on the market. In similar situations the only alternative is to compare the risk arising from a product defect with the problem of non-availability which would be caused by a ban on the sale of the preparation. Both of these aspects ought to be considered in choosing the measures required. If the risk to the user caused by the defect is difficult to assess, a principle of precaution has usually been followed and any measures taken have focused on minimising any undesirable effects caused by the defect.

... setting in motion the necessary measures ...

Defective products of Classes 1–3 are removed from sale and distribution. Defective products which may be life-threatening and may compromise the health of the user are also removed from consumption. To prevent or restrict the potential undesirable effects of a product defect, measures may have to be set in motion even if the assessment of undesirable effects caused by the defect was incomplete at the time. The marketing authorisation holder may, for instance, impose a ban on the distribution of the defective product immediately upon detection of the defect and decide to prohibit its sale as soon as possible after the precise risk assessment is concluded and the availability of a replacement product is ensured. A record should always be kept of the measures adopted in managing a product defect.

... and informing the relevant parties.

It is required by regulation 1/1999 of the National Agency for Medicines on product defects that the parties responsible for the management of a product defect inform the National Agency promptly following the necessary preliminary reviews and after any immediate measures have been taken. This procedure of notification is only part of the necessary communication associated with product defect management. The information should be disseminated quickly and reliably among all relevant parties, such as the pharmaceutical manufacturer releasing the drug for sale and consumption or other pharmaceutical manufacturer, the wholesaler responsible for the distribution, the pharmacy in charge of the supply for consumption, the hospital pharmacy or drug centre and the domestic and foreign drug control authorities. The information should also be extended to the consumer as necessary. It is important that both the communication aimed at the consumers and that among pharmaceutical entrepreneurs and the authorities is open, reliable and correctly timed and that its contents are clear.

A significant proportion of the reports on product defects are received as RAS (RAPID ALERT SYSTEM) reports from drug control authorities in other countries. The RAS reporting procedure is based on policies approved by the EU and on agreements between authorities. Reports on product defects or suspected defects are customarily also received from marketing authorisation holders, pharmaceutical wholesalers, hospital pharmacies and retail pharmacies.

For instance, when one drug was being checked and prepared for supply in a pharmacy in 2001, it was noticed that the name of the drug printed on the inner package was not the same as that on the outer package. The mistake was spotted by the pharmacy staff as they were attaching the instructions to the inner package. Had the instructions been attached incorrectly to the outer cardboard package of the drug and the package contents left unchecked, the mistake would have gone unnoticed.

Translation Mervi Moisander