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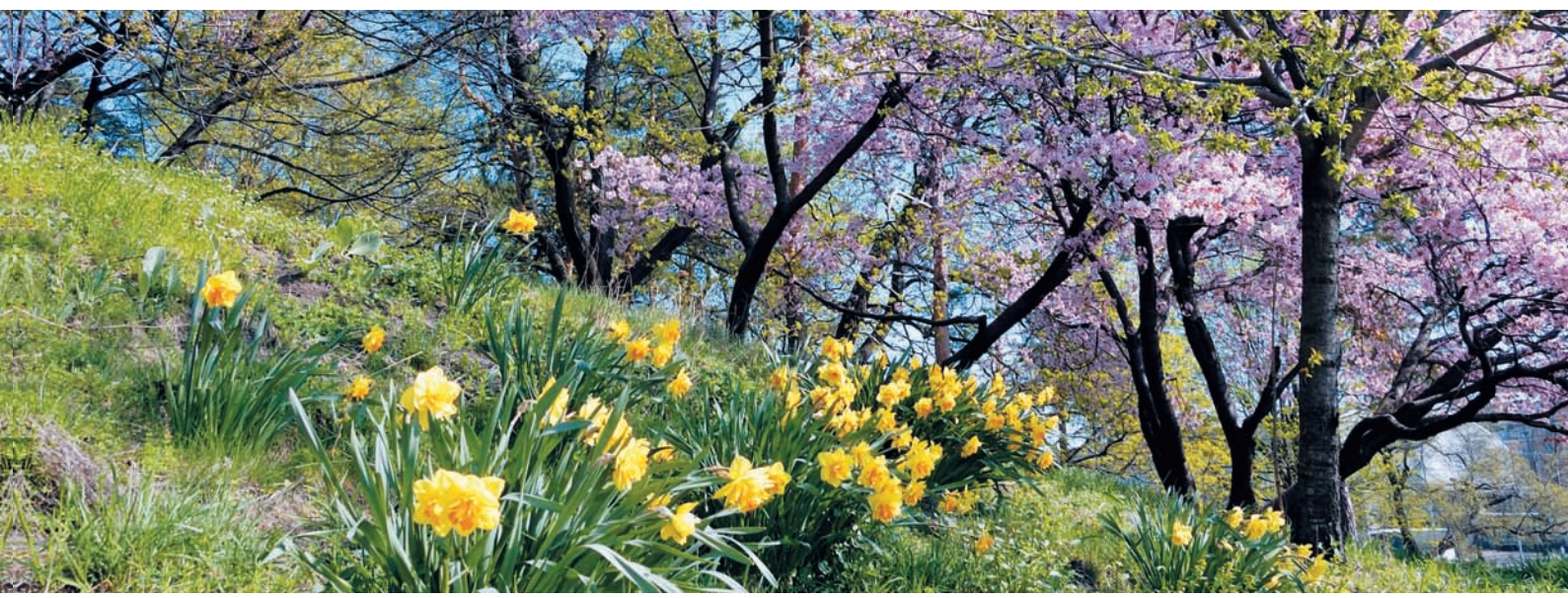

Läkemedelsinformation från Läkemedelsverket, Finland

Drug information from the National Agency for Medicines, Finland

På svenska | Översättning Mats Forsskåhl

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Editorial

Medication safety forms part of patient safety, but what about drug safety?

In January this year, the Ministry of Social Affairs and Health published its Finnish Patient Safety Strategy for 2009–2013. The aim of this strategy is to ensure safe, effective treatment. At the operational level this is realised through adherence to principles and methods that guarantee safe treatment and protect patients from harm.

Key elements in promoting patient safety include training, processes and structures, good practice, and learning from mistakes. These elements apply to the activities of organisations and to the people working in them, and they allow hazardous events occurring as a result of this work to be prevented.

