INTEGRITY OF BIOMEDICAL AND

PHARMACEUTICAL RESEARCH

Modern quality management in drug research

Inaugural lecture

Pronounced in abbreviated form on the assumption of his office of
Professor in Quality Management of Drug Research and Drug Production at
the Faculty of Mathematics and Sciences of
the University of Groningen

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by

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PREFACE

Right Honourable Rector,

Ladies and Gentlemen,

The systematic application of quality management in the course of a production process dates back to more than 2,000 years B.C. It was already applied to the construction of the pyramids in Egypt (for instance to the Pyramid of Cheops, 2,600 years B.C.). These buildings are the first samples of made-to-measure constructions based on product inspection. Even complete test reports have been found (Maas and Hoogendijk, 1996).

The oldest quality warranty known to man - on a clay tablet - was found in Babylon and dates back to the year 429 B.C. It was issued to guarantee a gold ring (Juran, 1995; Maas and Hoogendijk, 1996).

However, it is only recently, i.e. during the second half of this century, that people have become convinced of the great value of quality management in scientific research.

Its importance in the research of new drugs has only gradually become apparent during the last twenty to thirty years. The introduction of the Chair of Quality Management of Drug Research and Drug Production by the University of Groningen - the first in the world - stresses its importance in training the future generation of researchers in this field.

In the following chapters, I will give you my perception - also illustrated by some real-life examples - of the importance of quality management in scientific research, including drug research.

INTRODUCTION 1

Quality management

Quality management is striving for perfection. Perfection can only be reached by continuous improvement, carried out in a systematic manner. The examples given in the Preface illustrate that quality management is certainly not a new idea; apparently it has existed for several millennia.

Quality management
Ethics

Originally, quality management was in particular applied in industrial circles for reasons of management and product technology. Only much later it started to play a role of importance in scientific research. Particularly during the last decades this subject has been at the focus of attention because of its high social relevance. After all, in scientific research, ethics - the doctrine of standards and values - play an important role, perhaps even more so than in production.

Integrity
Social responsibility

Society at large is highly dependent on the integrity of those who carry out scientific research. These scientists should indeed be honest and incorruptible, for they have the unique mission to make new discoveries, a great number of which will possibly contribute to the wellbeing of the human race. In short, they carry a heavy social responsibility. Mankind should be able to put its trust in the results obtained by these researchers, as it is highly dependent on them. That is why it is of the utmost importance that scientists assure the quality of their research and, in doing so, guarantee its complete reliability. This applies to academic institutions as well as governmental and private research centres.

It is obvious that an important task is assigned here to the study directors. They should take all necessary precautions to prevent and detect inappropriate - perhaps even fraudulent - behaviour by their staff.

This social responsibility lies heavily with those who carry out biomedical and pharmaceutical research, an extremely expensive scientific discipline which should lead to improvement of health and quality of life of the human race.

To illustrate this: in the Netherlands approx. 750 million guilders are spent

yearly on the search for new drugs. Worldwide this amounts to about 75 billion guilders.

Nobody is perfect and that means that scientific researchers are subject to a whole range of factors that could compromise the integrity and the quality of their work. This phenomenon has been recognized a few decades ago; since then, increasing attention is paid to the ethics of research and guidelines have been published in this field as well.

Declaration of Helsinki

Initially, these rules amounted mostly to agreements within certain professional groups, such as the Declaration of Helsinki (World Medical Association, 1964). This code of conduct was adopted by the 'World Assemblée' of the World Medical Association, which took place in Helsinki that year. In this code of conduct, recommendations are made to members of the medical profession regarding biomedical research in man. In its revised form, this declaration is still of fundamental importance in conducting such research. Many of the current regulations regarding research in man are based on this Declaration of Helsinki.
Later, these recommendations were followed by specific Codes of Practice, set up by research institutes and universities, and later enforced by legislation.

GLP; GCP; GMP

As far as biomedical and pharmaceutical research is concerned, during the last two decades quality management has led to the introduction of extensive regulation, which in most cases has also been given force of law, for instance in the rules of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). For drug manufacturing, we can also add the rules of Good Manufacturing Practice (GMP).

...'Quality Assurance'... (illustration)

Furthermore, we see an increasing trend to apply general quality management systems to scientific research in order to increase its reliability and efficiency.

Total Quality Management

A combination of the above-mentioned rules and standards can lead to an efficient system of integral quality management - Total Quality Management - in drug research and drug production.

DEFINITION

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ut! Bladwijzer niet gedefinieerd.

Scientific misconduct

In spite of a comprehensive system of regulations and quality standards, the possibility cannot be excluded that a study is not executed in a completely perfect manner; the integrity - that is, the reliability of the results - is compromised. In these cases we use the terms scientific misconduct or fraud. Misconduct during drug research and during drug manufacturing brings evident dangers, both ethical and economic in nature, and is therefore unacceptable (Burgess, 1996).

Apart from the term 'misconduct' other terms are used, sometimes less strong, such as dishonesty, or even stronger, such as fraud (Macrina, 1995).

The production of incorrect and/or incomplete study results may take place on purpose (intentionally) or unconsciously (unintentionally). A further complication in correctly defining the issue is that opinions differ on what is right or wrong, based on differences in ethical standards. This situation results in a large 'grey area' of actions on the verge of what is only just acceptable or not acceptable anymore. Naturally this is not surprising. Science is by definition concerned with expanding the horizons of knowledge and an attitude of doubt is inextricably bound up with it, without, however, risking to compromise the integrity (Brinkgreve, 1997).

Examples of scientific misconduct

Scientific misconduct occurs in many forms, the best-known of which are: fabrication, falsification, misinterpretation and plagiarism.

Some examples are:
. negligence in carrying out research;
. invention of experiments, complete with fictitious results;
. invention of data (sometimes supplying research materials, such as in the case of subjects with forged Informed Consent forms);
. selective and undisclosed rejection of undesired results, i.e. concealment of data;
. alteration of data, i.e. replacement by fabricated data;
. erroneous use of statistical methods in order to draw conclusions diverging from those warranted by the study data;
. distorted interpretation of results and distortion of conclusions;
. suppression of unwelcome projects, hypotheses or results by

unwarranted rejection of manuscripts or grant applications;
. obstruction of a publication;
. designing an experiment so that its results are evitable and do not test any hypothesis;
. refusal to alter publications on work based on allegations which in the meantime have become known to be invalid or doubtful;
. analysing experimental results, e.g. by applying statistical methods frequently and erroneously, in such a way that they appear to point in a determined direction (data massage);
. interpreting experimental results in a way that supports a particular theory without exploring alternate interpretations;
. appropriation of research data produced by others for personal gain (plagiarism, from the Latin plagium - robbery);
. presentation of others' data, analyses or ideas without credit (plagiarism);
. wrongful or inappropriate attribution of (co-)authorship;
. systematic discrimination against particular individuals and/or institutions and favouritism of others;
. re-publication of findings or results for personal gain without reference to their previous publication;
. listing names of authors who have not contributed to the publication at all;
. misleading scientific grant or job applications;
. use of an (academic) title which has not (yet) been acquired.
(Grayson, 1995; Riss, 1996).

Not infrequently a combination of a number of these forms is found.

Probably these forms of dishonesty all occur in every science, but there will be differences in emphasis.

This enumeration is certainly not exhaustive and we are regularly confronted with new forms of scientific misconduct.

...'Plagiarism'.... (illustration)

Definition

In the course of time, a number of definitions for scientific misconduct, deceit and fraud have been devised.
The elements fabrication, falsification, misinterpretation and plagiarism are often found in many of these definitions, often completed by descriptions such as 'every serious deviation from the accepted practice in obtaining, handling or reporting results'. Sometimes in addition it is specified that errors or bona fide differences in interpretation are not covered by this definition. Originally,

the definition 'fraud' was used mainly for the practices of fabrication, falsification and plagiarism.
Scientific misconduct

The American government introduced the concept 'scientific misconduct' in order to enable a wider definition of 'research fraud' and to differentiate from the legally defined general concept 'fraud'. The most recent American definition dates from 1995 and contains all aspects stated.

It stresses its unethical character, reading as follows:

'Research misconduct is significant misbehavior that improperly appropriates the intellectual property or contributions of others, that intentionally impedes the progress of research, or that risks corrupting the scientific record or compromising the integrity of scientific practices. Such behaviors are unethical and unacceptable in proposing, conducting, or reporting research, or in reviewing the proposals or research reports of others (Commission on Research Integrity, 1995).

Conclusion

Summarizing, it can be determined that four different forms of scientific misconduct are predominantly found: fabrication, falsification, misinterpretation and plagiarism.

POSITIONING

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Extent

Of course the question arises: what is the extent on which dishonesty occurs in science? How important is this subject for the scientific community, for the authorities and for society at large?

In the past this subject was often kept under a discreet veil or trivialized, certainly in scientific circles. This was once more clearly illustrated when, in 1992, Van Kolfschooten sent a questionnaire on deceit in science to over 500 Dutch scientists and several professors mockingly rejected his efforts to gather information (Van Kolfschooten, 1992).

Questionnaire New Scientist

In 1976, for the first time, the New Scientist (St. James-Roberts, 1976a; 1976b) published some quantitative information on deliberate manipulation in science, based on a questionnaire. In 74% of a total of 199 reactions, data massage was reportedly found. In 34 cases (17.1%) experiments had been tampered with, on 14 occasions (7.0%) fabrication and falsification had taken place (plagiarism included) and four times (2.0%) deliberate misinterpretations were found.

Tip of an iceberg...

Until the eighties, the general public had hardly been aware of scientific misconduct and it had a rock-solid trust in the scientific world.
In 1987 the editor of Science, Koshland, was still able to write in a leading article that
"...99.9999% of (scientific) reports are accurate and truthful...", but a year later J.D. Dingell, member of the American Congress, said during a public hearing on fraud that "...there is growing reason to believe that we are only seeing the tip of a very unfortunately dangerous and important iceberg (Teich & Frankel, 1992).

Since the rapidly advancing democratic processes of the seventies, openness is required.
In this way it has gradually become possible to form a picture of the phenomenon. However, it is hard to give exact numbers on the extent of the problem, as these are unknown and - for practical purposes - will probably never become known. The reason is that they are almost impossible to discover and are also hard to quantify. Moreover, many cases will be found in

the grey area of what may still be permissible or what is not.
So it may be assumed that less serious cases occur much more frequently than the evident cases of scientific fraud that were discovered and published. However, it is almost impossible to determine whether these last cases are indeed the tip of an iceberg.
In quantifying the occurrence of scientific misconduct we must determine whether we discuss a total number of cases (per country, per period) or a percentage of the total number of scientific publications and reports produced.

Quantitative data

A number of quantitative data have become known from a survey by the American Association for the Advancement of Science (AAAS) held in 1991 (Grayson, 1995). A total number of 1,500 members were approached, 469 of whom responded. One hundred twenty-four of the responders (27%) reported that in the previous ten years they had come across research where falsification or fabrication of data had taken place.

However, some factual information is available in the United States, at the National Science Foundation (NSF) and the Office of Scientific Integrity, whose tasks were later taken over by the Office of Research Integrity (ORI) of the National Institutes of Health (NIH). The National Science Foundation recorded 99 accusations of scientific misconduct between October 1988 and January 1992, so approx. 30 per year, while on a yearly basis (1995) about 19,000 grants for research projects were awarded by the NSF (i.e. in 0.16% of all cases). For the OSI this number is 192 between April 1989 and January 1992, i.e. an average of approx. 70 cases per year, while 25,000 grants (0.28%) were given by the NIH (Teich & Frankel, 1992) But this only covers the cases reported; the number of cases in which scientific misconduct was indeed determined after an inquest is unknown. By the end of 1993 the ORI had identified 20 scientists who had fabricated or falsified results. All were excluded from receiving American grants. In 1994 the ORI started investigations on 64 new cases (Horowitz, 1996).

