Legal and regulatory update

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Legal and regulatory update

NOTES FROM THE EU

CAT wins Humira royalty case

Cambridge Antibody Technology (CAT) won its High Court battle against healthcare company Abbott over the level of royalties due on sales of the potential blockbuster drug Humira. CAT argued successfully that it was due a royalty of just over 5 per cent of sales, rather than the 2 per cent that Abbott had been paying. It is believed that CAT is due back payments from Abbott as well as future royalty payments at the higher rate on sales predicted to rise to over US$2bn per year.

The dispute was founded on two agreements, entered into in 1993 and 1995, in which CAT licensed its proprietary library creation and phage display technology to Knoll (which was subsequently acquired by Abbott, and will be referred to as Abbott in this paper). Abbott wanted access to CAT's technology in order to try to develop antibodies to particular targets, which it was hoped could be turned into pharmaceutical treatments for various diseases. The first target was TNFα and the research was very successful, leading to Humira, a treatment for rheumatoid arthritis which has been approved for marketing in 51 countries. Research on the other targets has also led to further successes, with several more potential drugs currently undergoing clinical development. The outcome of this case is therefore very important to CAT, as it will affect the level of royalties it is entitled to receive from sales of other relevant pharmaceutical products in addition to royalties on sales of Humira.

At the heart of the dispute between the parties were the royalty offset provisions of the agreements (which were both on substantially identical terms but concerned different targets). Abbott agreed to pay CAT a royalty of just over 5 per cent of net sales, but was permitted to offset half of certain royalties paid to third parties in respect of other patented technology which Abbott licensed in order to develop the product (in this case, Humira). The offset was subject to a cap which guaranteed a minimum royalty of 2 per cent for CAT. The relevant clause in the agreements was clause 5:

> Royalties paid to third parties. . .to practice or have practiced the technology claimed in [CAT's patents] will be borne equally by the parties provided that CAT's royalty pursuant to [the royalty clause] is not less than two per cent of [net sales of Humira]'

Abbott claimed that it was entitled to apply the offset and pay CAT the minimum royalty, as it had licensed various patents from third parties during development of the product, such as patents covering the production of the full antibodies contained in Humira. CAT disagreed and argued that the offset did not apply to the particular licences taken by Abbott, but only applied to technology that Abbott required licences for in order to use CAT's technology to create and screen libraries of single chain variable fragments in order to identify and isolate those with high, specific binding affinity for TNFα. Production of full antibodies containing the fragments isolated was downstream of CAT's technology and should not therefore be covered by the offset.

Abbott argued that, had the parties agreed that the offset would apply only to licences needed in order to exercise CAT's technology, the agreements would have been drafted accordingly, for example by using the phrase 'phage antibody technology' instead of 'the technology claimed in [CAT's patents]'. The phrase 'to practice or have practiced the technology claimed in CAT's patents' should be interpreted by reference to the claims of the relevant patents, which contained reach-through claims to a

method of production of the antibodies in Humira and to the antibodies themselves. The offset should therefore apply to those patents that Abbott licensed in order to produce the Humira antibodies by expression from the host cell. 'To practice or have practiced the technology claimed in [CAT's patents]' meant that the offset right only ended at the point where Abbott had produced a whole antibody which binds to TNFα. If Abbott was unable to make the antibody, it would not be able to 'practice or have practiced' the relevant technology.

The judge in the case, Mr Justice Laddie, looked carefully at the wording of clause 5 and the other relevant clauses, in particular clause 12, which concerned claims of infringement by Abbott of any third party's patents due to manufacture or sale of Humira. Under this clause, CAT had the choice of either defending the action itself and indemnifying Abbott against any judgments or granting Abbott the right to defend the action. If CAT were to choose the second option, Abbott would be entitled to offset half its litigation costs and damages against the royalty payable to CAT (subject to a cap which ensured CAT would get a royalty of at least 2 per cent). The important wording in this clause was as follows (emphasis added):

> Such [offset] may not be taken by [Abbott] where the action involves a claim or right of a third party based upon activities such as *packaging of [Humira] or improvements to [Humira] which are beyond the scope of the technology described in [CAT's patents].*

There was a further relevant clause (also part of clause 12) allowing Abbott to offset half the royalties or licence fees payable to third parties with relevant patents in order to enable Abbott to 'utilise or have utilised the inventions of [CAT's patents]', subject to CAT receiving a minimum royalty of 2 per cent of net sales. The crucial wording of this clause was (emphasis added):

> This offset shall not include royalties or licence fees which are beyond the scope of the technology described in [CAT's patents], for example *fees paid to third parties for delivery systems*.

The judge explained that, when construing the agreements, the royalty offset provisions of clauses 5 and 12 must be read consistently with each other. Therefore, although clause 5 does not contain express downstream limitations on the offset, the limitations in clause 12 (concerning packaging, improvements and fees for delivery systems) mean that the royalty offset of clause 5 cannot cover the whole of development, production and sale of Humira. In fact, this point was agreed between the parties, and Abbott was in the difficult position of having to argue that the offset applied up to the point where Abbott had produced the Humira antibodies by expression from the host cell, rather than production of the packaged, pharmaceutical product for placing on the market.

