COBRA Insight

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✯ COBRA 'kicks off'

The Kick off meeting for COBRA, held in Paris on the 16th and 17th of April was a great success and represented a strong start to the project.

✯ In the news

➔ Microbes researchers highlight drawbacks of antibiotics Antibiotics alter the normal bacterial flora in humans

Bacteria that are resistant to antibiotics can live in the human intestines for at least one year. Professor Charlotta Edlund from the Karolinska Institutet in Stockholm, Sweden, and Research Professor Pentti Huovinen from the National Public Health Institute in Turku, Finland, are keen to highlight the risks involved in the excessive use of antibiotics.

In their research funded by the Academy of Finland, the two professors are exploring the long-term impacts of antibiotic treatment on the bacterial flora in human intestines. At the same time, they are looking to develop new research methods for studying intestinal bacterial flora. The project is part of the Academy's Microbes and Man research programme, a joint effort among researchers from Finland and Sweden.

Antibiotic-resistant bacteria are one of the most serious threats to health care. Earlier it has been assumed that the effects of antibiotics disappear within a couple of months

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and that the intestinal bacterial flora is then restored to normal. Researchers believe that antibiotics also have characteristics which maintain and promote the health of the bacterial flora.

It has now been shown that the antibiotic studied, i.e. clindamycine, continues to have a clearly visible impact up to one year after treatment is discontinued. Even more surprisingly, it has been found that resistance also increases to other antibiotics, such as penicillins, tetracyclines, and macrolides. In other words, the use of one type of antibiotic simultaneously increases resistance to several other antibiotics.

The focus of research at the Karolinska Institutet in Stockholm is upon intestinal anaerobic bacteria that have poor tolerance of oxygen, while researchers at the National Public Health Institute in Turku are studying aerobic bacteria, which also grow in the presence of oxygen.

➔ 'Prophylactic antibiotic treatment before dental procedures may be unethical'

Several dental procedures cause bacteriaemia, which may lead to patients developing bacterial endocarditis (BE), a potentially fatal disease. In light of this, there are guidelines for dentists describing circumstances under which prophylactic antiobiotic treatment should be given prior to the procedure. A new review of the data available, however, concludes that there is not enough evidence to support (or refute) the effectiveness of using antiobiotics in this way.

The researchers who reviewed the data also gathered opinion amongst health care workers and dentists with known interests or experience in evidence based care. Health care workers and dentists who were not told what the intervention or conditions were, stated they would seek additional evidence and the opinion of patients before using the intervention. However, dentists who were aware of the topic said that they would use prophylactic antibiotics despite lack of evidence for effectiveness, citing medico-legal reasons for doing so. The researchers conclude, “There is a problem in that our work suggests practitioners feel that they are bound by current guidelines, and medico-legal considerations, to provide antibiotic prophylaxis, rather than to make decisions based on best evidence.”

➔ Education - *Acinetobacter baumannii*

Acinetobacter baumannii is an opportunistic pathogen operating in hospitals creating serious infections such as pneumonia. It principally affects patients who have weakened health and this is why we call it opportunistic. Moreover, the mortality rate from these infections are usually high given, on the one hand, the weakness of the patient and, on the other, *A. baumannii* is resistant to many antibiotics. Furthermore, once a specific course of treatment is prescribed for *A. Baumannii*, the pathogen has a great capacity for acquiring resistance to these antibiotics.

To tackle this problem it is essential to observe, in an ongoing manner, the new resistances the bacteria develops, in order to know what kind of antibiotic has to be used to treat patients. In order to carry out these analyses, the gene for the new acquired resistance has to be identified and isolated and also the presence or otherwise of integrons has to be determined.

Integrons

Integrons are chains of genes wherein many of the resistances acquired by the *A. baumannii* bacteria are found. The pathogen also has other options for their acquisition but it is the integrons that provide the most efficacious way to acquire and transmit the resistances, given that, apart from acquiring resistances, integrons have great mobility and can transfer from one location of the *A. baumannii* chromosome to another.

This mobility allows them to pass from one strain of the bacteria to another. This means that all the resistances acquired by a strain of *A. baumannii* can be transmitted to another and the species can

thus modify and regenerate itself continuously. Moreover, as it has a promotoros, the bacteria is always activating or expressing all the resistances held in the integron.

Attempting to improve control

Analysing and isolating a number of *A. baumannii* strains from hospitals, it has been shown that most have integrons. Thus, it is highly probable that *A. baumannii* becomes resistant to the best antibiotics that exist today and that this resistance is transmitted via integrons. Moreover, *A. baumannii* strains have been identified that are resistant to the most common antibiotics used today.

If this is confirmed, the mortality rate due to infections created by the bacteria may even be greater than thought to date, given that there is no antibiotic capable of tackling the infection. It should be taken into account that the number of hospital patients affected by infections caused by *A. baumannii* is not great, but the gravity of the problem lies in the rate of mortality of these cases.

There currently exist methods to genetically distinguish *A. baumannii* strains from each other, but the aim at the moment is to obtain a method of indicating the presence of integrons and their resistance in these strains. Of course, this method of detection has to be standardised and, at the same time, practical, for its clinical use.

That is to say, the option of the researchers has been to try to improve control with respect to *A. baumannii* given that there is currently no substitutes for the antibiotics used to date. In order to achieve this improved control, it is essential to detect the infection in time and know if *A. baumannii* has produced it. The resistances of the strains must also be known and if they have integrons. Once this detailed information is gathered, new systems for the control of infections can be introduced in order keep down the rate of mortality due to *A. baumannii*.

➔ Bacterial versus Viral testing

A rapid blood test to help distinguish between bacterial and other (predominantly viral) infections could substantially reduce the inappropriate use of antibiotics for common infections, conclude authors of a study in this week's issue of THE LANCET.

Lower respiratory tract infections are often treated with antibiotics-even though there is often no evidence of bacterial infection. Such inappropriate use of antibiotics is contributing to the increase of antibiotic-resistant bacteria with serious implications for public health. Blood concentrations of a calcitonin precursor protein known as procalcitonin are substantially raised during acute bacterial infection.

Beat Müller from University Hospital Basel, Switzerland, and colleagues assessed the effectiveness of a sensitive blood test to identify procalcitonin concentrations to guide antibiotic treatment among patients with lower respiratory-tract disease (eg, pneumonia, bronchitis).

243 patients with suspected lower respiratory tract infections were randomly assigned standard care (standard group) or procalcitonin-guided treatment (procalcitonin group). Antibiotics were given only if procalcitonin concentrations were above a specific threshold among patients in the procalcitonin group.