Extent of scientific fraud in the United States

To form a picture of the frequency of certain forms of fraud the following table gives an overview of 232 accusations of scientific deceit that were known at the NSF from 1989 to 1994 (Horowitz, 1996):

Accusations of scientific misconduct
(United States, 1989-1994; NSF)

	Accusations (% of 232)

Intellectual theft	50
plagiarism of words or ideas	
Fabrication and falsification	10
Other serious deviations, a.o.	19
breaches of confidentially of peer review	
tampering with experiments	
human subject's violations	
animal's welfare violations	
endangering the safety of colleagues or public	
Retaliation against whistle blower	01
Miscellaneous	19

This illustrates that 'intellectual theft' (plagiarism of words or ideas) is the most frequent (50% of all cases), while in 10% of the cases results had been fabricated. In 19% of these cases other forms of misconduct were found, amongst which tampering with experiments.

Extent of scientific fraud in the Netherlands

In the Netherlands, little research has been done on the occurrence of fraud in science. Tromp & Korzec (1977a; 1977b), after doing a survey for Intermediair magazine, concluded that fraud is not a rare occurrence in Dutch science. The survey Van Kolfschooten conducted in 1992 as a variation on the New Scientist survey was a worthy effort to quantify the problem. Of the 93 people who responded, 68 indicated that they were aware of cases of deceit (73.1%). Six cases of plagiarism (6.5%) and four cases of fraud (4.3%) were reported (Van Kolfschooten, 1992).

In view of the large interests involved, the possibility cannot be excluded that fraud and scientific misconduct take place more often in biomedical and pharmaceutical research than in the other sciences.

The 'Summerlin case'

It was in this field of study that one of the best-known cases of fraud was reported in 1974: W. Summerlin's 'painted mouse'.

Dr. W. Summerlin, immunologist at the Sloan-Kettering Institute in New York, was a researcher in the field of skin cancer. In this respect he investigated the use of tissue culture to facilitate the acceptance of genetically incompatible skin grafts. To make the success of his experiment plausible, he painted transplanted pieces of the skin of a white mouse black with a felt tip pen and claimed these to be transplanted from the skin of a darker mouse (LaFollette, 1996; Lock, 1996a; Teich & Frankel, 1992).

A few years before he had wrongfully claimed to have been successful in transplanting human corneous tissue on rabbit eyes. Summerlin was fired.

Interest from the general press

We must realize that fraud in this field greatly appeals to the general public and that consequently it receives a lot of lay press attention, resulting in front page articles.

The 'Buck case'

A case in point was the Buck case.

In 1990 an enthusiastic Professor H.M. Buck, Ph.D.(employed by the Technical University of Eindhoven, the Netherlands) claimed in a television programme that he had taken an important step forwards in the search for a remedy against the AIDS virus. Very soon this proved to be extremely premature and therefore misleading. It was predominantly a news item because it had given false hope to HIV patients. Buck claimed that he had refined the antisense-RNA technique, which can eliminate hereditary characteristics, and made it applicable to the virus-RNA by the use of 'phosphate methylated DNA'. Dr. J. Goudsmit (employed by the University of Amsterdam, the Netherlands) tested the material and found inhibition at low doses. In the end this turned out to be artefacts. It meant the end of Buck's university career (Van Kolfschooten 1996; Riis, 1996).

The 'Gelmers case'

A second, more recent case of fraud in the Netherlands also attracted a lot of media attention.

The Twenteborg Hospital in Almelo, where Dr. H.J. Gelmers works as a neurologist, participated in a large multicentre Phase III study with dipyridamole, a drug for the secondary prevention of a stroke. The study was financed by the pharmaceutical company Boehringer-Ingelheim and was carried out in 60 hospitals in 13 European countries in a total of approx. 7,000 patients. In the Netherlands, eight (mostly local) hospitals participated. The study started in 1989. After a few years the hospital in question attracted attention by the large number of patients, who furthermore adhered very well to the medication scheme.
Later the results were found to be very different from those obtained by other research centres. In 1996 an article on the study involved

appeared in the Journal for Neurological Sciences. This article stated that part of the results had not been used for evaluation (Diener et al., 1996). In press releases (Anonymus, 1996c; Enserink, 1996; 1997a) these results were reported as originating from Dr. Gelmers, who - allegedly - had invented 438 patients. In 1997, the Dutch Society for Neurology announced in a report 'that suspicion of irregularities is justified', which made Dr. Gelmers cancel his subscription (Anonymus 1997d; 1997e; 1997f; Enserink 1997b, Koenen, 1997). The report, however, is only available for the perusal of members. Neither the hospital, nor Boehringer-Ingelheim, nor governmental bodies can take measures based on its findings.

Footnote: In January 1998 the news broke that the hospital had applied for a dismissal order for Dr. Gelmers.

Trust in integrity of scientists

The public's fundamental trust in the integrity of scientists is betrayed by publications on specific fraud cases and this has led to government intervention, especially in the United States, in spite of initial opposition by the scientific community. We must bear in mind that the 'Summerlin case' came to light in the United States in a period of time that reporters Woodward and Bernstein publicly exposed the misconduct of America's first citizen (President R. Nixon) in the Washington Post (the 'Watergate Scandal'). Since then the detection of scientific fraud has become a rewarding subject for many journalists (Teich & Frankel, 1992).

The 'Slutsky case'

In the eighties a further number of remarkable cases of biomedical fraud followed, such as the Slutsky case (1985).

R.A. Slutsky, cardiologist/radiologist at the University of California in San Diego, wrote 137 articles, together with a number of co-authors, during a time span of seven years (from 1978 to 1985). A large number of these co-authors had been given an 'honorary' co-authorship: sometimes they had not even been approached at all. In 1985, a watchful referee discovered identical statistical results for two different sets of data given in consecutive articles. An inquiry was done, during which descriptions of experiments and measurements were found that had never been done; incorrect procedures had been followed and reports were found of statistical analyses that had not been performed at all. Slutsky's work was closely examined in its entirety. After reading all 137 articles, interviewing the co-authors and looking at laboratory logbooks, 12 articles were certainly found to

be fraudulent and 48 articles questionable. Often the co-authors had not been actually involved in the publication for the simple reason that no work had been done at all.
In the end, 15 articles published in eight journals were retracted. However, the editorial staff of the professional journals reacted very reticently regarding the publication of the retractions. Two of the seven journals that had placed the 12 fraudulent articles did not react at all.
The final report was made public and the government and the subsidizers were informed (Friedman, 1990; Lock, 1996a; 1996b).

The 'Imanishi-Kari case'

The Imanishi-Kari case received a lot of media attention as well.

In 1986, T. Imanishi-Kari, biologist at Tufts University (MA) in the United States, published data on transgenic mice in Cell, which were later found to be completely fictitious. One of the five co-authors was Nobel prize winner Professor D. Baltimore.
A postdoctoral employee, M. O'Toole, had strong suspicions that part of the work had not been done and took the matter up with the authorities. A commission was installed to investigate this; they found small aberrations, but no fraudulent actions. Another investigational committee, however, did indeed find suspicions of scientific misconduct. In 1988, this led to hearings in Congress. In 1990 the fourth hearing was held, resulting in a report by the Office of Scientific Integrity (OSI), in which serious misconduct is described.
In 1991 an extensive exchange of letters between Baltimore, O'Toole and Imanishi-Kari took place in Nature magazine.
The article in Cell was retracted. The final report of the Office of Research Integrity (ORI) (1992), the office that had replaced the OSI earlier that year, proclaimed 19 charges against Imanishi-Kari, in which extensive cases of fabrication and falsification of data are described (Lock, 1996a).

In 1993 O'Toole, initially even blamed for the fact that she had made the case public, was given the 'ethics award' of the American Institute of Chemists (Anonymus, 1991; Hamilton, 1991; LaFollette, 1996; Lock, 1996a).

These cases were taken very seriously and resulted in lawsuits that sometimes dragged on for years.

Over the past twenty years a total of at least one hundred serious cases have become public, most of which in the United States, Australia and England

(Lock, 1996a). Very recently, however, a number of shocking examples have also occurred in Germany (Rispens, 1997), Sweden (Atterstam, 1997) and, as mentioned earlier, in the Netherlands (Enserink, 1996). Thus far, no cases of scientific misconduct in Japan as published in the professional literature have been recorded.

Fraud by students

Most cases of scientific fraud that have become public are based on study results published in the biomedical literature. Less transparent is fraud committed by students as part of their theses and unpublished essays. The fact that plagiarism is frequently committed in these cases was illustrated in 1993 by Swazey et al. (Lock, 1996a), who reported that in the United States more than one third of the staff members in the survey had noticed this phenomenon. In The Netherlands, too, some cases of student fraud have been recorded (Van Kolfschooten, 1996).

Conclusion

In conclusion it can be stated that scientific misconduct is not a frequent occurrence. Light cases are found in a small percentage of all research projects, while serious cases occur with a frequency of 1 to 2 per thousand. Although this last incidence is notably low, the facts found had very serious consequences for the person committing the fraud and for mankind. That is why everything should be done to prevent scientific fraud completely.

MOTIVES FOR SCIENTIFIC MISCONDUCT 4

Motives

The question arises: what is the motivation for scientific misconduct?

Pathological aberration

In every profession - and thus among scientists as well - notorious cheats are found.
Their need to manifest themselves, of need be by scientific misconduct, is sometimes pathological, as in the case of J. Darsee (Grayson, 1995).

The 'Darsee case'

J. Darsee, cardiologist, managed to commit fraud during the main part of his career, working in various American universities of repute. Not until many years of fraud had passed this was discovered during his work at Harvard Medical School (Boston, MA) in 1981. It became apparent that he had committed fraud on a large scale even before the end of his studies, at Notre Dame University (IN). Later he continued this habit at Emory (GA) and Harvard (MA). Not only did he forge data, but also patients and even co-workers. Many of his procedures and results turned out to be impracticable in real life. Darsee was forced to retract more than 100 publications (Horowitz, 1996; LaFollette, 1996; Lock, 1996a; 1996b; Swan, 1996).

Which motives are involved that will make someone overstep the limits of the acceptable and commit scientific fraud?

Prestige and power

In most cases, acquiring scientific *prestige and power* is an important reason.

Scientific fraud, particularly in the category of the marginally unacceptable, is mostly committed by mainly young, self-important and over-ambitious scientists (LaFollette, 1996). There may be shortcomings in their education, but they most certainly have shortcomings in their ability to distinguish between the acceptable and the unacceptable.

...'Prestige and power'... (illustration)

A lack of experience in scientific interpretation certainly also plays a role: what is a 'mistake' and what is 'fraud'?

A forced pursuit of prestige, promotion and awards motivates many, mostly young scientists to violate the scientific truth.

'Publish or perish'

This is also caused by the fact that every scientist is judged by the number of publications in scientific journals. The more - quality - publications, the better: 'publish or perish'.
Every scientist is aware of the fact that he is personally opening up new horizons and strives to be well-known or even famous as a scientist of merit. Winning the Nobel prize one day is something every scientist dreams of from time to time.