Within the drug treatment process, medication safety forms part of patient safety, and is concerned with processes ranging from the prescription and administration of the drug to associated follow-up measures. Processes need to be developed with the help of benchmarks. A paper on this subject looks at benchmarks and the auditing of medication safety as development tools for use in hospital environments.

Drug safety is often to some extent understood to be the opposite of medication safety – in other words it is seen to be restricted to product safety and to evaluating substances' properties. But the specification for a drug includes not just its perceptible pharmacological effect, but also its therapeutic indication. When we talk about safe therapeutic indications, we are already looking at process guidelines for drug treatment. A very common observation in studies examining the frequency of undesirable effects of drugs is that over half of the undesirable effects leading to hospitalisation could have been prevented. In these cases, improving the process allows the level of safety to be increased.

A medicinal product that has been granted marketing authorisation is much more than a mere chemical compound in a package. The approved product's marketing authorisation also covers an extensive information pack in the form of a summary of product characteristics that specifies e.g. dosage, therapeutic indications, contraindications, necessary precautions and follow-up procedures, and sometimes also describes how to monitor the drug response and the emergence of any undesirable effects. A prerequisite for the use of many new drugs is often familiarity with a training package focusing on minimising risks. Similar information necessary for the user of the drug will be included in the package leaflet.

Instead of being seen as mutually exclusive, drug and medication safety should be seen as a seamless continuum that serves to ensure that drugs produce the best possible effect, and to protect patients from any adverse events. Simply including safety guidelines in the summary of product characteristics is not enough – guidelines also need to be correctly followed in practice. Reporting safety problems that can occur in drug treatment practice is an important tool for improving product information as guidelines for use of the drug.

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Summary

Regulation of drug marketing and drug information

Nearly 50 reports were processed by NAM's drug marketing regulation section in 2008. Where marketing of prescription drugs to the public was possibly involved, improved efficiency in regulation was targeted at drug company operations. Year by year the distribution of health information about diseases and their symptoms including treatment alternatives has increased in the media.

Background information about drug marketing regulation at NAM

NAM regulates the appropriateness of drug marketing in Finland, mainly according to the standards stipulated in the Medicines Act and Decree. Relevant EU Directives (2001/83/EC and 2004/27/EC) have been included in the Medicines Act and Decree. Even more detailed specifications about drug marketing are contained in Sections 91 to 93 of the Medicines Act contain stipulations about drug marketing. Sections 25 and 25 a to i of the Medicines Decree.

For example, regulation of drug marketing at NAM comprises in practice follow-up of marketing and the review of possible defaults and their rectification as well as advice relating to marketing issues. The most important part of the regulation concerns the review that takes place following reports of suspected misconduct relating to marketing submitted by medical professionals, the authorities, drug companies or private individuals. As far as regulation is concerned, most of these reports or complaints have been successfully resolved by NAM through requesting a report from or sending a caution to the relevant party. Only one case in 2008 advanced to the stage of marketing prohibition being imposed. One third of the requests for a report involved the marketing of a prescription drug to the public, one third concerned inappropriate marketing of a prescription drug and one third that of an over-the-counter drug.

Regarding prescription drugs, the requests for a report were often concerned with inappropriate figures or choices of the wording or insufficient information about the safe and correct use of the product in the relevant advertisement. Suspected marketing of prescription drugs to the public concerned health campaigns which contained indirect or direct sales promotion for a particular product.

At the beginning of 2009, a systematic review was made of the information given by drug companies on their websites about drugs or therapy groupings. This will become a relevant topic within the next few years because of a new proposition for a directive at present being discussed at EU level regarding the drug information that is being offered to patients.

Informative content of the drug companies' websites

Health information targeted at the public in general which does not even indirectly aim to promote the sales of any specific medicinal product falls in the category of freedom of speech and is allowed. In NAM's view the borderline between information and marketing should not be obscured. The truth is nevertheless that companies do offer information about the groups of therapy and diseases for which they have an appropriate drug in their ranges of products. Improvement of the level of information the patients receive can for example generate both an improved outcome of treatment and unnecessary medications by creating impressions of a need of medication for diseases associated with the high standard of living.