The number of patients in the procalcitonin group who received antibiotics was halved compared with the standard treatment group. This withholding of antibiotics had no adverse effect on health outcome (no overall difference between the two groups, with 97% of all patients making a good recovery). Around 80% of patients were later found to have viral infection for diagnoses such as pneumonia (36% of patients), exacerbation of chronic obstructive pulmonary disease (COPD, 25%), and acute bronchitis (24%). Conversely, in patients with acute exacerbation of COPD, 60% positive sputum cultures for bacteria were found regardless of whether procalcitonin concentrations were high or low;

however, those patients not treated with antibiotics because of low procalcitonin still had successful infection clearance: these patients were colonised with bacteria, but the bacteria were not responsible for the infection.

Beat Müller comments: 'Procalcitonin guidance substantially reduced antibiotic use in lower respiratory tract infections. Withholding antimicrobial treatment did not compromise outcome. In view of the current overuse of antimicrobial therapy in often self-limiting acute respiratory tract infections, treatment based on procalcitonin measurement could have important clinical and financial implications'.

➔ Resistance in the intensive care unit

Bacteria with resistance to multiple antibiotics will become more common in intensive care units unless hospitals improve their hygiene standards. Research published in Critical Care shows that there is an "unexpectedly high" level of transmission of bacteria between intensive care patients.

Intensive care patients are especially vulnerable to picking up infections in hospital, due to their poor health. Researchers from the Karolinska Institutet in Sweden found that 70% of intensive care patients studied were colonized with bacteria from other patients in the unit.

The researchers investigated the transmission of several strains of Staphylococcus bacteria, called CoNS. These strains are the primary cause of circulatory infections picked up in hospitals, and the third most common cause of all hospital infections. "These species have the ability to survive in the ICU surroundings on medical devices and equipment for weeks up to months," say the researchers. "They are specifically prone to causing catheter-related infections."

The team, led by Professor Charlotta Edlund, took swabs from the upper and lower airways of 20 intensive care patients that had required mechanical ventilation for at least three days. The researchers cultured the bacteria from these swabs and analysed the genetic fingerprints of Staphylococcus strains to identify bacteria that were identical or closely related. They could then assess the transmission rates of bacteria between patients, by seeing which patients harboured the same bacterial strains.

17 of the patients were colonised by CoNS during their hospital stay. In six of these cases, the bacteria had colonised the lower airways after the patient was ventilated, suggesting that the procedure itself had introduced the bacteria. 14 of the patients had either passed on a bacterial strain to another patient or received a bacterial strain from another patient. Worryingly, one patient passed on bacteria to a patient they had never met, having being discharged about three weeks prior to the other's arrival. This implies that the strain had survived in the ward during this period, perhaps on staff or on additional patients.

"Local guidelines for antibiotic use, close cooperation with infectious diseases specialists and restrictions with invasive treatment are strategies that can improve infection control and lower the incidence of hospital infections," write the authors. "Hand hygiene among hospital staff is [also] an important factor for preventing these infections."

The antibiotic resistance of the bacterial strains was analysed. 95% were resistant to penicillin, 86% to oxacillin, 48% to erythromycin, 42% to clindamycin, 54% to gentamicin, and 66% to ciprofloxacin. None were resistant to vancomycin, which is currently used to treat MRSA and other infections caused by other antibiotic-resistant bacteria.

Resistance to multiple antibiotics was commonly seen. 21% of the bacterial strains were resistant to six, 34% to at least five, and 59% to at least four of the tested antibiotics. "This multi-resistance will lead to higher consumption of broadspectrum antibiotics such as vancomycin, promoting the development of antibiotic resistance."

CoNS normally live on our skin without causing us any harm, but they can colonise airways or invasive devises (such as tubes used in mechanical ventilation), especially in people with weak immune systems. Although these bacteria do not always cause disease, colonisation is a risk factor for infection with other, more dangerous, antibiotic resistant bacterial strains.

➔ Cystapep versus hospital infection

The problem of hospital infection, severe disease caused by antibiotic-resistant staphylococcus bacteria, entails major costs and great suffering. Group A streptococcus bacteria, also called meat-eating killer bacteria, are another growing problem. A team of Lund scientists in Sweden has now developed a substance called Cystapep, which seems to work on bacteria that nothing else seems to be able to knock out.

If Cystapep delivers what it promises, this is nothing short of sensational. Sweden is in a better position than other countries when it comes to antibiotic resistance, but in other parts of the world dangerous strains of bacteria have developed resistance to most of the antibiotics doctors have in their arsenal, and the problem is growing worse every year in Sweden as well.

The name Cystapep is based on the fact that the new substance is a peptide derivative from a larger larger protein called cystatin. Cystatin occurs in various forms in the body and is part of our natural protection against bacteria, fungi, and viruses. The Lund researchers Aftab Jasir and Claes Schalén, medical microbiology, and Anders Grubb, clinical chemistry, have collaborated with a team of Polish scientists to synthesize a peptide based on the inhibitory centre of human cystatin C.

“The substance has been shown to be effective against infectious staphylococci, streptococci, enterococci, and pneumococci bacteria, which include many dangerous and more or less antibiotic-resistant strains. On the other hand, the body’s own flora of bacteria is not affected, which is good news,” says Aftab Jasir.

Cystapep has also been shown to attack polio and herpes viruses. The fact that one and the same substance works against not only infectious bacteria but also viruses is unique. And the substance seems to have its very own modus operandi that bacteria cannot easily defend themselves against. The Lund team has tried to induce resistance to Cystapep by creating mutations, a procedure that is usually not very difficult, but it didn’t work at all in this case.

The researchers have just published their findings in APMIS, Acta Patologica Microbiologica Immunologica Scandinavica. Before transferring an eventual patent to the pharmaceuticals industry, they want to learn more about the way the substance works, try to make it even more effective, and try out its efficacy against foreign strains of bacteria.

Since Aftab Jasir and Claes Schalén are the project leader and coordinator, respectively, of a major EU project on Group A-streptococci, they have ready access to bacteria cultures from other countries. Clinical use of the substance may become a reality in 5 to 10 years’ time.

➔ Eat more Garlic !!

A compound extracted from garlic is effective against even the most antibiotic-resistant strains of MRSA, the killer ‘hospital superbug’, and can cure patients with MRSA-infected wounds within weeks, according to new research by microbiologist Dr Ron Cutler of the University of East London (UEL).