Many a medical researcher would like to become famous for the discovery of a new treatment or a new drug, or is in pursuit of scientific power as director of a research institute or as professor.....
Professor Christien Brinkgreve (1997) gives the following resume:
'The pressure for quick successes and particularly the self-assurance one needs to acquire funds lead to dishonesty, an attitude of grandiloquence and exaggeration which goes against much that science stands for: love of truth, curiosity and an attitude of critical doubt. But by force of circumstances - the permanent competition for rare funds - the intellectual becomes a self-assured dealer in projects; more some kind of salesman than a searcher for truth. And sometimes - in the last resort - an embellisher of research data, down the slippery slope of boasting and scoring to bluffing and fraud. As in all other fields, the most important thing in academe is, increasingly, presentation, and those who are not proficient in the art of 'window-dressing' are given the go-by.'

Money

The factor *money* also often plays a role, directly or indirectly.
The fact remains that a fast career also frequently means an improvement in the personal financial position of the researcher.

A researcher can also require payment for results that are too fast or too favourable when participating in the development of a new product, e.g. a new drug.

Fraud caused by hope of financial gain is found with medical researchers as well as clinicians and general practitioners involved in the development of a new drug. These are short-sighted dealings, as forged results in the course of drug development are often contradicted by research elsewhere and will, in the end, be qualified as fraud.

Time pressure

Time pressure is often considerable for a scientist, especially to finish a large project within the agreed time limits, e.g. before a grant or fund runs out, before a conference where a lecture will have to be held or before the end of the contractual period within which his doctoral research will have to be finished.

The factor time pressure increasingly plays an important role in the development of new drugs. Now that the pharmaceutical industry is forced by the authorities to follow an extremely careful but highly time-consuming course of development, with a limited cost recovery period, there is a need to act as efficiently as possible and to make very clear time commitments with the medical specialists involved in the trial.

If time pressure becomes too high for the researcher - for instance by other professional commitments in an environment of decreasing budgets - he will be liable to slip into objectionable practices (Brinkgreve, 1997).

Conflict of interests

Finally a *conflict of interests* may be both a circumstance and a motive for fraud; if the results of a trial imply that a personal interest is damaged or advanced, this may lead to falsification of data.

Even if the motives to commit fraud are present, the fact remains that fraud is not possible unless the circumstances allow it. Lack of supervision and a negative example by the principal investigators may create the circumstances for fraud, regardless of the motive.

Conclusion

In conclusion we see that the reasons for fraud are often founded on an (over)diligent pursuit of fame and scientific power; sometimes it is induced by greed and time pressure. In a few cases a combination of a number of these factors is found, often caused by much stress and an increasing pressure to perform. In view of the latter the possibility cannot be excluded that scientific misconduct will increase in the future.

DETECTION OF SCIENTIFIC MISCONDUCT 5

Detection and proof

Detection and proof of scientific misconduct are delicate processes that can and must be executed with the greatest possible care by a number of authorities, either separately or in collaboration.

Scientific director

Obviously it is the task of the supervisor in charge, i.e. the *scientific director* of a research institute, to make sure that the quality and the integrity of the trial are beyond reproach. It is his or her task to create circumstances that will exclude the possibility of fraud or, if it does occur, to bring it easily into the open.

In a well-organized biomedical or pharmaceutical research institute, where work is carried out in accordance with current regulations and laws in the field of drug research, fraud will be detected at the outset.

Scientific community
'Whistle-blowers'

It is also the responsibility of *every member of the scientific community* to inform the principal investigator of any suspicion of fraud (social control). Most cases of fraud have come into the open in this way, through 'whistle-blowers'; that is, by colleagues on the work floor or working close by.
It is every scientist's task to report dishonest scientific actions or actions by colleagues that are contrary to the research norms.
Such informing should not be considered as the betrayal of a colleague, but as a form of self-regulation that contributes to maintaining the quality of scientific research. As most research these days is done by a team, supervision by colleagues seems to go without saying. But in view of existing contacts between colleagues who are sometimes friends as well, many scientists are loath to play the role of 'whistle-blower'. In practice we also find that the reporting of suspicions of fraud often has far-reaching consequences for the 'whistle-blower', too. This is why it is important that regulations are set to protect the rights of the 'whistle-blower'.

Professional organizations

A number of American *professional organizations* and, *for instance, professional associations* such as the Association of American Medical Colleges (AAMC, 1982) and the Association of American Universities (AAU, 1988) have

included directions for the reporting of inappropriate scientific conduct by colleagues in their guidelines for maintaining high ethical standards in scientific research.

In the Netherlands it was also a professional organization, the Dutch Association for Neurology, that played an important role in ultimately establishing the definite fact that scientific fraud had been committed by one of their members, that is in the Gelmers affair (Anonymus, 1996d; 1997f; Enserink, 1997a).

Colleagues also play a role of importance while perusing new scientific data in publications in specialist literature and at conferences. These provide the opportunity to address critical questions to the scientist who brings the news and as such enable the detection of possible dishonest conduct.

…'Detection'… (illustration)

Editorial staff of professional journals
Peer review

A heavy responsibility in this field lies with another prominent group within the scientific community, i.e. with the *editorial staff of professional journals* and the expert reviewers chosen by them. By having a manuscript judged confidentially and critically by a number of researchers (the referees) in the same field (peer review), mostly kept anonymous, the editor hopes to ascertain that a manuscript is the reflexion of high quality research and that plagiarism or other forms of dishonest scientific conduct are excluded. Guidelines for editors and referees for careful execution of this so-called peer review have been described by Bailar et al.(1990). However, as these referees generally have no direct access to the original data, their possibilities are limited. Only recently the importance of careful peer review to prevent fraud was stressed by Williams (1997).

On the other hand, peer review by dishonest referees may indeed lead to dishonest scientific conduct. In accordance with honoured academic practice, the referees are not supposed to use the information they have. However, in practice the referee may sometimes make improper use of this scientific foreknowledge and use the information for his own research projects. In this context the Immunex case occurred in the United States in 1984 (Marshall, 1996).

The 'Immunex case'

Cistron, a biotechnology firm in New Jersey, accused an employee of its competitor Immunex in Seattle of copying information about a

protein playing a role in the immune system during review of a potential publication and having used it with his colleagues in research of their own as well as in a patent application. A long legal battle followed. However, the accusations in the field of scientific fraud were limited by the judge to breach of company secrecy and unfair competition only. Cistron claimed damages of dozens of millions of dollars. The legal battle still continues. Meanwhile Cistron has gone bankrupt.

The 'Herrmann case'

In Germany a major fraud case has recently been brought to light. According to the charges, F. Herrmann, a scientist in cancer research at the Max-Delbrück-Zentrum für Molekulare Medizin in Berlin, systematically forged measurements between 1992 and 1996. In addition, he made improper use of a research proposal by B. Löwenberg, professor in haematology in Rotterdam, The Netherlands. The latter submitted a research proposal to the Dutch Cancer Foundation/Queen Wilhelmina Fund. Herrmann was asked to judge this proposal on its scientific merits. His opinion was negative, but meanwhile he had it translated and adapted and submitted it, together with his co-worker and partner M. Brach, to the Fritz Thyssen Foundation in Cologne. The proposal was accepted and received a high priority. Since then, four publications by Herrmann were proved to be based on fraud. In twenty others there are strong suspicions in that direction. Herrmann has been fired, he has had to lay down his academic duties, all his financial support has been suspended and he has been denied access to the clinic and the laboratories (Anonymus, 1996b; 1996d; Enserink, 1996; Rispens, 1997); Wildermuth et al., 1997).

In April 1997, the editorial staff of the Journal of the American Medical Association (JAMA) comprehensively discussed the role of editors of scientific journals in those cases where attempts are made to delay publication, which should also be seen as a serious form of dishonest scientific conduct (Blumenthal et al., 1997). A number of recommendations was also made.

The 'Dong case'

The reason for making these recommendations was the Dong case. In April 1994, a manuscript was submitted to the Journal of the American Medical Association on a bioequivalence study with a number of generic preparations and two brand names containing levothyroxine by B. Dong and six co-workers of the University of

California in San Francisco. The preparations examined turned out to be somewhat different, but bioequivalent all the same. The submitted manuscript was accompanied by a letter stating that the sponsor, the pharmaceutical company Boots, heavily criticized the manuscript. After peer review, the manuscript was accepted for publication in January 1995 (Dong et al., 1997; Rennie, 1997).
However, Dong then retracted the article because Boots threatened that they would press charges against the University of California. What had actually happened? In 1987, Flint Laboratories, later taken over by Boots, had assigned this bioequivalence study to Dong, and regularly paid sponsor visits. In 1989, Boots wanted to break the blinding code of an in vitro study, which Dong refused. The in vivo study was finished at the end of 1990 and Dong sent the data to Boots. Boots then tried to discredit the study and asked for observations which had not been provided in accordance with the protocol.
Boots also reported alleged ethical problems. Dong refuted everything (Borst, 1977; Bouvy, 1997; Eckert, 1997; De Ree, 1997; Scholtens, 1997; Spigelman, 1997; Wise, 1997).
In 1994, Boots prevented publication for reasons of confidentiality, but for the University of California the freedom to publish is a fundamental right.
In 1995, Boots merged with Knoll. Later, Boots/Knoll staff published the results in the American Journal of Therapeutics (Manowitz et al., 1996) without any reference to Dong. Besides, in this publication the outcome of the research turned out to be partly contradictory. The conclusion was that, although the preparations were bioequivalent, they were not therapeutically equivalent. Meanwhile the Food and Drug Administration (FDA) had started to investigate the matter. Partly forced by the FDA and because the publicity around this case was very negative, Knoll decided not to obstruct publication any longer.

It was not until 1997 that Dong's article was finally published without any changes in the Journal of the American Medical Association, accompanied by a comprehensive article on the phenomenon (Dong et al., 1997) and by the manufacturer's point of view in a separate article (Spigelman, 1997).

The case was far from closed now, for many legal cases followed (Anonymus, 1997a). The manufacturer was reproached for his wrongful attempts to safeguard the turnover of his original product by preventing the publication, as a result of which the equivalent and cheaper generic preparations were hardly prescribed at all. In a first settlement, the manufacturer has promised to pay a compensation of

98 million dollars to the aggrieved parties (Anonymus, 1997b, 1997c).

Subsidizer

In a study (partly) financed by a third party, this *subsidizer* also has an important task in detecting inappropriate scientific conduct. This may be done by critical evaluation of interim results. At the American National Science Foundation, it is the task of the Office of the Inspector General to detect deceit and fraud, while within the Department of Health and Human Services the afore-mentioned Office of Research Integrity plays an important role.

Pharmaceutical industry

If biomedical research is sponsored by a party that has a commercial interest in the research leading to the development of a new product, this party also has a great responsibility in detecting fraud in time. In the same way the *pharmaceutical industry* has a task here during the comprehensive course of the development of a new drug.
In 1992, the Association of the British Pharmaceutical Industry (ABPI) took on a pioneering role by publishing the guideline 'Fraud and malpractice in the context of clinical research' (ABPI, 1992). In this guideline a standard operating procedure is included, laying down how a pharmaceutical company sponsoring a study should act in the case of possible scientific misconduct. In the guideline a form can be found for the reporting of such cases to the General Medical Council. In practice this procedure is followed several times a year.

Here we find a remarkable initiative by an interest group regularly sponsoring medical and pharmaceutical research, of which the members greatly benefit from reliable results.

Government

An important task is set aside for the *government.* A number of guidelines and laws relating to clinical and laboratory research that have appeared over the past years provide the possibility for control of this kind. In the Netherlands, inspectors of the Public Health Inspectorate are authorized to carry out extensive inspections on location. During their inspection visits to research institutes that want to comply with the norms of Good Clinical Practice (GCP) they will pay careful attention to see whether scientific misconduct may have taken place.

The American government (FDA, Food and Drug Administration) has the authority to carry out so-called 'for cause' inspections at the institutes of those researchers (also outside the United States), who have provided results that

are doubtful in comparison with the results of other researchers who conduct studies with the same (experimental) drug, for instance in so-called 'multicentre trials'.