At present, the informative content of the websites examined falls as a rule into the category of information compliant with freedom of speech. According to this review, as to their extent and scientific nature, the informative contents of drug company websites vary significantly.

Of the websites examined (n=131) 44% (57) were in the Finnish language; 90% of these had the package leaflet and/or data about the summary of product information either published in Finnish or gave a link to the proper site. The links were to the website of NAM or to the database of *www.lääkeinfo.fi*. It is important that the information approved by the authorities about the drugs should be easily available to patients on the Internet.

Health information in the Finnish language about prescription drugs or information oriented towards the disease or symptoms by therapy groups was published by 23 (40%) drug companies. The websites of these 23 drug compa-

nies were examined further in greater detail. There were 140 of them in total. The websites included a mention of 163 groups of therapy. The majority of the websites involved issues relating to cancer and blood diseases followed in frequency by sites involving issues relating to psychotic and neurological diseases.

In accordance with various groups of therapy, basic information on the drug company websites is published about diseases, occasionally including additional information about cell level changes in the various diseases. The websites very often discuss the symptoms and frequency of a disease and the risk factors for it. Some sites also include information about the various alternative methods for detecting the disease, the tests necessary and the interpretation of laboratory results. More extensive sites discuss information about the prevalence of the disease, various treatment alternatives and advice on change of lifestyle. On the more advanced websites patients are prompted to turn to medical experts with their queries about the company's prescription drugs.

The proposition for a directive on information about prescription drugs given to patients is at present being discussed by the European Commission and Parliament. NAM also submitted a statement on the issue at the beginning of the year. NAM does not support the idea of giving drug companies novel opportunities for distribution of information, except for information about summaries of product characteristics and package leaflets. In NAM's opinion, the borderline between information and marketing should not be obscured. NAM does not support the new directive in all its parts because, among other considerations, it would increase the regulatory workload of the authorities. The increase in drug information referred to in the directive may in fact increase the number of doctor's appointments made by the population, the use of drugs and drug costs. The future will show what type of information drug companies may distribute to patients in the future.

Pharmacy-initiated internal monitoring program as a tool for improving medication safety – medication safety audit at Satakunta Central Hospital

According to the latest legislation from the National Agency for Medicines, hospital pharmacies must have an internal monitoring program to ensure medication safety in their associated hospital units. To enable a monitoring programme of this kind to be developed, a study was carried out at Satakunta Central Hospital as a part of the regional "Safe Pharmacotherapy" programme. The main objective of this research was to enable medication safety audits to be performed on the basis of a validated self-assessment tool, and to implement this activity as a hospital pharmacy-directed practice. A medication safety audit is an internal review which assesses the appropriateness of the pharmacotherapy plan on the basis of medication safety criteria. The audit tool was based on the original self-assessment tool (241 items) created by ISMP (Institute of Safe Medication Practices), which has been used extensively in the United States. The original tool was adapted to take account of Finnish healthcare practices and the modified version (121 items) was tested at the pilot ward. The self-assessment responses were discussed by the audit pharmacist and senior nurse during the audit visit. The area in which the highest number of guidelines were found to be either fully or partially in place was "pharmaceutical services" (89 %), which includes the ordering, storage, preparation and return of drugs. The section in which the lowest number of guidelines were observed to be fully/partially in place was "the pharmacotherapy process" (22%), which involves the transmission of the prescription for and prescription, labelling, distribution and administration of drugs, patient information and counselling, and assessing the effectiveness of pharmacotherapy.

The medication safety audit is a new tool for integrating pharmacists into nursing care in hospital wards, in compliance with national safe pharmacotherapy guidelines. Medication safety audits could also improve the scope of pharmaceutical services in primary healthcare wards, especially those that do not have their own pharmacy units. However, in order for this type of pharmacy-initiated medication safety programme to be implemented regularly, healthcare professionals will need to be prepared to take on new roles.