In a paper to be published in the New Year, Dr Cutler, an expert in the antimicrobial properties of plant extracts, claims that allicin - a compound that occurs naturally in garlic – kills not only established varieties of MRSA, but also destroys the new generation of ‘super-superbugs’ that have evolved

resistance to Vancomycin and Glycopeptides, the powerful antibiotics widely considered to be the last line of defence against MRSA.

MRSA (Methicillin-resistant Staphylococcus aureus) now causes an estimated 2,000 deaths in UK hospitals each year mainly through secondary infection of surgical wounds. Though MRSA organisms can live harmlessly in humans and are carried in the nasal passages and on the skin, they can cause fatal infection in immune-suppressed patients, the elderly, the young and those with surgical implants.

Doctors have become increasingly alarmed over the past few months by the emergence in UK hospitals of new generations of resistant strains of MRSA known as VISAs, and GISAs (Vancomycin or Glycopeptide resistant Staphylococcus aureus). MRSA has also become endemic in many hospitals, especially in London and the South-East, prompting the NHS to review its hygiene procedures.

Dr Cutler, recently proved that allicin destroys the MRSA microbe in laboratory trials, has now teamed up with a new company, Allicin International, to develop topical treatments to prevent MRSA infection. The group have developed a nasal cream, oral capsules and soaps that have proved effective against both MRSA and GISA.

In partnership with colleagues in the NHS, Dr Cutler is now embarking on a major clinical trial involving around two hundred volunteers, including patients at several hospitals in London and the South East.

Dr Cutler said: "The trials we have conducted so far show that this formulation is highly effective against MRSA, and it could save many lives. This finding is backed up by initial findings a number of recent case studies. We have been trying to set up a clinical trial for many months now, and at last we have secured funding from sources including Allicin International.

“MRSA is causing a genuine crisis in our hospital system in Britain and worldwide. Antibiotics are increasingly ineffective, but we do have a powerful natural ally. Plant compounds have evolved over millions of years as chemical defence agents against infection. Garlic has been used in medicine for centuries, and it should be no surprise that it is effective against this very modern infection.”

The research on the laboratory effects of allicin on GISA was presented in part at the Institute of Biomedical Scientists congress in Birmingham, October 2003, and is being prepared for publication in the Journal of Biomedical Science, to appear in the New Year. A full clinical study involving the use of allicin to reduce nasal carriage in healthy volunteers, including in hospitals in London and South East England, is underway and initial results are due to be published in summer 2004.

Case Study: Deborah’s story
Deborah Brown (34), a probation service officer who lives in Rainham, Kent, contracted MRSA after a major spinal operation in November 2000.

The painful wounds on her spine failed to heal despite constant applications of both oral antibiotics and creams, which also failed to reduce the levels of MRSA in her tissue.

In December 2002, Deborah’s mother Pauline contacted Dr Cutler after seeing an item on TV about MRSA and received a course of Allimax cream and capsules by post. Within two months, the MRSA had mostly cleared from Deborah’s tissues and the wounds had begun to heal, allowing an operation to remove her spinal supports to be carried out in June 2003.

Deborah said: “The effect of the treatment was dramatic - I am making a good recovery now – but it was really awful at the time. Having weeping wounds on my back that never healed for two years was incredibly painful, and I became increasingly depressed as the MRSA didn’t respond to repeated courses of antibiotics. If my case helps to show that allicin works against MRSA then I am glad that something good might come of it.”

✯ Intellectual property news

➔ Patenting of biotech inventions in Europe: New developments

Bio-Science Law Review (12 February 2004)

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Introduction
Now that scientists have completed the sequencing of the entire human genome, new and interesting perspectives are developing with respect to the study of drug action and pharmacogenetics in drug discovery. In the fields of genomics and proteomics, for example, DNA microchip arrays have proved to be useful in the identification of specific gene expression patterns in different tissues or organisms generally, thus allowing a better understanding of cell differentiation and proliferation.

The progress in the fields of molecular biology, biotechnology and molecular medicine since the sequencing of the human genome highlights the importance and potential of these technologies for the pharmaceutical industry. One important way to benefit from these developments is to successfully convert such biotechnological discoveries into patentable inventions in order to obtain an enforceable protective right for potential new compounds, methods or their uses, for example, in treating illnesses or disorders. The steadily increasing number of patent applications in the field of biotechnology at the European Patent Office (EPO) in the past few years reflects the growing significance of biotechnological inventions.

This review will summarise the most relevant recent issues and legal developments under the European Patent Convention (EPC) in the field of biotechnology that are critical for obtaining patent protection in Europe. In particular, we will focus on recent case law established by the Technical Boards of Appeal and the Enlarged Board of Appeal at the EPO.

What is Patentable in Europe?
Patentable Biotech-Inventions (Article 52 EPC)
General

For European patent applications, Article 52(1) of the EPC defines the basic requirements for the patentability of any invention: it must be susceptible of industrial application, must be new, and must involve an inventive step. A further requirement is that the applicant must provide an enabling disclosure which allows the person skilled in the art to carry out the invention (Article 83 EPC).

Of particular interest to those seeking to obtain patent protection for biotechnological inventions are the regulations under Article 52(4) EPC, since this Article excludes from patentability any method of treating humans or animals by surgery or therapy and diagnostic methods practised on humans or animals. The policy behind the exclusion of such methods is grounded in the interest of public health to ensure that those who practise such methods as part of the medical treatment of humans or the veterinary treatment of animals should not be hindered by patents (see T 116/85).1 In Decision G 5/83,2 the Enlarged Board of Appeal emphasised that 'the intention of Article 52(4) EPC … is only to free from restraint non-commercial and non-industrial medical and veterinary activities'. According to several decisions of the Technical Boards of Appeal, an exclusion clause such as the one in Article 52(4) EPC shall be narrowly construed (see, for instance, T 385/86 or T 144/83).3

Therapeutic methods

In a recent decision, T 789/96,4 the Board of Appeal considered the question of whether a method (applied to humans or animals) using a pacemaker and having therapeutic effect was a therapy within the meaning of Article 52(4) EPC. The Board came to the conclusion that the use of such a device having an effect on the heart (within the animal or human body) is, in principle, a method of treatment by applying a therapy. However, in the case at issue, the claimed method was directed to a refinement of technical steps in order to reduce the energy consumption of a pacemaker, which did not have the effect of preventing or treating a pathological condition. The Board noted that the parameters defined by the pacemaker are not used to regulate the amplitude, stimulation frequency or any other value acting directly on the heart. Thus, there is no functional link between the value which is measured and the therapeutic treatment which is applied (see also Decision T 82/93).5 As a consequence, the Board concluded that