The society at large

Last but not least control by the *society at large*, where notably the role of the (scientific) journalists must be mentioned. These may play an important role, as they are professional readers of scientific literature. This specifically applies to detecting plagiarism, as was demonstrated in 1996 by reporters of Vrij Nederland, a Dutch weekly magazine, in the work of psychologist Professor R. Diekstra, Ph.D.

The 'Diekstra case'.

In August 1996, plagiarism by Diekstra, professor of psychology in Leiden, was reported in Vrij Nederland (Van Kolfschooten, 1996). In his bestseller Het onderste boven (No stone unturned) 8, 48 and 16 pages respectively turned out to be copied from three American books ('How to heal depression' by Bloomfield and McWilliams; 'Caring for the mind' by Hales and Hales and 'The anxiety and phobia workbook' by Bourne).
Hereupon Leiden University established the Hofstee committee to investigate the case. During the course of the investigation more suspicions of plagiarism by Diekstra, who was very popular with the general public, surfaced in seven other publications in the lay press. Also in an occasional scientific article plagiarism was found. The committee came to the conclusion that both Diekstra's position in the field of education and research as well as his functioning in committees (and the like) had been severely damaged. The committee also concluded that in more than one publishing house the sense of values was insufficient (Investigational committee regarding accusations against Diekstra, 1996). In December 1996, Diekstra resigned from the university (Anonymus, 1996c; Dijkhuis and Janssen, 1997).

Conclusion

It can be concluded that the scientific community (particularly scientific directors of research institutes and colleagues), professional organizations, the editorial staff of scientific journals, subsidizers, the government and the society at large all play important roles in detecting scientific misconduct.

CONSEQUENCES OF SCIENTIFIC MISCONDUCT

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Consequences of detection of scientific fraud

In many cases scientific fraud will not be detected. According to Köbben (1996) the chance of being caught when committing plagiarism is not much higher than when stealing a bicycle (in the Netherlands, that is). However, should it be discovered, then the consequences are often considerable.

Reputation of the scientist

Almost in all cases the scientist's reputation is seriously damaged. Far-reaching sanctions may also be imposed. Often he is compelled to retract the articles in which research of a fraudulent nature was described from the professional literature, while he is denied access to funds for research. The broken career may result in degradation, loss of academic position or even dismissal. Occasionally the person committing the fraud ends up with serious mental problems. A student in South Africa, for instance, committed suicide after his fraud had been detected. The psychological distress of those who have wrongly been accused of fraud can be even more dramatic. A professor in Montreal (Canada) killed four co-workers after having been wrongly accused of fraud. He was sentenced to life imprisonment (Lock, 1996a).

Obviously, the question also arises "What are the legal consequences for the person committing scientific fraud?'
In the Netherlands, fraud is not a legal term and neither is scientific fraud). Legal terms that apply are swindle, deceit (cunningly raising false expectations in the other person) and forgery.

Criminal law

In the Netherlands a scientist committing fraud could be sentenced according to *criminal law* (Article 326-339 of the Dutch Criminal Code) to a maximum of three years imprisonment or a fine of a maximum of Dfl. 100,000.-- In The Netherlands, such sentences have not been imposed yet.

Civil law

The person who commits scientific fraud can be held accountable according to *civil law* (Article 44 part 3 book III of the Dutch Civil Code) and can be sentenced to pay damages. This might happen in the case of accountable shortcomings (default) towards a sponsor of a drug study. As far as known

this has not yet happened in the Netherlands. The person who commits plagiarism may also be held civilly liable for infringement of copyright.
Disciplinary jurisdiction

It is also possible to prosecute a medical or pharmaceutical scientist according to *disciplinary jurisdiction* and/or association law.
In the Netherlands it has not yet been seen that a Medical Disciplinary Tribunal has given a verdict on a member of the medical, dental or pharmaceutical profession who has committed fraud in a scientific field. According to association disciplinary jurisdiction a physician, a dentist or a pharmacist could be formally warned, expelled or even fined. This has never been recorded in the Netherlands, either, as far as known.

Labour law

Obviously, according to *labour law*, a scientist in paid employment risks losing his job in case of fraud.

Educational law

According to *educational law*, the situation is such that the Dutch Higher Education and Scientific Research Act has laid down in what way academic titles can be acquired. However, this law does not contain any provisions for taking away academic titles after scientific fraud may have been established. Recently, however, a professor who was under the suspicion of fraud voluntarily resigned after moral pressure was exerted by the university board, namely in the Diekstra case (Dijkhuis and Janssen, 1997). Furthermore, in 1994 the examining board of the University of Amsterdam invalidated the master degree certificate of two students. However, it remains to be seen whether this is legally admissible (Van Kolfschooten, 1996).

Legal sentences abroad

Contrary to the situation in the Netherlands, several cases abroad are known where scientists who committed fraud have been given disciplinary or, in an occasional case, criminal or civil sentences. Notably in the United Kingdom it has repeatedly occurred that disciplinary sanctions have been imposed on fraudulent doctors, while they were removed from the medical register. This is the most serious disciplinary sanction that the General Medical Council can impose (Hodges, 1996).

...'Legal prosecution'... (illustration)

In the United States fraud usually leads to (voluntary) dismissal.

The 'Poisson case '

In Canada in 1993, R. Poisson was sentenced to pay a fine, after it had been proved that he had committed 115 cases of fraud between 1973 and 1991, a.o. by fabricating and changing laboratory data. He was also given an offical reprimand, was not to receive any grants for eight years, and could no longer act as principal investigator (Gorman, 1994; Lock, 1996a; ORI, 1997).

There is only one distinct case in which a civil as well as a criminal sentence were given, namely in the Breuning case.

The 'Breuning case'

In 1987 S.J. Breuning, psychologist at the University of Pittsburg, falsified data in such a way that it was demonstrated that stimulantia in mentally handicapped children would be more effective and have fewer side effects than the tranquillizers that are part of the standard treatment. This led to changes in the therapeutic policy. As this case obviously had or could have had distinct direct consequences for the patients, Breuning was given a suspended criminal law sentence in 1988 of 60 days service in a halfway house and 250 hours of community service and five year of probation. According to civil law he was required to return his salary of US$ 11,352.-- to the university and given a five-year banning order to practice the profession of psychologist (LaFollette, 1996; Lock, 1996a).

Apart from the afore-mentioned consequences for the people directly involved, others could be victimized as well.

Damaged reputation of research institute

Naturally, the reputation of the *research institute* (in many cases a university) can be seriously damaged.

Professional organizations

The same applies to *professional organizations or associations*. In the case of the neurologist Gelmers of Almelo, the Netherlands, the Dutch Association for Neurology, for instance, was worried about possible damage to its reputation (Enserink, 1996; 1997b).

Subsidizer

Fraud can also be a disgrace for the potential *subsidizer*, in the Netherlands

for instance the Dutch Organization for Scientific Research.

Pharmaceutical industry

If financially supported product development is involved (for instance research paid by a manufacturer of a possible new drug), the *pharmaceutical industry* may be seriously duped. This may result in loss of sales, or even having to take the product off the market.
A manufacturer may even face large claims by users of the product, as happened in the case of McBride in Australia (Andersen et al., 1992; Swan, 1996).

The 'McBride case'

In 1979 W. McBride, director of Foundation 41, a private institute studying the first 41 weeks of life, announced suddenly that the drug bendectin (Debendox) worried him.
This drug was regularly used by pregnant women against sickness and vomiting. He suspected the drug of causing damage to the foetus, in the same way as he had described for thalidomide in the sixties. The drug stayed on the market until 1981, while McBride kept trying to discredit it in the media on the basis of its alleged teratogenic characteristics. The pharmaceutical company was bombarded with hundreds of claims for millions of US dollars. For commercial reasons the drug was withdrawn from the market and in 1984 the company agreed to pay 120 million US dollars over a period of twenty years in a fund set up for all claimants. In 1988, at the initiative of one of McBride's co-workers, P. Vardy, an inquiry was initiated. The accusations against bendectin turned out to be based on very incomplete and fraudulent research by McBride on the effect of hyoscine, a drug related to one of the components of bendectin, in rabbit foetuses.
The inquiry committee concluded in its final report that McBride was guilty of lack of scientific integrity. He was fired on the spot, Foundation 41 was closed and in 1993 McBride was removed from the medical register.

In case of fraudulent research with a drug that has not yet been registered the consequences can be far-reaching. A serious delay in the registration process may be the result. This will have grave financial consequences for the company involved as the cost recovery period is limited.

The society at large

But also, and this may be the most important aspect, scientific fraud may

have serious consequences for *the society at large.* An effective drug may be wrongfully withheld from the patients as was the case with bendectin. It may also happen that a new and effective drug is not available to the patient until later (which is perhaps too late).

Very serious was the situation in Australia in 1971, when many female users of imipramine had procured abortions after the afore-mentioned McBride had wrongfully claimed that the drug could lead to birth defects (Andersen et al., 1992; Swan, 1996).

It could also happen that negative characteristics of a medicine are disguised with the result that a drug which is not completely safe is marketed.

Fraud in scientific research with life-saving medical instruments (such as pacemakers and cardiac valves) can have disastrous results. In other words: the society at large might have to pay a very high price, both literally and figuratively.

Conclusion

In conclusion it can be stated that the consequences of scientific fraud can be very serious for the person committing the fraud, his (direct) environment, the subsidizer and the society at large, but most importantly it could directly affect the patient.

PREVENTION OF SCIENTIFIC MISCONDUCT

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Conditions research environment

If we describe the prevention of fraud from a positive point of view, we end up with 'safeguarding the integrity of scientific research'. Or in other words: What conditions should a research environment meet to prevent fraud completely?'

Research climate

In the first place we must mention the general atmosphere in which the research takes place, in other words, the *research climate*. High quality scientific research can only take place in a good research climate.
The role model of an incorruptible director whose behaviour is beyond reproach, and who exudes responsibility, is of vital importance. Good coaching and control by this research leader and by the most experienced colleagues during the study is very important. It is a matter of good management, with an aim to deliver high quality study results.

Scientific community

It is the collective task of all members of the *scientific community* to make sure that they are properly introduced in the code of good research practices. Several research institutes, in particular universities in the United States, have drawn up their own guidelines regarding the ethical aspects of science.

Guidelines scientific ethics

The University of Scranton (PA) (University of Scranton, 1989) and the Oakland University (MI) (Oakland University, 1996), for instance, have their own *guidelines* regarding *scientific ethics*. After a fraud incident the University of Stanford (CA) decided to compose guidelines for multidisciplinary research (Lock, 1996a).
Harvard Medical School, Boston (MA) does not only have "Guidelines for Investigators in Scientific Research" (Tosteson, 1988), but also 'Faculty Policies on Integrity in Science' (Harvard Medical School, 1994). The latter promote high standards for research practice. These guidelines require that co-workers are carefully monitored. The collecting, storing and archiving of data must be done with accuracy. Departments should develop a policy regarding authorship and co-authorship and the number of publications that a candidate is allowed to submit for his or her thesis should be restricted.

Other examples of universities that have drawn up their own guidelines for the

advancement of the integrity of scientific research are:

- Queens University (Canada): A Code of Research Ethics (1987) and Policy on Academic Dishonesty (1989);
- University of Waterloo (Canada): Research ethics: Human Research, Animal Care, Policies and Guidelines. Administrative Guidelines on Misconduct in Research (1994);
- University of California, San Diego (CA, United States): Integrity of research (1995);
- University of Toronto (Canada): The Purple Book; Chapter 7: Ethical Conduct in Research. Chapter 12: Intellectual Property. Chapter 13: Collaboration with Industry (19965);
- Monash University (Australia): Code of practice for the supervision of masters degree candidates undertaking a thesis/research project (1996);
- University of Delaware (DE, United States): Policies and Procedures Manual (1996);
- University of California, Los Angeles (CA, United States): Integrity in Research: responding to allegations of misconduct in science (1997);
- University of South Florida (FL, United States): Guidelines for the responsible conduct of research (Draft) (1997).