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Own observation of an adverse reaction

Telithromycin and visual disturbances

Our patient cases

Case no. 1. The first patient is a 34-year-old female member of an airline company's flying personnel. She is a healthy women. She had previously experienced allergic reaction after the administration of phenoxy methyl penicillin. Following a flight she sought treatment for ear symptoms. Auroscopy and anterior rhinoscopy revealed perceptible swelling and poor mobility of the tympanic membranes, together with postnasal irritation and profuse drip. The patient was prescribed a 5-day course of telithromycin 800 mg daily. She was also given a spray of beclomethasone dipropionate. Within 30 minutes of the first dose of telithromycin she experienced a visual disturbance. She was unable to focus her sight properly and various items appeared distorted. Since she took the drug in the evening, she was unable to evaluate the duration of the symptom. In the morning, however, her eye sight had returned to normal. She continued taking the medication and visual symptoms no longer appeared. At an appointment four days thereafter the patient's vision was normal for both reading and at 5 metres' distance. Eye movements were normal, and using finger perimetry the visual fields were found to be normal, as were the fundi of the eyes. Distortion of images did not occur in the patient's vision. Romberg's test was steady, blood pressure while seated was 124/84 mm Hg and the pulse was regular 72/min.

Case no. 2. A 33-year-old male patient is presented as a further case. He had previously been in good basic health, but phenoxy methyl penicillin had provoked an allergic reaction. He had had a very sore throat and a profuse postnasal drip for about a week. He was found to have coating of the pharyngeal mucosa and swollen palatal tonsils. His tympanic membranes were normal and his lungs were found to be normal on auscultation. He was prescribed telithromycin 800 mg daily for seven days. Following the first dose of this drug the patient could not detect anything unusual, but 2 to 3 hours after the second dose he felt stiff and almost as if inebriated. He also described objects in his surrounding vision as having become distorted. He reported these symptoms by telephone. He subsequently stopped using the medication and was asked to consult if symptoms persisted.

Background

Telithromycin (Ketek) is a ketolide antibiotic which has been in use in Finland since 2002. Ketek has been granted centralised marketing authorisation in the EU, and the safety of this medicinal substance is mainly regulated by the European Medicines Agency, EMEA. In 2007 EMEA stipulated restrictions on the use of telithromycin after an extensive evaluation of safety of the drug (1). EMEA focused on the therapeutic indications and certain undesirable effects of telithromycin in particular. Its significant undesirable effects include transient visual disturbances. An additional warning on telithromycin associated visual disturbances was included in the Summary of Product Information (SPC), stating that "*because of the possibility of visual disturbances patients should minimise activities such as driving a vehicle, using heavy machinery or performing similar hazardous tasks*". Prescribers were also reminded that patients should be informed about the possibility of this undesirable effect emerging even following the initial dose.

Table 1. ADR reports concerning telithromycin and visual disturbances (Adverse drug reaction register of NAM, DLP 31.3.2009).