… the use of a pacemaker with a therapeutic effect is not a therapy within the meaning of Article 52(4) EPC if the invention consists in refining said method but the refinement does not have the effect of preventing or treating a pathological condition.6

Diagnostic methods

Regarding the patentability of diagnostic methods, the recent Decision T 964/997 addresses inter alia the question of whether all the steps involved in reaching a medical diagnosis are required to define a diagnostic method, or whether the mere step of sampling a substance from the living human or animal body for diagnostic purposes must be considered a diagnostic method within the meaning of Article 52(4) EPC. In answering this question, the Board considered Decision T 385/86,8 where it concluded that the only diagnostic methods to be excluded from patent protection were those whose results immediately made it possible to decide on a particular course of medical treatment. A method was therefore considered to be a diagnostic method if it contained all the steps involved in reaching a medical diagnosis. Consequently, those methods providing only interim results may not be diagnostic methods within the meaning of Article 52(4) EPC (1st sentence), even if they can be utilised in making a diagnosis. A restrictive interpretation of this rationale implies that diagnostic methods practised outside the body, such as comparing data with normal values which are based on mental acts, or typical diagnostic procedures practised on the human body such as percussion, auscultation or palpation, could, in principle, be patentable because they do not constitute a complete diagnosis and certainly do not fall within the further medical categories of surgery and therapy. However, in Decision T 964/99, the Board emphasised that the expression ‘diagnostic methods practised on the human or animal body’ should not be considered to relate to methods containing all the steps involved in reaching a medical diagnosis. Consequently, any sampling of a substance from a body for the purpose of medical examination is considered to be a diagnostic method within the meaning of Article 52(4) EPC.

Surgical methods

Article 52(4) EPC also excludes methods for treatment by surgery on human and animal body. In Decision T 775/97,9 the Board of Appeal had to decide on a claim submitted by the applicants having the following ‘second medical indication’ claim format:

Use of a [device] for the manufacture of a device for use in a surgical method …10

The appellant asked whether purpose-related use claims in the second medical use claim format are also applicable to surgical products and functional combinations.

In the Enlarged Board of Appeal Decision G 5/83,11 it was decided that any claims directed to ‘a method of treatment’ or ‘use of a substance for treatment’ are not allowable since such claims

contravene Article 52(4) EPC. The Board concluded, however, that any claim directed to 'the use of a substance or composition for the preparation of a pharmaceutical composition' is allowable.

Thus, in Decision T 775/97, the Board of Appeal was obliged to follow the above claim, pointing out that

… the reason why claims in the second format of claims ('Swiss type claims') qualify as representing an 'industrial' activity outside the scope of the exclusion from patentability under Article 52(4) EPC is simply the fact that the mere manufacturing of a product, irrespective of whether that product is (also) a 'medicament' because of its capacity to produce certain effects on or in the human or animal body when administered to it, does not necessitate or comprise any action on an individual human or animal body and, therefore, does not constitute a treatment of such body by surgery or therapy. Such treatment would, by definition, require that the product be actually used on an individual human or animal body or bringing about a certain effect on that body; but this is clearly a further and quite different activity of a therapeutical nature because it is directed to the maintenance or restoration of health (e.g. decisions T 19/86,12 T 438/9113 and T 820/9214). The difference between the two is also exhibited in real life, where the manufacturing and distribution of medicaments is a matter of industry and commerce which is performed by persons who need not and normally do not have a medical qualification, whereas the exercise of therapeutical activities including those involving the treatment by medicaments is reserved for medical practitioners or other persons having a medical knowledge (cf. T 385/86,15 T 24/9116 and T 329/9417) (emphasis added).

Thus, the Board concluded that the use of a known material as starting material for a medical activity is quite different from the use of a known composition for manufacturing a medicament which is otherwise merely an industrial process. Thus, no analogy can be drawn between the use of materials or devices in a surgical method and the use of substances or compositions within the second medical indication. The Board further concluded that no European patent application can be granted with claims directed to a new and even possibly inventive way of using materials or devices like, in this case, endoprotheses, involving treatment by surgery. This would be equally true in the case of product per se claims which are typically defined by a construction which is only arrived at in the human or animal body following a surgical step.

A further aspect regarding second medical use claims is that the concept of a second or further medical use can only be applied to claims directed to the use of substances or compositions for the preparation of a medicament intended for use in therapy or therapeutic application. According to Decision T 4/98,18 the particular illness or disease to be treated with a specified substance or composition must be indicated. The Board of Appeal noted that in the absence of the identification of at least:

(i) the illness or disease to be treated or the ailment to be cured, or

(ii) the nature of the therapeutic compound used for treating or curing the disease, or

(iii) the subject to be treated,

a mere process feature cannot be construed as specifying a particular method of treatment or therapeutic application within the meaning of Article 52(4) EPC.

As a consequence, claims that do not fulfil these requirements must be understood as relating to a non-therapeutic technical activity (process) and therefore assessment of novelty and inventive step has to be done on the basis of this interpretation (see T 4/98, reasons, 8.2 and 8.3).

The requirement of industrial applicability (Article 57 EPC)

According to Article 57 EPC, an invention shall be considered as susceptible of industrial application if it can be made or used in any kind of industry, including agriculture. The question of industrial applicability is particularly important with respect to inventions that concern DNA or protein sequences.

Patenting of DNA and protein sequences

Patent practitioners are often confronted with the question as to whether a mere sequence or partial sequence of a gene is patentable within the meaning of Rule 23e (2) EPC. These sequences can be patentable as long as the industrial application of the sequence of partial sequence is specifically disclosed in the patent application.19 This means that a concrete technical function must be disclosed somewhere in the patent to satisfy patentability requirements under the EPC.

A decision handed down by an Opposition Division dated 20 June 2001, 'Novel V28 seven transmembrane receptor', addresses this issue.20 The Opposition Division had to deal inter alia with the question of whether a purified and isolated polynucleotide encoding the amino acid sequence of V28 seven transmembrane receptor, or a fragment thereof, possessing at least one ligand/antiligand binding activity or immunological property specific for said V28 seven transmembrane receptor (claim 1), fulfils the requirement for patentability under the EPC. The specification discloses both a genomic and a cDNA clone encoding the V28 protein. Several methods are disclosed that may be used to identify extracellular and intracellular ligands for the V28 protein, however, no specific ligand is disclosed.