Cooperative bodies between universities also have their own guidelines on the ethics of scientific research, such as the guideline 'Maintenance of High Ethical Standards in the Conduct of Research', published by the Association of American Medical Colleges in 1982 (AAMC, 1982). In 1989 the same organization published the 'Framework for Institutional Policies and Procedures to Deal with Misconduct in Research ' (AAMC, 1989).

Other relevant examples are publications by the Association of American Universities (AAU), representing 62 of the largest universities in the United States and Canada, such as 'Integrity of Research' (AAU, 1985) and 'Framework for Institutional Policies and Procedures to Deal with Fraud in Research' (AAU, 1988).

Education

But prevention of scientific misconduct, however, cannot be reached by the mere drawing up of guidelines.
At least as important is solid *education* in the standards and values of scientific research. This could be accomplished by a compulsory course in 'Research ethics' during the schooling of the scientific researcher.

A good example of prevention through training is the course 'Science ethics'

given at the University of Groningen, the Netherlands by Prof. T. Kuipers, Ph.D., and which can be taken by pharmacy students as an optional subject. The manual "On being a Scientist' by the American Committee on the Conduct of Science of the National Academy of Science (NAS, 1989) and can be seen as a good starting-point for schooling in research ethics. This document is used by Prof. D.D. Breimer, Ph.D. of the University of Leiden, the Netherlands, LACDR (Leiden/Amsterdam Center for Drug Research) when training scientific researchers.

...'Research ethics Course'... (illustration)

Professional organizations

Furthermore, several *professional organizations* play a preventive role, having voluntarily drawn up standards for research ethics for their members. In England, for example, such guidelines on a voluntary basis have been drawn up by the parties concerned, such as the professional organizations for physicians, the 'Royal College of Physicians of London' which published guidelines in 1991 for the prevention of fraud in scientific research in man (RCP, 1991).
Apart from the afore-mentioned AAMC a number of other American professional organizations have drawn up guidelines, i.e.:

- Amercian Association of University Professors (AAUP): Statement on plagiarism (AAUP, 1989);
- American Federation of Clinical Research (AFCR): Guidelines for the responsible conduct of research (AFCR, 1989);
- Association of Academic Health Centers (AAHC): Conflicts of Interest in Academic Health Centers (AAHC, 1990).

(Frankel, 1993).

Other large educational projects to improve the ethical standard in scientific research are carried out among others by the American Association for the Advancement of Science (AAAS), such as the project 'Integrity in Scientific Research (Frankel, 1996). In this project the National Institutes of Health, the Office of Research Integrity of the US Department of Health and Human Services and the Agricultural Research Service of the US Department of Agriculture also participated. The project has also attracted international attention and has great educational value.

Editorial staff of professional journals

Furthermore, the *editorial staff of professional journals* has an important task in detecting scientific fraud, as well as a distinct educational and preventive task, particularly by 'peer review'. Details were already discussed in the

chapter 'Detection of scientific misconduct'.

Subsidizer
Organizations coordinating research

An important task in laying down a code of practice for scientists seems to have been assigned to the *subsidizer*. Often these are large *organizations coordinating research*, such as the American National Institutes of Health (NIH) and the National Science Foundation (NSF).

In 1989 the US Department of Health and Human Services decided to establish an Office of Scientific Integrity (OSI) within the National Institutes of Health as well as an Office of Scientific Integrity Review (OSIR) within the Office of the Assistant Secretary of Health, a higher organizational level within the Department of Health and Human Services. As this structure proved to be unsatisfactory in practice, these offices were abolished in 1992 and a new office was founded, the Office of Research Integrity (ORI) within the Department of Health and Human Services, which gives government more direct control.

A second government institution dealing with this subject is the National Science Foundation (NSF).

Notably the NIH (in the Guide for Grants and Contracts) and the NSF (in the Federal Register) play an important preventive role, having drawn up guidelines that should prevent fraud in science.

In Australia, the country where a number of the most sensational cases of fraud in biomedical science have occurred, a comprehensive guideline was published in 1990 (NH & MRC, 1990). This 'Code of Practice', the 'Statement on Scientific Practice' of the National Health and Medical Research Council, gives several recommendations for the prevention of fraud.

Danish 'example is better than precept'

Among the other European countries it was Denmark in particular that set the example. In spite of the fact that, to date, fraud has been reported relatively rarely in this country, a centrally coordinated action of all parties involved in scientific research was initiated. In 1992 the Danish Committee of Scientific Dishonesty started its activities to detect and prevent fraud. Under the chairmanship of a High Court judge, participating members are university staff, members of (scientific) professional organizations, representatives of editorial staff of medical journals and hospital owners. The system functions satisfactorily.

This initiative was later followed by the other Scandinavian countries (Andersen et al., 1992).
In the Netherlands:
'Note on scientific misconduct'

In the Netherlands, too, an important initiative has been taken, that is by the Royal Dutch Academy of Sciences, the Association of Cooperating Dutch Universities and the Dutch Organization for Scientific Research. In 1995 these organizations published a joint policy document entitled '*Notitie inzake Wetenschappelijk Wangedrag*' (Note on Scientific Misconduct) (KNAW, VSNU, NWO, 1995). In this - short - note ample attention is given to prevention. A plea is also made for the implementation of broad procedures to be followed in case misconduct is found. Advice is given to the effect that the individual universities, the Royal Dutch Academy of Sciences and the Dutch Organization for Scientific Research each introduce their own independent committees of experts to conduct an investigation in case of fraud. In the report reference is made to the afore-mentioned 'Danish model'.
However, to date no information about the functioning of such committees has become available.

Ombudsman

Apart from schooling and guidelines, the appointment in research institutes of an *ombudsman* for scientific research could have a preventive effect. Köbben (1995, 1996) says in this respect: 'His presence might have a preventive effect, could exculpate those who have wrongly been accused of fraud or other unsuitable activities in science and could replace gossip and slander by an honest process; for the fact remains that a number of ethical problems in science present themselves, both old and new ones...'. And he continues:' ... such a functionary would not so much have to be an "Avenging Angel", but would offer a normative hold to individual scientists and institutions'.
Although no examples are known of ombudsmen for science at individual Dutch universities, a task could be set aside here for these universities. It may, however, also be conceivable that the appointment of a national ombudsman for science takes place in a larger context, e.g. by the agency of the Royal Dutch Academy of Sciences.

Government

The Dutch *government* has not yet taken any legal measures for the prevention of scientific fraud in its broadest sense. However, in the Netherlands thought has been given to the question whether there should be an authority dealing with the problem of fraud in science.
The thought was repudiated, as it was felt that fraud only occurred sporadi-

cally; a completely different point of view from the one taken in the United States. In fact this idea implies the assumption - which has long since been abandoned in the United States - that the professional group can handle its own problem (by auto regulation).

GLP; CGP; Medical Research Involving Human Subjects Act

However, the government institutions have been intensively involved - also directly - in implementing strong regulations applying specifically to biomedical research.
The best-known ones are: the rules for *Good Laboratory Practice* (GLP), for *Good Clinical Practice* (GCP) and the *Medical Research Involving Human Subjects Act*.

Conclusion

In conclusion we can state that various 'self-regulation' initiatives have been taken to prevent fraud, such as by co-workers, universities, professional organizations, the editorial staff of journals, subsidizers and by the semi-governmental bodies dealing with the coordination of scientific research. The authorities are active in this field as well.

GOOD LABORATORY PRACTICES

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GLP

An important step forward in the prevention of fraud in biomedical research, particularly in pharmacology and toxicology, was the establishment of the regulatory system of Good Laboratory Practice (GLP).

Main purpose

The main purpose of the GLP rules is to improve the quality, and with it the reliability of study results. In fact it can be stated that the principles of GLP form an initial but important initiative towards structural quality management of scientific research in the laboratory.

Definition

The Organisation for Economic Co-operation and Development (OECD) defines Good Laboratory Practice as follows:

Good Laboratory Practice is a quality standard for the execution of preclinical laboratory studies by means of planning, execution, reporting and archiving, where extensive support is given through 'monitoring' (OECD, 1981).

Monitoring implies an intensive interaction with the executor of a study before, during and after the execution to arrive at maximum reliability of the results.

Reason:
FDA and EPA inquiries

The introduction of the regulatory system of Good Laboratory Practice has come into existence, among other things, as a result of the situation in the mid-seventies in the United States of America.
By order of the Senate, a large inquiry was done by the FDA (Food and Drug Administration) and the EPA (Environment Protection Agency) in the pharmaceutical and chemical industrial world.
During this inquiry various deficiencies were found in the execution of scientific research (Anderson, 1995; Horowitz, 1996; Taylor, 1989).

The 'BioTest case'

Serious discrepancies were found in the leading contract research laboratory Industrial BioTest Corporation (IBT) in Northbrook, Illinois. This laboratory had executed a number of thousands of animal studies on the safety and efficacy of hundreds of drugs and pesticides.
The irregularities included:
. falsification of laboratory work;
. replacement of test animals that died during the study by new test animals without correct documentation;
. fabrication of study results;
. excluding study results when the sponsor felt these to be unfavourable.
IBT's management was found guilty of misleading the government and was given long imprisonment sentences.
It goes without saying that the company is no longer in existence.

Results FDA-inquiry

From the results of this large inquiry the FDA concluded, among other things, the following:
. experiments were poorly conceived, carelessly executed and inaccurately analysed or reported;
. technical personnel were unaware of the importance of protocol adherence, accurate observations, accurate administration of test substance, and accurate recordkeeping and record transcription;
- management did not assure critical review of data or proper supervision of personnel;
- studies were impaired by protocol designs that did not allow the evaluation of all available data;
- assurance could not be given for the scientific qualifications and adequate training of personnel involved in the research study;
- there was a disregard for the need to observe proper laboratory, animal care, and data management procedures;
- sponsors failed to monitor adequately the studies performed in whole or in part by contract testing laboratories;
- firms fails to verify the accuracy and completeness of scientific data in reports of nonclinical laboratory studies in a systematic manner before submission to FDA.
(Anderson, 1995; Taylor, 1989).

GLP rules have thus been composed with the aim of improving the integrity of the study results and consequently to further the decline of fraud. The results will have to become more reproducible by increasing the transparency of the total execution of the study.

Another, very important objective of GLP rules is improving the wellbeing of

laboratory animals.

…'Good Laboratory Practice'… (illustration)

Relevant aspects GLP

Some of the most relevant aspects of the principles of GLP are the following:

- a study should be carefully designed and executed in accordance with a strategic plan, implying, among other things, an accurate protocol. An elaborate system of standardized procedures (Standard Operating Procedures - SOPs) laid down in writing must be used;
- the researchers should be well-trained and kept up to date by a system of refresher courses. This system should be put down in writing;
- clear responsibilities should be laid down, with one person, the Study Director, who has the final responsibility;
- during the study continuous monitoring should be carried out to check whether the study is executed in accordance with the protocol;
- the study should be executed in a well-organized laboratory with quality equipment which is carefully maintained, calibrated and standardized;
- working circumstances should be such that personnel can carry out the work in safely and in accordance with the safety instructions which have been laid down in writing;
- test and control articles should be checked carefully on concentration, uniformity and stability;
- during the full duration of the study all activities and findings should be well-documented and a good final report should be written stating reliable results ('not documented = not done');
- an independent Quality Assurance Unit should be in operation, carrying out audits before, during and after the study in accordance with a programme for quality control laid down in writing;
- finally, the study documents and possible other items of evidence should be carefully archived.