Age and sex	Latent time	MedDRA terms for the adverse reactions	Description of the adverse reaction	Recovery	Discontinuation of medication
36 y. female	6 days	Blurred vision, Arrhythmia, Hypoaesthesia	Blurred vision half an hour after intake of tablet; lasted for a couple of hours.	Recovered without special treatment	Discontinued
37 y. female	Less than one day	Blurred vision, Malaise	Symptoms started one hour after intake of the first tablet at 1 p.m. and continued until late at night.	Recovered	
44 y. male	Less than one day	Blurred vision	Blurred vision after intake of the first tablet; the vision was not restored to normal for the rest of the day.	Unknown	
40 y. male	9 days	Blurred vision, Nuchal rigidity	Visual acuity became impaired.	Had not recovered by the day of reporting	
23 y. female	2 days	Blurred vision, Dizziness	About 30 to 45 minutes following initial intake of the drug developed dizziness and blurred vision on long sight.	Recovered after restling	Discontinued
32 y. female	One day	Visual disturbance, Eye pain	Prolonged visual disturbance and pain in the eye.	Unknown	
35 y. male	Less than one day	Abnormal accommodation	Impaired accommodation one hour after intake of drug, unable to read or to see for a short distance, and unable to even see his doctor clearly.	Unknown	
38 y. female	Less than one day	Visual disturbance, Dizziness	Visual disturbance, dizziness.	Unknown	Discontinued
34 y. female	One day	Abnormal vision	30 minutes after intake of drug difficulties seeing accurately at a short distance, also long distance e.g. TV text. Distortion of image also occurred.	Recovered	Discontinued after 4 days
44 y. female	Less than one day	Abnormal vision	Difficulties in seeing at a short distance. Recovered before intake of subsequent tablets, and symptom-free after the course of treatment.	Recovered	A 5-day course of treatment
26 y. female	Less than one day	Abnormal vision, Dizziness	Visual disturbance and dizzines lasting for a couple of hours after each intake of tablet.	Recovered	Discontinued
42 y. female		Abnormal accommodation, Diplopia	About 1.5 hours after intake of drug difficulties supervened in accommodation, visual field appeared blurred and diplopia developed.	Recovered the following day after discontinuation of medication	Discontinued
50 y. female	Less than one day	Abnormal vision	The patient was unable to see clearly either at a short or a long distance.	Recovered	
25 y. female	Less than one day	Oculogyric crisis	The eyes were paralysed, shifting of vision became difficult.	Recovered on the same day	
30 y. female	Less than one day	Abnormal vision, Eye pain, Speech disorder	45 minutes after intake of drug, visual disturbances developed, the eyes were sore, and speech was blurred.	Recovered during follow-up in hospital	
53 y. female	Less than one day	Diplopia, Headache, Dizziness, Insomnia, Diarrhoea	Headache developed about 2 hours after intake of drug. Other symptoms on the second day including double vision.	Had not recovered by the day of reporting	Discontinued
17 y. male	One day	Blurred vision	Blurred vision lasting for a couple of hours developed about 2 hours after intake of drug, unable to do computer work and the TV appeared unclear.	Had not recovered by the day of reporting	Discontinued after 4 days
27 y. female	Less than one day	Abnormal vision, Dizziness, Nausea	Dizziness developed about half an hour after intak of drug, together with difficulties on locating the visual field for about 1.5 hours.	Recovered	Discontinued
15 y. female	Less than one day	Blurred vision	Blurred vision on the day of the use of the drug.	Recovered	A 5-day course of treatment
25 y. female		Diplopia, Headache, Blurred vision, Dizziness, Feeling strange	Tinnitus and double vision developed during the second 5-day course of treatment about 48 hours after intake of drug. The symptoms lasted for 3 weeks.	Had not recovered by the day of reporting	

Visual disturbances associated with the use of telithromycin

A total of 52 reports of suspected adverse reactions related to the use of telithromycin have been reported to the NAM's ADR register until the cut-off date of March 31, 2009. Of the 52 reports, 20 cases were related to various visual disturbances (Table 1). Three quarters of the reports on visual disturbance concerned young adults (20 to 40 years old). The majority, 85%, were of female patients. Ten patients (50%) did not exhibit any other symptoms besides visual disturbances. The onset of symptoms usually occurred 30 minutes to 2 hours after the intake of the drug and lasted for over 2 hours. Over half of the patients (12) recovered, and symptoms in four patients continued during the time of reporting. The course of treatment with telithromycin was discontinued in seven patients due to adverse reactions. Four patients continued with their course of treatment despite the adverse reaction.

Discussion

The approved therapeutic indications of telithromycin in adults include outpatient treatment of pneumonia, exacerbation of chronic bronchitis and acute sinusitis if the infection is known to be betalactam and/or macrolide resistant.