The Opposition Division had to decide patentability of this granted patent based on the question of Sufficiency of Disclosure. According to Article 83 EPC, the European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The Opposition Division pointed out that the specification discloses the V28 7TM protein which is predicted but not shown to function as a receptor. The prediction that V28 is a receptor is based on structural elements such as the presence of seven hydrophobic domains separated by hydrophilic domains as well as homologies to known 7TM receptors. The specification does not demonstrate in any way that V28 protein actually is a receptor. Instead, it discloses several methods which can be utilised by the person skilled in the art in order to verify the prediction that V28 protein is indeed a receptor. There might be cases where a predicted function of a protein may be demonstrated in a technically undemanding way such as predicting a specific enzyme activity, in which case the disclosure of the predicted function in combination with a method of verification of said predicted function satisfies the requirements of Sufficiency of Disclosure according to Article 83 EPC. However, the Board noted that the specification of the case at issue does not refer to any group of ligands and thus the skilled person seeking to identify said ligand needs to test a multitude of available candidate compounds using the described method. This undertaking surely constitutes an undue burden for the skilled person seeking to perform the claimed invention.

For these reasons, the Opposition Division held that the disclosure of the amino acid sequence of the V28 protein and prediction of a function as a receptor in combination with the method disclosed for identification of the respective ligand was not sufficient to disclose a receptor protein.

The patent also included claims that related to an antibody substance specific for V28 protein without such antibody substance being specifically disclosed. The Opposition Division held that the generation of these antibodies is not considered to be a routine matter because of the labour-intensive exclusion of cross-reactivity of the candidate specific antibody with any other protein. Therefore, the identification of specific antibodies suitable for counteracting a speculative activity of V28 protein, that is, induction of inflammation, is not enabled by the disclosure of the specification.

Similarly, the Opposition Division concluded that since no antagonists of V28 protein are disclosed in an in vitro method, the use of an agonist or antagonist of the V28 protein is not sufficiently disclosed.

The requirement that patents are granted only for inventions which are suitable for industrial application (Article 57 EPC) is further explained in Rule 23e (3) EPC. This indicates that the industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

In case of the V28 seven transmembrane receptor, the Opposition Division held that no function of the claimed protein is disclosed. Potential uses of the invention are disclosed in the specification, which are based on a proposed function of the V28 protein as a receptor that was not supported by the description. Thus, the potential uses disclosed in the patent application are speculative, that is, they are not specific, substantial and credible so as to meet the standard for an industrial application.

The case described above of the V28 seven transmembrane receptor shows that the proposal of an activity or function of a nucleic acid or protein should be credibly shown in the examples, and that at least one way should clearly be indicated of enabling the person skilled in the art to carry out the claimed invention. It also follows from this case that a mere laundry list disclosed in the patent specification summarising speculative functions of a protein is not in itself a reliable basis for recognising the industrial application of this protein. In order to fulfil the requirement of industrial applicability for biotechnological inventions, it is not sufficient for the specification simply to show that a protein or nucleic acid sequence can be made and used. Therefore, the disclosure of the function of a nucleic acid and/or protein is and remains a basic requirement for obtaining patent protection for nucleic acid or protein sequences in Europe.

Patenting of Expressed Sequence Tags (ESTs)

Within the European patent community, there has been controversy regarding patentability of Expressed Sequence Tags (ESTs) in the last few years. ESTs are partial sequences which are derived from complementary DNA (cDNA) clones. They are generated by the sequencing of either one or both ends of an expressed gene. ESTs have applications in the discovery of new human genes, mapping the human genome, and identifying coding regions in genomic sequences. The problem underlying the patenting of ESTs is that they are sequences with an unknown function. The only credible function is their use as a probe for screening libraries, identifying nucleotide sequences, and mapping their position within a genome. However, only one sequence per patent application would be patentable due to the unity requirements of Article 82 EPC as long as they are not linked by a single general inventive concept. In conclusion, even though there is no explicit case law concerning the patentability of ESTs, it is generally accepted that ESTs are not patentable in Europe as long as their functions are credibly disclosed in order to fulfil the requirements for industrial application (Article 57 EPC).

Exceptions to Patentability (Article 53 EPC)

Article 53(a) EPC indicates that European patents shall not be granted for inventions of which publication or exploitation would be contrary to ordre public or morality. In Decision T 356/93,21 it is stated that the concept of ordre public covers the protection of public security and the physical integrity of individuals as part of society (see T 356/93, reasons, 5). This concept also encompasses environmental protection. Accordingly, under Article 53(a) EPC, the exploitation of inventions which are likely to breach public peace or social order, or to seriously prejudice the environment are excluded from patentability as being contrary to ordre public. However, the Board emphasised that approval or disapproval of the exploitation by national law(s) or regulation(s) does not constitute per se a sufficient criterion for the purposes of examination under Article 53(a) EPC.

According to Rule 23d EPC, the following European patents shall not be granted which, in particular, concern:

(a) processes for cloning human beings;

(b processes for modifying the germ line genetic identity of human beings;

(c) uses of embryos for industrial or commercial purposes; and

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

As far as the human body or its elements are concerned, the legislative intention clearly excludes from patentability the human body at various stages of its formation and development, and the simple discovery of any of its elements, including the sequence or partial sequence of a gene.22 On the other hand, an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene may constitute a patentable invention even if the structure of that element is identical to that of a natural element.

Patenting of plant or animal varieties

According to Article 53(b) EPC, plant or animal varieties or essentially biological processes for the production of plants or animals are also excluded from patentability, whereas microbiological processes or the products thereof are not.

On 20 December 1999 the Enlarged Board of Appeal decided Case G 1/98 (Transgenic plant/Novartis II).24 The Enlarged Board of Appeal held that a claim directed to transgenic plants may not be excluded from patentability in view of Article 53(b) EPC, even if plant varieties fall within the scope of the claim.

This is now also evident from Rule 23c (c) EPC, which states that inventions are patentable if they concern plants or animals if the technical feasibility of the invention is not confined to a particular plant or animal variety.

Patenting of embryonic stem cells

Rule 23d (c) EPC defines which inventions are for morality reasons excluded from patentability (Article 53a EPC) and provides that human embryos for industrial or commercial purposes shall not be patented.

According to established case law, exceptions to patentability must be narrowly construed.25 According to the Guidelines for Examination in the EPO, Chapter IV, 3.1:

a fair test to apply is to consider whether it is probable that the public in general would regard the invention as so abhorrent that the grant of patent rights would be inconceivable.

Rule 23d (c) EPC leaves open the question of what is exactly excluded. For example, what is encompassed by the term ‘embryo’ in Rule 23d (c) EPC? A further question is whether cells obtained from embryos or processes involving human stem cells are also excluded.