United States: FDA-GLPs

The first set of GLP rules was published in the *United States* in 1978 by the *Food and Drug Administration* under the title 'Good Laboratory Practice Regulations for Nonclinical Laboratory Studies' (FDA-GLPs) and came into force in 1979 (FDA, 1978). Over the years many amendments were to follow. These regulations apply to all preclinical laboratory studies (wherever in the world they are performed) meant to provide information for a file for a trade permit (registration, market authorisation) of a new drug in the United States. This not only applies to drugs for use in man, but also to those meant for animals. The FDA-GLPs also apply to studies with food additives, colouring

agents, medical devices for human use, biological and electronic products ('for use in man').
EPA-GLPs

In 1983 another department of the American government, the US *Environment Protection Agency* (EPA) published two guidelines "Good Laboratory Practice Standards', especially for environmental research (EPA, 1983a; 1983b).

Apart from these GLP guidelines that have been drawn up by the American government, regulations in the same field have been composed and implemented by other organizations.

Japan

Japan has two sets of guidelines for good laboratory practice, i.e. by the Ministry of International Trade and Industry and by the Ministry of Agriculture, Forestry and Fishery.

ICH guidelines

Supplementary GLP guidelines were also introduced under the terms of the *International Conference on Harmonisation* (ICH).
The aim of this ICH is to attain harmonization of requirements and procedures in applying for a trade permit (registration) of a new drug.
Representatives of the government and the pharmaceutical industry of the United States, Japan and the European Union take part and observers from the World Health Organization (WHO), Canada and the European Free Trade Association (EFTA) are present.
In the meantime, the ICH has already published a number of guidelines in subsectors of pharmacology and toxicology.

OECD-GLPs

A set of regulations with a lot of impact is the one introduced by the *Organisation for Economic Co-operation and Development* (OECD, Paris), that is the 'OECD Principles of Good Laboratory Practice (OECD GLPs), drawn up in 1981 (OECD, 1981). Since then a number of important supplements have followed. In 1997, the guideline was revised (OECD, 1998).
Although these rules were endorsed by a great number of countries, they do not have any force of law in themselves.

European Community

In 1986 the *European Community* adopted the OECD-GLPs and by means of a

Directive the member states were asked to implement them in their national legal systems (EEC, 1987).
The Netherlands

In *the Netherlands,* this system acquired force of law in that same year, as it was laid down in the 'Act on environmentally hazardous substances'.
In our country there is a requirement to implement GLP principles in all safety research (toxicological, pharmacological and physical-chemical) into drugs for human use, drugs for use in animals, industrial chemicals and pesticides (Helder, 1993).
By giving the GLP rules force of law, the Dutch government has come into possession of a powerful tool to prevent and fight fraud.

Furthermore, it is an important 'management tool' for the management of a scientific research centre, so that they can make sure that the quality of the research is high and remains that way.

FDA inspections: The investigator examined

The American FDA has an Office of Compliance with over 1,000 inspectors who carry out inspections on the site to see whether GLP rules are complied with. These FDA inspectors regularly find deficiencies, which should, however, not all be considered as attempts to commit fraud, but are rather the result of careless actions and non-compliance with the very strict and severe requirements.

Between June 1979 and September 1995 a total of 1.054 inspections were carried out, in which a total of 2.630 deviations were found (Horowitz, 1996). Deviations were found in all fundamental aspects of GLP, i.e.:

	Percentage of deviations
standard operating procedures	**36**
protocol and conduct	**34**
personnel/management/study director	**30**
equipment (maintenance, calibration)	**26**
quality assurance	**24**
final report	**23**
test and control articles	**19**
animal care	**16**
records	**15**
animal testing facilities	**9**

refusals 1

The Netherlands: Veterinary Supervisory Inspection

The FDA audits are not restricted to the United States only. Apart from GLP audits, audits in the field of Good Clinical Practices also take place (see Chapter 9).

In the Netherlands, FDA GLP inspections will normally not take place, as in 1988 the FDA signed a Memorandum of Understanding with the Dutch government in which is stipulated that both countries recognize each other's GLP inspectorate (FDA, 1989). The Dutch government has signed comparable agreements with the Japanese government in the same year (Ministry of Health and Welfare of the Government of Japan et al., 1988; Pharmaceutical Affairs Bureau, Ministry of Health and Welfare of the Japanese Government and Ministry of Welfare, Health and Cultural Affairs of the Netherlands, 1988).

In the Netherlands the supervision on the compliance of GLP rules lies with the Staatstoezicht op de Volksgezondheid, in casu the Veterinary Supervisory Inspection.

'Endorsement of Compliance'

After an elaborate - prospective -inspection an official declaration, a so-called 'Endorsement of Compliance' can be obtained, certifying that a laboratory is in compliance with the requirements. Such inspections usually take place every two to three years. Laboratories that do not have such a certificate cannot claim that studies are carried out in accordance with GLP. On December 31, 1996, 34 Dutch laboratories were in possession of this certificate, three did not comply when inspected and four applications were still under consideration (VWS, 1996).

Among the laboratories which have been given this certification, no university laboratories can be found.

Schooling

Generally speaking it can be said that the results of the inspections prove that there is considerable room for improvement. It is, indeed, unlikely that the deficiencies are completely based on deliberable scientific misconduct by the researchers. Rather will it be a matter of careless application of the rules and probably above all insufficient knowledge of regulations with those who carry out the research. This is among other things caused by the fact that schooling in quality management of scientific research has thus far hardly been provided

at universities and higher educational institutes.

Conclusion

In conclusion it can be said that in almost all countries of the world a quality standard for the conduct of (nonclinical) laboratory research is part of the official law (GLP).
The inspections carried out by the government prove that these rules are still insufficiently adhered to, possibly also because of a lack of formal schooling in the field.

GOOD CLINICAL PRACTICES

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GCP
Main purpose

Following the regulatory system of Good Laboratory Practice, a similar system has been set up for Good Clinical Practice (GCP).
The Good Clinical Practice rules are also a quality standard, so a suitable means for quality management of a clinical study.

The International Conference on Harmonisation (ICH) defines Good Clinical Practice as follows:

Definition

'Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
(ICH, 1996)

It is important that the words 'ethical quality standard' are used here.

Immediate cause:
thalidomide tragedy

Just as in the Good Laboratory Practice (GLP) rules the necessity of the introduction of a system of GCP rules was initiated after it had been established in the sixties and seventies that there were deficiencies in the conduct of biomedical and pharmaceutical research.
As already pointed out in the afore-mentioned examples of fraud, the vulnerability of the participants in the studies was a particular cause for concern. The thalidomide (Softenon) tragedy made the medical and pharmaceutical world realize that profundity and accuracy of drug research would have to be increased.

Thalidomide was marketed for the first time in Germany in 1956. In the following years a great number of cases of congenital deformations and stillbirths became known, particularly in Germany, England, Wales and Japan. Worldwide, the number of victims is

estimated at approx. 10,000. By the end of 1961 the drug was taken off the market (Griffin, 1992; Powell, 1996; Schardein, 1985).
'Declaration of Helsinki'

However, before these GCP guidelines had been issued by the government, a code of practice had already been agreed on in the field of clinical research. At their annual meeting in Helsinki in June 1964, the World Medical Association adopted the so-called 'Declaration of Helsinki', a set of recommendations for physicians regarding biomedical research in man (World Medical Association, 1964). Since then, the Declaration was adapted on many occasions, the last time being in 1996.

Although the Declaration mainly deals with medical and medical-ethical aspects, it also contains means to prevent fraud, in particular where it is stated that 'in publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results'.

Medical ethics

The purpose of the GLP and GCP rules is in general the same, namely to obtain more reliable results. However, the *ethics* of research in man, including the protection of the participants, is one of the most important aspects of the GCP rules. This had already been laid down in the abovementioned Declaration of Helsinki and contains items such as:
. participating of one's own free will (and written informed consent);
. submission to an institutional review board of independent ethics committee;
. the foreseeable risks and inconveniences should be weighed against the anticipated benefit;
. sufficient preclinical and clinical information to justify the study;
. medical care given to subjects should be the responsibility of a physician;
. right to privacy.
(EMEA, 1996)

Approval by an Independent Ethics Committee (IEC) is mainly meant to acquire an objective opinion whether it is a well-founded decision to carry out the study, from a medical as well as an ethical point of view. This assessment also means a significant addition to the afore-mentioned possibilities of preventing fraud and protecting the participants. In itself, it is an important means of quality management in the conduct of a clinical study.

…'Good Clinical Practices'… (illustration)

FDA-GCPs

In contrast with the GLP guidelines, the rules for GCP have not been published by the FDA as one complete document in the *United States*. On the contrary, individual guidelines have been published in the course of the years, starting in 1977, and these are collectively referred to by the name of Good Clinical Practice (FDA,1977; 1980; 1981; 1985; 1987, 1988).

European Community
In the course of the years, GCP guidelines have been written in Japan and in a number of European countries as well. There is no doubt that the primary European guideline is the one published in 1990 by the *European Community*, i.e. by the Committee for Proprietary Medicinal Products (CPMP). This Note for Guidance is entitled: "Good Clinical Practice for Trials on Medicinal Products in the European Community' (Final July 11, 1990; Effective July 1, 1991) (CPMP, 1990).

By a Directive of the Committee of the European Communities (91/507/EEC-July 19 1991) (EEC, 1991b) all member states were called upon to lay down in their national legislation that all phases of clinical research, including bioavailability studies and bioequivalence studies, should be designed, conducted and reported in accordance with Good Clinical Practice.

The Netherlands

As from August 01, 1994 the Note for Guidance has gained force of law in *the Netherlands* when it was incorporated in Article 55 of the 'Besluit bereiding en aflevering van farmaceutische produkten' van de 'Wet op de geneesmiddelenvoorziening.

World Health Organization

In 1994 the *World Health Organization* (WHO, Geneva) published its own guideline, entitled 'Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products' (WHO, 1994). This guideline has no force of law.

ICH regulation becomes global standard

In 1996 the afore-mentioned *International Conference on Harmonisation* approved a guideline entitled: 'ICH Harmonised Tripartite Guideline - Guideline for Good Clinical Practice' (ICH, 1996). In the same year this guideline was accepted by the European Union as a directive entitled 'Note for Guidance on Good Clinical Practice' (CPMP/ICH/135/95) and it has come into effect on January 17, 1997 (EMEA, 1996). This directive, too, will not have force of law until it has been adopted in the national legislation of the individual countries. Nevertheless, the ICH-GCPs are already applied on a large scale. This ICH

regulatory system promises to become the new global standard for GCP.

Both these regulatory systems are strongly based on the above-mentioned Declaration of Helsinki of the World Medical Association (1964).