Visual disturbances related to telithromycin should be kept in mind in the clinical practice. Telithromycin has been reported to have caused visual disturbances including blurred vision, difficulties of visual acuity and double vision. In their degree of severity they have generally varied from mild to moderate, but severe cases have also occurred.

According to a recent analysis of data from an Italian adverse reaction register, adverse reactions associated with the eye disorders were 2.2% of the reports (n=1 017) (3). In this register, the majority of the eye disorder reports concerning tablet form were on telithromycin. In another recent Italian analysis of macrolide antibiotic induced eye reactions (n=622 cases) revealed that telithromycin had caused 47% of the cases (4). A further analysis showed that the most common adverse reactions were blurred vision (43%), unspecified visual disturbance (19%), impaired visual acuity (14%) and double vision (10%). The majority of these reactions emerged after the first or second dose and were reversible. In only a few of these cases was no immediate recovery seen. Even though telithromycin is not known to have caused permanent visual disturbance, repeating the course of telithromycin treatment is warned against if it has caused visual disturbance (5). Repeated use could in theory result in optic neuropathy (5).

About 40% of the adverse reaction cases reported to NAM where telithromycin was a suspected medication are associated with visual disturbance. The risk of visual disturbance associated with the use of telithromycin appears to be transient. It is not known whether this is dose dependent. According to FDA, visual disturbance occurred in 0.4% of the subjects (40/1 003) in phase I studies during high dose therapy and in 0.7% of the patients (14/2 045) in phase III studies (2). Visual disturbances were mostly reported in females under the age of 40 years. According to analysis by EMEA, the frequency of visual disturbance is estimated at 1% (1). Telithromycin-associated visual disturbances were studied in two trials; the mechanism may be a short-acting effect of telithromycin on the ciliary body causing a delay in the relaxation of the ciliary muscle and visual acuity being consequently impaired (1).

This review has focused on telithromycin-associated visual disturbances. With regard to other potential adverse reactions it should be borne in mind that the most common ADRs are gastrointestinal disorders and headache (1, 6). Use of telithromycin may also have resulted in severe adverse reactions such as exacerbation of myasthenia gravis, transient loss of consciousness, hepatic failure or even irreversible liver damage. Before the treatment with telithromycin risks should be carefully weighed against the benefits. In certain difficult situations, taking a bigger risk can be considered in the treatment of a severe infection (7). The safety profile of telithromycin is being continuously monitored.

Summary

The visual disturbances are occasionally associated with the use of telithromycin, and the risk is greater than with the use of other antibiotics. It is recommended that the risk of this adverse reaction which appears to be higher in females under the age of 40 years be consistently kept in mind in the clinical practice. The advice already mentioned in the SPC should be followed, i.e. "*while using telithromycin patients should minimise activities such as driving a vehicle, using heavy machinery or performing similar hazardous tasks*". Taking telithromycin before bedtime can decrease the potential complications of visual disturbances.

Literature

See page 19.

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Summary

Mission of the Finnish OMCL

The official medicines control laboratory (OMCL) responsible for the independent quality control of medicines in Finland is the Laboratory of National Agency for Medicines (NAM). The NAM-laboratory is part of the European Official Medicines Control Laboratory (OMCL) -network, within which the laboratories co-operate in many fields of medicines testing and control.

The medicinal products to be tested are selected e.g. on the basis of product defect reports, risk evaluation, and random sampling. The strategic preferences of NAM are taken into consideration in setting up sampling and testing plans. The medicinal products are usually ordered from wholesales. Inspectors sample both active pharmaceutical ingredients and medicinal products when they inspect pharmaceutical industries and pharmacies. Samples from other European countries are obtained in projects where the NAM-laboratory has the responsibility to test medicines within the frame of the joint EU/EEA- testing schemes.

NAM also participates in the work of the European Pharmacopoeia Commission and its Groups of Experts. The duty of the Groups of Experts is to elaborate and update the European Pharmacopoeia monographs. The Finnish OMCL has been represented in the European Pharmacopoeia Commission since 1975 and in the Groups of Experts since 1978.