According to Rule 23b (1) EPC, the Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions shall be used as a supplementary means of interpretation. Article 7 of the Directive states that the European Group on Ethics (EGE) is charged with the general evaluation of the ethical aspects of biotechnology.

On 7 May 2002, the EGE released Opinion no.16 on the ethical aspects of patenting inventions involving human stem cells. It is the opinion of the EGE that:

– Isolated stem cells which have not been modified do not, as product, fulfil the legal requirements of patentability;

– Only stem cell lines which have been modified by in vitro treatments or genetically modified so that they have acquired characteristics for specific industrial application, fulfil the legal requirements for patentability;

– As to the patentability of processes involving human stem cells, whatever their source, there is no specific ethical obstacle, in so far as they fulfil the requirements of patentability (novelty, inventive step and industrial application).

This means that processes which involve human stem cells, for example as starting material, should not be excluded from patentability for morality reasons alone. Regarding product claims to human stem cell lines, the EGE recommends that patent protection should only be possible for modified or specific differentiated stem cell lines for specific therapeutic or other uses. Furthermore, the EGE holds the view that applicants should declare the source of human stem cells described in an application. In addition, the view is expressed that patents should only be granted when the patent claims (product claims) refer to a specific and sufficiently accurately described stem cell line. It remains to be seen whether or not the EPO will deal with patent applications in this field according to the guidance provided by the EGE.

Allowability of disclaimers at the EPO

The question of admissibility of the introduction of a disclaimer at the EPO has been controversial and has been referred to the Enlarged Board of Appeal (cf. T 451/9926 and T 507/9927). The Enlarged Board of Appeal will have to decide in the two respective pending decisions, G 1/0328 and G 2/03,29 whether the introduction of a disclaimer into a patent claim is admissible within the ratio legis of Article 123 (2) EPC even in the absence of explicit support in the application as originally filed. According to Article 123 (2) EPC, a European patent application may not be amended in such a way that it contains subject matter which extends beyond the content of the application as originally filed. For example. in decisions T 426/9430 and T 934/9731 of the Technical Board of Appeals, it was noted that the prior art which the disclaimer excludes must be accidentally novelty-destroying prior art. A disclaimer introduced in order to establish novelty should exclude precisely that subject matter which is disclosed in the prior art. In decision T 351/98,32 the Board of Appeal reflected the interpretation that in case an overlap occurs between prior art that falls under Article 54(3) EPC (elder European right) and the claimed subject matter, a disclaimer may be admissible under Article 123(2) EPC. On the other hand, the decision T 323/9733 stated principles which are expressly in contrast to the established case law. Accordingly, a disclaimer may not be introduced into a claim to meet an objection due to lack of novelty when the specification as originally filed provides no support for the disclaimer. The introduction of a disclaimer would therefore contravene the requirements pursuant to Article 123(2) EPC.

The outcome of the pending decisions G 1/03 (referral decision T 507/99) and G 2/03 (referral decision T 451/99) of the Enlarged Board of Appeal will clarify the matter of admissibility of disclaimers at the EPO.

➔ Patents, IP strategy and the development of pharmaceuticals

Pharmalicensing (13 April 2004)

According to Tufts University in 2003, a new chemical entity (NCE) costs on average US$897 million to develop, including cost of post-approval research (rising from US$803 M in 2001). New formulations and indications for existing NCEs are also costly. To justify its considerable investment, the pharmaceutical industry must have a period of exclusivity in order to be able to recoup the costs for successful drugs, cover the costs of failed developments, and, if possible, make a profit for shareholders and investors. Without this protection, future investment in innovative development is unlikely.

There are a number of types of intellectual property (IP):

- Copyright
- Designs
- Trade Marks
- Patents
- Know-how
- Regulatory exclusivities
- Plant breeders' rights (of relevance to natural products and phytochemicals)

Of these, patents, know-how and regulatory exclusivities are the most relevant to the development of pharmaceuticals. Sometimes when natural products are involved, and where the plant has been cultivated to enhance the quantity or quality of the desired product, plant breeders' rights may be of relevance, but such cases are relatively infrequent.

Patents

A patent is a time-limited monopoly (usually 20 years) covering a specific country or territory. Getting a patent requires a detailed and complete description of the invention, which is published at a fairly early stage of the patenting process. This has both advantages and disadvantages - for example, an advantage is that it becomes public knowledge that the invention will be protected; a disadvantage is that details of the invention becomes public knowledge at an early stage - but this is part of the bargain that, in return for the protection, the invention can be used once the protection has expired.

To get a patent the subject matter has to be new, technically useful and unobvious. 'New', means that the invention must not have been made available publicly anywhere in the world. To establish this novelty, inventors and/or patent attorneys need to make thorough searches of the literature, including the patent literature.

Most countries grant patent rights to the first person to file the patent application at a patent office - however, in the US the patent rights go to the first to invent rather than the first to file. The criterion of 'technically useful' is not generally difficult to fulfill. It does not require demonstration of clinical utility - an assertion of pharmacological activity is generally sufficient.

'Obviousness' is subjective and arguable, and some ways of establishing unobviousness are:

- having an unobvious chemical structure
- demonstrating unexpected properties (for example a surprising effect such as increased activity or decreased toxicity)
- finding a solution to a problem with an unknown cause

Getting a patent

There are a number of questions to be answered in the process of getting a patent:

- What is there that is patentable?
- How is a patent application filed?
- When is a patent application filed?
- Where should the patent application be filed?
- How many patent applications should be filed?

What? A patent for a new chemical entity (NCE) is the gold standard - to get around such a patent a competitor has to find an equivalent chemical entity and spend all the money necessary to get health registration for this equivalent.

Patents for subsequent inventions based on an NCE can extend the effective monopoly for the product, or at least for some forms of that product. These subsequent inventions include new forms or formulations of the NCE, new uses for the NCE and new chemical processes or intermediates. Subsequent inventions can also be useful in defending things which the originator does not want to do itself, but does not want others to do.

How? There are a number of stages involved in getting a patent, each with a range of different decisions required. The overall process can take a considerable time. The process starts with a patent attorney drafting the description. The patent attorney will require as full a technical description of the invention as possible from the inventor, and will ask questions. There will then be a number of iterations of drafts and comments. Completing these iterations as quickly as possible will help avoid a competitor filing first. This is also the stage where inventors need to make the decision whether to file a patent with a broad or a narrow specification.