Relevant aspects GCP

The most important aspects (the 'principles') of the ICH-GCPs are described as follows:

. clinical research should be carried out in accordance with the ethical principles that originate from the 'Declaration of Helsinki' and which are consistent with GCP and the relevant legal requirements;
. before the start of a clinical study the risks and discomforts to be expected must be balanced against the advantage to be expected for the individual volunteers and the community at large. A clinical study can only be initiated and continued if the advantages to be expected justify the risks;
. the rights, safety and wellbeing of the volunteers constitute the predominant considerations and must prevail over the interests of science and community;
. the available preclinical and clinical information regarding an investigational product must be sufficient to form the basis of the research proposal;
. clinical research must be scientifically sound and must be described in a clear and detailed protocol;
. a clinical study must be carried out in accordance with the protocol which has been assessed beforehand by a Medical Ethics Committee (MEC);
. the medical care for and the medical decisions on behalf of volunteers must always be taken under the responsibility of a qualified physician or, if applicable, a qualified dentist;
. each person involved in the execution of a clinical trial must be qualified by education, training and experience to carry out his or her respective tasks;
. prior to participation in a clinical trial, written informed consent should be obtained from every volunteer on a completely voluntary basis;
. all data regarding a clinical trial should be laid down, handled and filed in such a way that they remain available for accurate reporting, interpretation and verification;
. the confidentiality of the documents for identification of the volunteers must be protected, and the rules for privacy and confidential treatment should be observed in accordance with the relevant legal requirements;
. investigational products must be manufactured, handled and stored in accordance with the relevant Good Manufacturing Practice (GMP). They must be used in accordance with the approved protocol;

. systems should be introduced containing procedures for quality assurance of every aspect of the trial.

In the directive very detailed mention is made of:

. the procedures relating to the approval by a Medical Ethics committee (MEC);
. the responsibilities of the researcher;
. the responsibilities of the Sponsor;
. the contents of the clinical research protocol;
. the contents of the 'investigator's brochure';
. the contents of a number of other essential study documents.

Medical Research Involving Human Subjects Act

In September 1997, a bill was accepted by the Dutch Lower Chamber, entitled '*Medical Research Involving Human Subjects Act*'. This Act, too, mainly provides for ethical aspects, but on many points it can certainly be used as a means to control and support the quality of medical research.

The researcher examined

The question arises to what extent the inspections, based by the government on the guidelines for GCP, will prove to be effective as a control in quality management of drug research.
The starting-point must be that one learns from one's mistakes and that quality management is a continuous process of improvement.

FDA inspections

The FDA can carry out inspections in the field of GCP in accordance with a number of so-called 'Monitoring Programs' and - as already mentioned in the chapter on GLP inspections - it has a body of over 1,000 inspectors at its disposal.

Just as during the GLP inspections, the FDA found a large number of so-called 'deviations' during the GCP inspections.
In the United States, between January 1977 and January 1996, over 3,700 inspections were carried out by the FDA (Anonymus, 1996a; Brown, 1997; Horowitz, 1996). The most important deviations found were:

Deviations in fundamental aspects of GCP
(United States, 1977-1996)

	Percentage of deviations
Insufficient written informed consent	53
Protocol not completely followed	30
Record keeping incomplete	25
Errors in drug supply records	20
MEC not kept completely informed	12

From the results of inspections held by the FDA in Europe until October 1995 the following deviations come to light (Horowitz, 1996):

Deviations in fundamental aspects of GCP
(Europe, until October 1995)

	Percentage of deviations
Record keeping incomplete	82
Protocol not completely followed	79
Errors in drug supply records	41

The Netherlands: Public Health Inspection

In The Netherlands GCP inspections are carried out by the Public Health Inspection. The Inspection began its activities in 1993. Periodic inspections of health institutes are carried out on a prospective basis, while one or more trials are completely inspected as well.

'Statement of Compliance'

In case of approval, the Inspectorate issues a so-called *'Statement of Compliance'*, with a validity period of three years. It is remarkable that this has only happened on five occasions as yet. In all cases so-called Contract Research Organizations were the recipients. This means that no large medical research centres (such as academic hospitals or their departments) have been given GCP approval by the Inspectorate.

Schooling

From the information on inspections by the authorities, important conclusions can be drawn regarding the improvement of the clinical drug research.

Improvement may be reached in particular by better schooling of the persons

involved (namely physicians, research nurses and pharmacists) on the basic principles of Good Clinical Practice.

However, it is to be expected that an increase in GCP inspections will lead to a further improvement of the standard of drug research in The Netherlands.

Conclusion

In conclusion it can be stated that in most countries a quality standard for the execution of clinical (drug) research (GCP) has become part of the legislation. The inspections as executed by the authorities prove that there is ample room for improvement in following these rules. This improvement may be obtained by more extensive of training and by stricter control.

GOOD MANUFACTURING PRACTICES

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GMP

A third very important quality standard in the field of drug research is the Good Manufacturing Practice (GMP) standard, or good method of producing.

In spite of the fact that this regulatory standard does not apply directly to scientific research, but rather to manufacturing, it ought to be mentioned here. Mainly in the field of production and inspection of the investigational product there is a certain interaction with the quality systems mentioned earlier. In this way, GMP indirectly contributes to greater reliability in drug research.

Main purpose

However, GMP regulations mainly relate to the production process, in particular after registration (market authorization, trade permit) has been obtained. The rules have been formulated because it is important that every batch of the product meets the required specifications and that a possible decreasing quality of the product will not cause any undesired effect.

A definition of Good Manufacturing Practice which is often used can be found in the regulations of the European community and runs as follows:
Definition

Good Manufacturing Practice is the sum of all factors that should make sure that the quality, safety and efficacy of the product meet the specifications and that consequently the product is fit for use as meant in the registration dossier (EEC, 1991a; Kendall, 1996).
(ICH, 1996)

Therefore, Good Manufacturing Practice is a distinct quality standard. The implementation of this system was also inspired by the already mentioned thalidomide tragedy.

United States

The concept 'Good Manufacturing Practice' was introduced for the first time in the legislation of the *United States* in 1962, in the Kefauver-Harris Amendment on the Food, Drugs and Cosmetics Act (Heir, 1994; Kendall, 1996). The first American legislation regarding GMP for drugs dates from 1975

(FDA, 1975), and many other countries have followed since then.

European Community

In 1991 a European Directive entitled: 'Good ways to produce drugs (91/-356/EEC) (EEC, 1991a) was issued.

The Netherlands

In *the Netherlands*, GMP has been part of the "Wet op de geneesmiddelenvoorziening" since 1992.

Conclusion

***In conclusion it can be stated that the legal rules for Good Manufacturing Practice (GMP) only have an indirect importance for drug research, namely only where production of the investigational product is concerned. However, in this indirect way these rules still contribute to more reliable drug research*.**

THE ISO 9000 QUALITY NORM 11

ISO 9000 series

Next to the GLP, GCP and GMP quality standards, which were discussed earlier and which are mandatory regulations, the ISO 9000 quality standard may also be of great use in drug research and drug production.

The ISO 9000 series of international standards for quality management and

quality assurance was published by the International Organization for Standardization (ISO, Geneva) in 1987 (ISO, 1987; ISO, 1994a). ISO is a global federation of national standardization institutes from 120 countries (ISO, 1997).
The 'Nederlands Normalisatie-instituut' (NNI) in Delft participates in ISO representing the Netherlands. Adherence to the ISO standards takes place on a voluntary basis; ISO in itself has no legal powers.

Guidelines for effective quality management

The ISO 9000 series of standards represents an international consensus on good management practices.
Its primary aim is to provide guidelines for organizations to set up an effective quality management system which will be the basis of a system of continuous improvements.

The series contains three quality standards: ISO 9001 (ISO, 1994b), ISO 9002 (ISO, 1994c) and ISO 9003 (ISO, 1994d), that can be used by a supplier as a quality assurance means to demonstrate his proficiency. The main purpose of the specified requirements is to reach client satisfaction by preventing deviations in all stages from design to follow-up.

ISO 9001

The most elaborate standard, ISO 9001, describes the requirements which should be met by an organization engaged in design, development, production, installation and follow-up.

Relevant aspects ISO 9001

The quality system requirements according to ISO 9001 comprise:

. management responsibility

. quality system
. contract evaluation
. design control
. document and data control
. purchasing
. control of the products supplied by the client
. identification and accountability of products
. process control
. testing and evaluation
. control of testing , measuring and evaluation methods
. status of testing and evaluation
. control of aberrant products
. corrective and preventive methods
. handling, storing, packaging, preserving and delivery
. control of quality registrations
. internal quality audits
. training
. follow-up
. statistical techniques

Applicability drug research

Originally, the ISO 9000 series was designed for industrial circles, that is for suppliers and/or producers. However, given the aspects mentioned above - with a strong emphasis on management responsibility, design and production, document flow, internal audits and responses - ISO 9001 can also be very suitable for scientific research and certainly for drug research (and drug production). ISO 9001 can be a very useful means - certainly in combination with GLP and GCP) to ensure that an organization is continually focused on the delivery of useful results of a drug trial.

Although it is not yet common practice, drug research organizations can be expected to be be guided increasingly by ISO 9001. The Dutch institute Pharma Bio-Research International b.v. (Zuidlaren) is the first research institute in the world to work in accordance with the ISO standard (since 1994).

Difference with GLP and GCP

An importance difference between ISO 9001 and the GLP and GCP standards as discussed earlier is to be found in the fact that ISO 9001 deals with the total organization (and its management in particular) and that GLP and GCP specifically deal with individual studies. Thus, ISO 9001 assesses the system - not the study results - and requires adaptation should any shortcoming be found. In this way a continous process of improvement takes place (= quality

management).

Certification

An organization can apply for certification according to ISO 9001 at an certification/registration agency qualified by ISO. In The Netherlands, the following firms act as such: Bureau Veritas, Det Norske Veritas Industry - DNV Certification, KEMA Registered Quality Nederland B.V. and Lloyd's Register Quality Assurance Ltd. Certification can take place after an audit by such an institution. The certificate has a three-year validity. During that period follow-up takes place every six months.

An ISO 9001-certificate is proof that an external agency has established that an organization works with systems and procedures that are consistent with this quality standard.

As opposed to GLP and GCP certification, ISO 9001 certification takes place on a voluntary basis.

Conclusion

In conclusion it can be said that, although the ISO 9001 standard has been implemented for very general use in industrial circles, it can be very suitable for scientific research, as the subjects 'design' and 'development' are extensively addressed. This means that ISO 9001 can be a very important means of quality management for drug research and drug production.

TOTAL QUALITY MANAGEMENT

12F

out! Bladwijzer niet gedefinieerd.

Guarantee of integrity

All standards mentioned (GLP, GCP, GMP and ISO 9000) have the aim to guarantee the integrity of the activities performed during drug research and drug production. In other words, to improve the reliability of a process, which should lead to high-quality results.

Quality

But how exactly should quality be defined? ISO uses the following definition:

Definition
Quality is the sum of characteristics of a product, process or activity, organization or person with the ability to satisfy stated and implied needs (ISO, 1994e)

An entity is here defined as a product, a process, an activity, an organization or a person.

A less complex definition of quality is 'fitness for use'.
In drug research, the product could mean the final report of a study. The quality of a study depends on the design, the execution in accordance with the protocol and with the standard operating procedures and the correct interpretation of the results in the final report.

Quality Management

In order to deliver this quality, Quality Management is necessary, also defined as concern for the quality of the organization.

Quality Control

According to GLP and GCP rules, this concern should contain aspects of *Quality Control* as well as *Quality Assurance*.

Again ISO gives the clearest definition of these concepts:

Definition
Quality Control contains all operational techniques and activities used to comply with the quality requirements (ISO, 1994e).

In the GCP rules the same definition is generally used.
In the GLP rules there is no specific reference to the term Quality Control, although the Quality Assurance programme is described as a controlling system here.

The most important principle of quality expert Deming in relation to the upgrading of the quality level, by careful planning, then execution, subsequent control and finally improvement - if need be - is certainly also applicable to drug research (Legat, 1997; Oakland, 1993). Thus: correction during and after the process is required.

Quality Assurance

According to ISO, Quality Assurance means the following:

Definition
The process to provide confidence in the fulfilment of the quality requirements.