Testing the wide variety of medicines

Testing the wide variety of medicines places high demands on the personnel, facilities, and equipment. Many methods are needed ranging from chemical methods like mass spectrometry and capillary electrophoresis to sterility testing and determination of endotoxins.

In addition to the common synthetic medicines, novel biological medicinal products become more and more common. These biological medicinal products vary from recombinant proteins to the very advanced cell therapy products. The recently established cell culture facility in NAM provides new possibilities for in vitro determination of the biological potency of such products. It also facilitates pre-authorisation testing and evaluation of the methodology already during the evaluation for marketing autho-

Assistant researcher Yvonne Ylitolonen at work in the laboratory.

rization, thus starting a new era in the activities of the laboratory.

The microbiological purity of parenteral products is extremely important for the safety of patients. Not all authorities within EU/EEA have microbiological laboratories of their own. As an example of the collaboration with other European medicines control laboratories NAM-laboratory has performed microbiological analyses for Latvia, Estonia, Ireland and Sweden,. Development of the advanced therapeutic products also sets novel challenges for microbiological testing.

OMCL-network

The European OMCL laboratories form a collaborative network. Collectively they provide the multidisciplinary array of methods needed to reliably monitor the quality of the several thousand medicinal products available on the European market. Within this network, the laboratories exchange samples and data, thus minimizing the overlapping work between laboratories and maximizing the number of tested samples. The support provided by this network is particularly important for small member states like Finland.

The OMCL-network is coordinated by the Department of Biological Standardisation, OMCL Network and HealthCare (DBO), which is a part of European Directorate for the Quality of Medicines & HealthCare (EDQM). The network is for example utilized by the European Medicines Agency (EMEA) to carry through the annual sampling and testing programme with the aim to test the quality of Centrally Authorized Products (CAP).

In order to become full member of the OMCL-network, a laboratory has to be financially and administratively independent, and it has to have a formally recognised quality management system. The NAM-laboratory has been a full member of the OMCL-network since it was established.

Quality assurance

As a guarantee for a high standard of performance, the NAM-laboratory has implemented a quality management system in accordance with standard ISO/IEC 17025 (General requirements for the competence of testing and calibration laboratories). According to this standard, all factors affecting the quality of analysis results must be controlled: the personnel must have a high standard of knowledge and skills, the work must be standardised and described in standard operation procedures. The laboratory of NAM has regularly participated in the external proficiency testing studies and managed well. All the most essential techniques have been accredited by the Finnish accreditation body (*FINAS*). Because of the special nature of testing, the accreditation is based on the so-called flexible scope. This type of accreditation sets special requirements for the management system and the competence of the personnel. In Finland, the NAM-laboratory was the very first one to achieve accreditation based on flexible scope.

Laboratory on alert

The medicinal products sold through the legal distribution chains in Finland can generally be considered safe. Sometimes it happens, however, that medicines of unacceptable quality reach the market. Therefore it is important that NAM-laboratory is capable to react rapidly to investigate such suspected quality defects. A good example of such a case occurred in 2008: a cheap, harmful substance had been added to heparin, thus causing the deaths of numerous patients worldwide. In order to ensure the safety of Finnish patients, all batches of heparin on the Finnish market on that time were tested.

A growing problem is medicines sold illegally via the Internet. There is a great risk these being counterfeit drugs. NAM-laboratory collaborates with Customs Laboratory in order to extend the control to this type of illegal products. Another novel and important field of collaboration both nationally and Europe-wide is the European OMCL-network initiative to monitor the quality of stockpiled medicines. These activities are examples that stress the importance of the work done by the official control laboratories, not only in assuring the quality and safety of medicines sold to patients via the legal distribution chain, but also in monitoring the health hazards of illegal products and assuring the quality of medicines to be used only in a state of emergency.

Translation Jaana Vesterinen & Tom Wikberg