Twelve months after the filing of the initial application, the complete specification is due. The complete specification is an expanded form of the initial specification, and includes any additional work completed since the initial filing. This is a real decision point for the originator and there are many factors involved in making this decision.

Once the inventor files the complete specification, the international and/or national patent offices examine the patent application for novelty, technical utility, obviousness and various formal requirements. This process usually requires considerable negotiation with the patent examiners and often limitation of the patent claims (which define the monopoly sought). Hopefully, it will result in the grant of a patent. In some countries, third parties can oppose this granted patent.

When? There are different opinions within the pharmaceutical industry on when to file a patent application - some argue correctly that a delay in filing the initial application will delay the expiry of the granted patent and that therefore the initial application should be filed as late as possible. However, this risks a competitor filing an overlapping patent application (so blocking the originator), an inadvertent disclosure by the inventor, or a third party publication which will damage the novelty of the invention.

Where? The complete specification will be filed in those countries where protection is required. Rather than having to make individual filings in every country, the Patents Cooperation Treaty (PCT) enables inventors to file one application as the equivalent of filing in all countries belonging to the treaty (which is most countries of the world). The PCT, however, does delay the examination of the patent application, but also delays the expensive business of translation of the application into many languages and the payment of national/regional fees.

After the PCT stage the application enters the national or regional phase. As there is a cost for each country or region, and each granted patent in each country will attract renewal fees (usually on a yearly basis and usually on the anniversary of its filing), this is the time to decide just where protection is really needed. Other than the traditional pharmaceutical markets of the US, Japan and Europe, the choice of markets depends on the importance and subject matter of the invention. For example, some countries, such as India and China, have rapidly growing populations and economies, but other countries with large populations may have slow-growing economies. Countries such as Australia, Canada and New Zealand have small populations, but sophisticated pharmaceutical markets. Disease demographics and the location of competitors' headquarters should also play a significant part.

While patent protection is effective in most countries, there are some countries where the legal system is just not developed enough to make the enforcement of patents possible or worthwhile.

How many? Several patents may provide more protection than the sum of the individual cases - for example, one may block an alternative to another. Getting around, or attempting to invalidate, a lot of patents is considerably more effort than dealing with only one or a small number of patents.

Litigation
Patent litigation is not something to be undertaken lightly, and not to be undertaken at all unless there are substantial funds to hand. Small enterprises that lack the financial resources to enforce a patent may be tempted not to patent their inventions in the first place, but simply keep them secret. However most small enterprises hope to grow, and judicious choice of a large partner could help provide the relevant funds and effort.

Know-how and regulatory exclusivities
During the development of any drug, a great deal of information will accumulate, both for health registration purposes and through the general handling of the drug. It is important that the developer keeps such information secret as once it is published in detail competitors can use it to help obtain their own health registration. All major markets recognize the value of this regulatory data. These countries have statutory exclusivity periods during which the regulatory authorities will not allow a copyist to cross-refer to the originator's data. Some countries may provide market exclusivity to 'orphan drugs' - drugs for which there is only a small market.

Conclusion
This is a game. The originator tries to weave as strong and complex a web of protections as possible around the product while the potential copyist tries to find a way around or through that web. For important products, the stakes in monetary terms are extremely high. For the originator the effectiveness or not of the web can make the difference between independent corporate survival and the need to merge.

To weave this web, R&D workers and their patent attorneys need to be aware of the possible protections available, and must remain vigilant over many years to make sure that all, or at least most, opportunities are taken up. It is surprising how often patent protection can be obtained for a development that on the face of it seems unpatentable. It is however quite certain that if a patent is not applied for it will not be granted. If a patent is applied for it may not be granted, but the very existence of the published patent application may cause third parties to hesitate or desist.

The web is likely to consist of strong protections and weaker protections. Part of the strength of the web is that those outside the originator are uncertain as to which is which. In some instances, there is a strong element of bluff.

A danger with a web of protections is that the management of the originator may believe that the web is stronger than in fact is the case. The management should be aware of the weaknesses of the web, but will doubtless present to the outside world that they have many important protections which last for a long time and that they are prepared to fight anybody who tries to break through the web.

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➔ Proposed new technology transfer block exemption and guidelines

Eversheds National Bioscience Group (29 March 2004)

Do you licence technology or manufacture and distribute under licence within the European Economic Area ("EEA")?
If so, you should know about the proposed revisions to the existing Technology Transfer Block Exemption (TTBE) published by the European Commission on 1 October 2003.

Why should you care about the TTBE?
Because the TTBE provides a safe harbour from certain elements of European competition law (antitrust law for US readers), and EU competition law almost certainly applies to your company's activities in Europe where there is an affect on trade between Member States of the EEA. More specifically, EU competition law applies to activities and agreements with the potential to have a significant impact on competition within the EEA. To the surprise of many owners of intellectual property rights, the "ordinary" exercise and protection of one's intellectual property rights frequently can violate EU competition law.

Why are licences of technology often caught by EU competition law?
A key objective of EU competition law is to ensure that there are no internal barriers to trade between Member States. From the perspective of the European Commission, which promulgates EU competition law, all of the countries in the EEA ideally make up a single free market. Unsurprisingly, companies that deal in intellectual property rights typically have a different view: Intellectual property rights are primarily national in nature, and most companies naturally expect to exploit their intellectual property rights on a national rather than EEA-wide basis. However, licensing restrictions that are unexceptional in other parts of the world, such as territorial restrictions with strong restraints on passive sales, can have the effect of creating barriers to free trade within the European internal market. Accordingly, there is an inherent tension between EU competition law and the "ordinary" exercise of intellectual property rights.

What sort of agreements are covered by the TTBE?
The existing TTBE provides a limited safe harbour to parties who engage in technology transfers where the primary intellectual property rights consist of patents and know-how. Patents are taken as including patent applications, (applications for registration of) utility models, topographies of semi-conductor products, supplementary protection certificates and plant breeders' certificates. The proposed new TTBE will also apply to copyright in software and to design rights, so software and other design companies can take advantage of the safe harbour that benefits patent and know-how licensors.

Licences of copyright other than software copyright are not covered by the new TTBE although the same rules will be applied by analogy to some copyright licences (but not to licences of performance rights). Trade marks also are not covered by the new or old TTBE.

As with the old TTBE, the new TTBE only applies to agreements between two parties. Patent pools and other multi-party agreements must be assessed in the light of the accompanying Guidelines.