Fundamentally, quality assurance is an independent verification of quality. GCP and GLP rules very much focus on inspecting whether the study has been conducted in accordance with the standards and the standard operating procedures with special attention paid to the reliability of the results.

Quality Assurance Unit

Generally speaking these quality assurance activities are carried out by an independent department, of which the staff does not report to those involved in the execution of the process, but to a specially appointed executive. In the GCP rules this task is assigned to the Sponsor for a clinical study, while the GLP rules specify that this task should be carried out by a Quality Assurance Unit of the organization conducting the study.

These two quality standards for drug research very much concentrate on the execution of the study, while ISO is highly focused on the whole organisation.

Total Quality Management

The worldwide acceptation and implementation of the ISO 9000 standards have contributed to making quality management a matter of course in business circles.

In many cases the term Total Quality Management is used, namely when both quality control and quality assurance are intensively used.

ISO defines total quality management as follows:
Definition
All activities of the overall management function that determine the quality policy, objectives and responsibilities and implement these by means of e.g. Quality Control, Quality Assurance and quality improvement.

Conclusion

In conclusion it can be stated that by using a combination of the requirements of GLP, GCP and GMP, which particularly address the final product and the way it is achieved (study, production process) and ISO 9000, which deals with the whole organization, a very efficient system of integral quality management can be created, which is very useful in drug research and drug production.

EPILOGUE

Right honourable Rector,
Ladies and Gentlemen,

I have tried to give you an overview of the current state of affairs regarding integrity in biomedical and pharmaceutical research.

A number of the most blatant examples of misconduct during the execution of drug research have been discussed. We have found, much to our chagrin, that some very serious cases have taken place in the Dutch scientific world. That is a pity, for The Netherlands have always had a very good reputation in the field of biomedical and pharmaceutical research.

This can be concluded, among other things, from the fact that a relatively very large part of the scientific literature in this field has been written by Dutch scientists. Not less than 8% of global drug research takes place in The Netherlands (personal comment: Nefarma, 1997).

Statistics from the United States show that only in one or two of every thousand trials scientific fraud is found. This is a low incidence, but sometimes it has very serious consequences for mankind. There were bond to be preventive measures, as dishonesty during drug research should be reduced to nil.

We have seen that a number of initiatives - particularly abroad - have led to codes of conduct.

As far as the prevention of scientific misconduct in our country is concerned, in 1995 the Royal Dutch Society for Sciences took an important initiative by publishing a note which, however, runs to a mere six pages.

Unfortunately, the recommendations given have not been followed yet. I am of the opinion that here a paramount directive task has been set aside for the Royal Dutch Society for Sciences and for the Dutch Organization for Scientific Research to further develop these recommendations on a national scale. The Danish model discussed earlier would have to set a clear example.

However, this does not mean that the individual universities would not have to set up their own policies on this subject.

Just like Köbben (1995, 1996) I am a strong advocate of the appointment of a special ombudsman for science. The activities of such a mediator could also be

coordinated on a national basis by one of the organizations named earlier.

Furthermore, the governmental auditing teams would have to have more means at their disposal to carry out their activities. In comparison, the American FDA has twenty-five times more staff at its disposal - in proportion to the number of inhabitants of the country - than the Dutch Inspectorate.

Although the results of audits performed by the government show that there are numerous shortcomings in drug research in accordance with the rules of good research practices, we may assume that only in a limited number of cases obstinacy and conscious manipulation will be found. In most of the cases insufficient knowledge will be the cause of these shortcomings. In these cases the lack of knowledge can in future be remedied by better schooling.

In other words, first-class schooling in scientific ethics is essential. At the moment, this is still an optional subject for pharmacy students at this university. In my opinion, it would have to be a compulsory part of the training of all scientists engaged in biomedical research.

We have also seen that after codes of conduct, guidelines for good research practice have been drawn up, particularly abroad. Activities of harmonization have resulted in international agreements, regulated by law.

The clearest examples, GLP and GCP rules, have only recently been laid down in Dutch law: GLP in 1986, GCP in 1994. Still, they have already been implemented soundly in the industrial pharmaceutical research. But in my opinion scientists in the pharmaceutical industry are rather spastic in following these rules, possibly out of fear of narrow interpretation by the government, in particular the FDA. This is not as it should be.

We must realize that close observance of the strict rules is only a means to reach the final aim, which is to arrive at drug research of high morality and quality, which will in the end contribute to improving the quality of life. Furthermore, we must be aware that we are dealing with advancing insight; what was considered good or sufficient a few years ago is now sometimes considered to be outdated.

As an illustration, I think of my own situation. In this auditorium, exactly twenty years ago, I had the honour of upholding my thesis on the human pharmacokinetics of a registered drug, the pharmacology of which had been tested by a French company of renown in two rabbits only: 'le lapin blanch' and 'le lapin noir'.

Meanwhile a lot has changed. We can almost be certain that cases such as the thalidomide affair will no longer be found these days.

An important question is whether nowadays academic researchers do their research in the same way, in view of quality management, as their industrial colleagues. This is an essential condition for a fruitful cooperation and both parties know that they need each other for the development of new drugs.

I have my doubts here.

It is significant that to date not one academic research institute or hospital has been accredited by the authorities in the field of GLP and GCP, while the ISO quality standard is not yet applied either. It looks as if the academic world is lagging behind here!

Science flourishes in chaos. Chaos is necessary for creative work during innovation, but it clashes with bureaucracy - the paper mammoth - of quality management rules. It is often said 'that adherence to GLP would restrict the researcher too much in his scientific freedom. However, GLP is not in the way of scientific freedom, but it is in the way of freedom to handle procedures and data at one's own discretion' (Helder, 1993).

An objection to the introduction of GLP and GCP rules is that it would be an expensive process. This is unmistakably the case. However, the invested amount will soon be recovered, as there will certainly be an increase in efficiency and quality of the research.

Furthermore, these days it is no longer socially acceptable to conduct research without observing these rules. The cited examples illustrate this only too poignantly.

Anyway, registration authorities in most countries have explicitly proclaimed that they will no longer accept studies which have not been carried out in accordance with GLP and GCP. The same applies for the editorial staff of a number of leading scientific magazines.

This will force the academic institutes as well to adapt themselves to the situation.

If not, a primary source of research sponsoring, namely support by the pharmaceutical industry, will run dry. Furthermore, the important synergy between industrial research and academic institutes will be at risk.

In some academic circles research done under Good Academic Research Practice, GARP, is under consideration (Della Paschoa, 1997). In my opinion this is just a weakened version of GLP and GCP. We must well realize that GARP has no legal status at all. I also strongly wonder why drug research done in academic centres does not have to meet legal quality standards, while

this is indeed required from industrial research centres.

Thus, there is no doubt that there is ample room for improvement in this field.

I consider it an honour and a duty to take care of rational implementation of the rules for good research practices in the research carried out at this university as part of the Groningen Institute for Drug Studies (GIDS) and in collaboration with the University of Utrecht under the terms of the Groningen Utrecht Institute for Drug Evaluation (GUIDE).

We must not forget that every innovation is founded by dissemination of information, that is, thorough schooling. Until this moment no opportunities for academic schooling in the field of good research practices were available in The Netherlands.

The governors of the University of Groningen showed remarkable vision when they, as the first in the world, decided to fill the gap in knowledge and experience by the introduction of the Chair of Quality Management of Drug Research and Drug Production.

The fact that the executive committee of GUIDE, as soon as one year after the start of the GLP/GCP course, decided to make it compulsory for all Ph.D. students confirms my views on the importance of this kind of schooling for young scientists.

I consider it to be my foremost task to provide thorough schooling in Quality Management of Drug Research and Drug production and to install a great quality awareness in the future generation of researchers. This quality awareness will finally lead to a research climate where quality will have become a matter of course and where every study complies with all international requirements of good research practices. In doing so, I hope to make it perfectly clear that it is the moral duty of every scientist to conduct quality research.

I am also convinced that rational application of the rules, supplemented by the general rules of quality management, will lead to improvement of integrity in biomedical and pharmaceutical research, where painting mice and fabricating patients will be practices of the past.

Right honourable Rector, Ladies and Gentlemen,

In front of this auditorium there is a statue which was made by Mari Andriessen in 1964 entitled 'Unveiling Truth'. It is a symbol of the great store set by this university on truth. Only by conducting truthful research the Netherlands will be able to maintain its excellent reputation in the field of drug

research.

May integrity be considered of paramount importance at all times.

Nil nisi veritas - nothing but truth.

RESUME

During the second half of the twentieth century people have become convinced of the great value of quality management in scientific research. Its importance in the search for new drugs has only gradually become apparent during the last two or three decades. In this overview I give my perception of the importance of quality management in drug research.

Society as a whole is highly dependent on the integrity of those who carry out scientific research. This is even more valid to those who conduct biomedical and pharmaceutical research.

We use the terms scientific misconduct and fraud when incorrect and/or incomplete study results are produced erroneously (unintentionally) or on purpose (intentionally). The best-known forms of scientific misconduct or fraud are fabrication, falsification, misinterpretation and plagiarism. Not infrequently, a combination of a number of these forms is found.

Scientific misconduct and fraud are not found very often, namely with a frequency of 1 to 2 per mil, but this is still too frequent.

Reasons for committing scientific fraud are often the forced search for fame and scientific power; sometimes it is induced by greed or time pressure.

Detection and proof of scientific misconduct is a delicate process, that can and should be performed by different parties.
Examples are: scientific community (by 'whistle blowers'), professional organisations, editorial boards of (scientific) journals, subsidizers, governmental organisations and society as a whole.

The consequences of scientific misconduct can be very serious for the persons that commit it, but also for his/her immediate (working) environment, the subsidizer and the society as a whole, specially the patient.

Scientists in the field of biomedical and pharmaceutical research have a great social responsibility; their research should lead to an improvement in the health and quality of life of mankind.

So the results of such research should be above reproach. However, in practice some scientists are found to be unable to resist the temptation to do harm to reality.

In this book a historic survey is given on scientific misconduct and fraud in conducting biomedical and pharmaceutical research, in which the most remarkable cases are treated. Motives, detection, consequences and preventi-

on are comprehensively discussed.

These last decades quality management in drug research is at the centre of attention. The possibilities of a forceful system of total quality management based on the legal rules of Good Laboratory Practice and Good Clinical Practice in combination with the voluntary application of the ISO 9000 norm are treated.

The integrity of the study results can be improved by stringent application of this total quality management in combination with strong improvement of the schooling in this field.

The introduction of the chair of Quality Management of Drug Research and Drug production at Groningen university is an important step towards this aim.

Prof. Dr. Jan H.G. Jonkman

Jan H.G. Jonkman (1946) studied Pharmacy at Groningen University and got his Ph.D. thesis in 1977 in the field of bioanalysis and pharmacokinetics. During several periods of study at the University of California, San Francisco, United States (1979 -1981) he specialized in pharmacokinetics and got acquainted with the recently introduced principles of good research practice (Good Laboratory Practice, Good Clinical Practice).

In the years 1982 and 1983 he stayed with the Food and Drug Administration (FDA, Washington DC, United States) at the invitation of the American government and further specialized in good research practices and regulation regarding the registration of new drugs.

In 1984 he founded an independent institute for drug research in Assen (Pharma Bio-Research International B.V., having its main residence in Zuidlaren today), with an aim to conduct research in accordance with the strict rules of the FDA. Since then, Pharma Bio-Research carries out research in accordance with (inter)national legislation and regulations, by applying of total quality management and grew to be the largest institute for drug research in Europe.

In 1996, Dr. Jonkman was appointed as professor in the field of Quality Management of Drug Research and Drug Production, the first chair in this field in the world.