How do the requirements of the new TTBE differ from the old TTBE?
In recent years, the European Commission has been moving away from a relatively abstract rules-based approach and toward a market effects-based analysis of potentially anti-competitive practices. In other words, your market share and the likely effect of your proposed agreements and activities on competition within the EEA are absolutely critical.

The draft new TTBE makes a strong distinction between restraints that are permissible when licensor and licensee are not competitors, and those restraints that are permissible when licensor and licensee are competitors. For example, a licensor who competes with its licensee in a relevant technology or product market cannot restrict the licensee's ability to determine sale prices, agree to limit output or sales, or allocate markets or customers (except that it is possible to impose a field of use restriction on the licensee and to require that the licensee manufacture the contract products only for its own use). It is not permissible to restrict the licensee's ability to exploit its own technology or conduct R&D, unless the latter restriction is indispensable to protect the licensor's know-how. When a licensor and licensee are not competitors, the licensor can (under certain conditions) restrict the territories into which or the customers to whom the licensee sells the contract products, and the licensor can impose a maximum sale price on the licensee or recommend a sale price. Reference should be made to the TTBE for a full list of prohibited clauses and also to the Guidelines for a proper understanding of the scope of these prohibited clauses.

Controversially, the new TTBE introduces market share caps for determining which licences may benefit from block exemption. If competing undertakings have a combined market share exceeding

20% on any relevant technology or product market, their agreement cannot benefit from block exemption in respect of that market. The market share cap is 30% each for non-competing undertakings. The draft Guidelines give examples of when companies will qualify as competitors and how to calculate market shares.

Subject to the block exemption being withdrawn owing to the anti-competitive effects of a given licence, the new TTBE will apply to the licence until the date of expiry, invalidity or the coming into the public domain (in the case of know-how) of the last intellectual property right which the licence covers and which constitutes "technology" within the meaning of the TTBE.

What should you do with existing licences?
The proposals are due to come into force 1 May 2004. There is a transitional period for licences which at the time satisfy the conditions for exemption stipulated in the old TTBE. The transitional period expires 31 October 2005. During that period it will advisable to review existing agreements and negotiate any amendments necessary to comply with the new rules in order to remain within the safe harbour of the block exemption. Agreements outside of the scope of the TTBE will require individual assessment in the light of the Guidelines.

This is a fairly complex area of law but extremely important, particularly as breaches of EU competition law can result in fines of up to 10% of group world-wide turnover, clauses which infringe the competition rules (and thus potentially the whole licence) are void and unenforceable and third parties harmed by an anti-competitive agreement can seek damages from the parties involved.

If you would like to learn more about the proposal for a new Technology Transfer Block Exemption, please send an e-mail to Jamesfry@eversheds.com requesting a copy of Eversheds' more detailed note introducing the new TTBE, or please contact Paul Hughes or Trudy Feaster if you have specific queries (contact details given below):

➔ Pharmaceutical companies accused of manipulating drug trials for profit

(Jeremy Laurance Health Editor, The independent, 23 April 2004)

The multibillion-pound global pharmaceutical industry is accused today of manipulating the results of drug trials for financial gain and withholding information that could expose patients to the risk of harm.

The stranglehold that the industry exerts over research is causing increasing alarm in medical circles as evidence emerges of biased results, under-reporting and selective publication driven by a market worth more than £10bn a year in the UK.

In cancer, heart disease, mental health and related fields the industry has sponsored trials of new drugs which have held out great promise for patients. But when the same drugs have been tested in independent trials paid for by non-profit organisations - governments, medical institutions or charities - they have yielded different results.

Heart drugs prescribed for abnormal heart rhythm introduced in the late Seventies were estimated to kill more Americans each year by 1990 than the Vietnam War. Yet early evidence which suggested the drugs were lethal, and might have saved thousands, went unpublished.

Expensive new cancer drugs introduced in the last decade and claiming to offer major benefits have increasingly been questioned. Evidence published in the *Journal of the American Medical Association* showed that 38 per cent of independent studies of the drugs reached unfavourable conclusions about them, compared with just 5 per cent of the studies funded by the pharmaceutical industry.

In the latest case, researchers commissioned by the National Institute for Clinical Excellence (Nice) to develop guidelines for prescribing antidepressant drugs to children, say they were refused access to unpublished trials held by the pharmaceutical companies.

Published evidence suggested that the antidepressant drugs called SSRIs (selective serotonin re-uptake inhibitors) were safe and effective for children.

But when researchers obtained the unpublished evidence by contacting individual researchers who had worked on the trials, a picture emerged of increased risk of suicidal ideas and attempted suicide. Only one drug, Prozac, was safe.

Antidepressants, though not recommended for children, were widely prescribed until last year when the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a warning to doctors, prohibiting their use. This followed safety concerns raised by campaigners and taken up in two BBC television*Panorama* broadcasts.

Writing in *The Lancet*, the authors say: "On the basis of published evidence alone, we could have considered at least tentatively recommending use of these drugs for children and young people with depression. However, our review of combined published and unpublished data ... suggest that these SSRIs are not efficacious. Moreover a possible increased risk of suicidal ideation, serious adverse events or both, although small, cannot be ignored."

Tim Kendall, from the Royal College of Psychiatrists, said the researchers had been "unnerved" by the possibility that Nice could have issued wrong or harmful advice because it did not have access to the full data.

The same concerns would apply to advice issued about other drugs in other specialist areas, he said. Guidelines were being drawn up for the use of antidepressants in adults based on 1,000 published trials but it was possible there were tens or hundreds of unpublished trials they had not seen.

The Lancet says the possibility that the suicide of a child could be provoked by a supposedly beneficial drug would be a "catastrophe" and the idea of the drug's use being based on "selective reporting of favourable research" should be "unimaginable." It says the story of research into SSRIs in childhood "is one of confusion, manipulation and institutional failure."

It cites an internal GlaxoSmithKline memo, published in the *Canadian Medical Association Journal* last month, referring to a study of the antidepressant Seroxat (paroxetine) in children. The memo said: "It would be unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."

Billions of pounds are spent on the basis of published evidence, assembled by organisations such as Nice, *The Lancet* says. Global sales of GlaxoSmithKline's Seroxat amounted to $4.97bn last year.

Andrew Dillon, chief executive of Nice said: "The institute's ultimate objective is to be given and to be able to use freely all data relevant to the guidance which it is asked to develop. We continue to work to that objective."

The Association of the British Pharmaceutical Industry said it was prevented under Nice's rules from supplying unpublished data for the preparation of clinical guidelines. But, it has set up a register of clinical trials, and regulations to be introduced next month under the European clinical trials directive would make monitoring easier.

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