Mr Justice Laddie explained that the modern approach to construction by the courts is to look, in an objective sense, at what a reasonable person to whom the wording was addressed would have understood by those words, rather than the subjective intention of the author. If Abbott's claims were accepted, this would lead to a construction of the relevant clauses which was inconsistent with the remainder of the agreements and which made no commercial sense. For example, the warranty clause would not mesh with Abbott's construction:

> CAT gives no warranty, express or implied, that the technology covered by [CAT's patents] will work when applied to any particular purpose.

This clause was clearly only concerned with CAT's *own* library creation and phage display technology and not any technology used in Abbott's plant up to and including the production of full antibodies. Furthermore, Abbott's argument that the scope of the offset

should be determined by the claims of the patents would mean that the scope would vary according to the wording of the claims in the different patents granted in each country. At its extreme, this approach would give CAT an incentive to make only very narrow patent claims in order to avoid the offset biting.

Another relevant consideration was that Abbott's obligation to pay royalties was totally independent of eventual grant of CAT's patents (which were only at the application stage when the agreements were entered into). This would mean that, according to Abbott's interpretation of the relevant clauses, if CAT did not obtain any patents, the offset provisions could never apply and Abbott would have to pay the full royalty throughout the term of the agreements.

Mr Justice Laddie ruled that the royalty offset provisions applied only where Abbott had taken patent licences necessary in order to use CAT's technology. He said that this interpretation of the relevant clauses was not only consistent with the wording used, but also made commercial sense. The only technology that CAT brought to the table under these agreements was its own technology and all activities downstream of that were to be undertaken solely by Abbott. Abbott was not required to notify CAT of the technology it proposed to use in the downstream stages of development, nor to discuss the royalty rates Abbott would pay such third parties. It was obvious therefore that the royalty offset should protect Abbott only against the impact of third party licences where these related to the part of the research for which CAT was responsible.

It is possible that this judgment may be subject to appeal by Abbott, but in the meantime, biotech companies would be well advised to ensure that, where they may in future receive royalties on sales of final pharmaceutical preparations initially identified with their enabling technology, the limitations on any royalty offset provisions, which may have a significant impact on their future income stream, are explicitly set out in the agreement. Where patents contain reach-through claims downstream of the use made of the enabling technology, the royalty offset should be expressed to relate specifically to the enabling technology used, rather than being linked to the wider term 'to practice or have practiced the technology claimed in the patents'. Although CAT was successful with its use of this wording, it would not be prudent to rely on the courts to determine the boundaries of royalty offset clauses by reading them consistently with other clauses in the agreement and considering whether, when all the clauses are taken together, the agreement makes commercial sense.

Case C-36/03 R (on the application of Approved Prescription Services Ltd) v The Licensing Authority (acting by the MHRA) December 2004

ECJ's latest case on 'hybrid' abridged applications for marketing authorisation

Approved Prescription Services Limited (APS) won the right to rely on Eli Lilly's bioequivalence data for Prozac liquid when applying for marketing authorisation for a generic version, even though Prozac liquid had not been authorised for the requisite ten year period. This was because Eli Lilly had used Prozac capsules, which had been authorised for over ten years, as its reference product when applying for authorisation for the liquid form. In coming to this conclusion, the ECJ applied the same principles as it had in the Novartis case (*Case-106/01 R (on the application of Novartis Pharmaceuticals UK Ltd) v The Licensing Authority (acting by the MHRA) April 2004*).

Under Article 10(a)(iii) of Directive 2001/83/EC, an applicant for a marketing authorisation need not submit toxicological, pharmacological or clinical trial results if the medicinal product that is the subject of the application is *essentially similar* to a medicinal product that has

been authorised in the Community for ten years or more (the time period may be six years or ten years – the UK has implemented the ten year requirement). Article 10(a) is known as the 'abridged' procedure for applications. There is a proviso to the abridged procedure where the product in question is to be administered by a different route, or in a different dose, in which case appropriate toxicological, pharmacological and/or clinical trial data must be supplied after all. This is known as the 'hybrid abridged' procedure.

Eli Lilly had obtained marketing authorisation in the UK in 1988 for the capsule form of Prozac. In 1992 Eli Lilly used an abridged application procedure under the then applicable legislation (which was to become the abridged procedure under Article 10(a)(i)) to apply for marketing authorisation for Prozac liquid. The liquid form was not regarded as essentially similar to the capsule form. However, Eli Lilly, as marketing authorisation holder for the capsule form of the drug, was able to rely on the toxicological, pharmacological and clinical trial data supplied for the capsules plus some extra data to demonstrate bioequivalence of the two forms.

In 1999, more then ten years after the capsule form was first authorised in the UK but only seven years after the liquid form was authorised, APS applied under the abridged procedure of Article 10(a)(iii) for marketing authorisation for generic fluoxetine liquid on the basis that it was essentially similar to Prozac liquid. Prozac liquid was therefore its reference product. In its application, APS claimed as the date of grant of the first marketing authorisation the date of authorisation of the capsule form in 1988. The Medicines and Healthcare products Regulatory Agency (MHRA) refused the application on the basis that the reference product, Prozac liquid, had not been on authorised for the requisite ten years. To succeed in its application, the MHRA said APS would have to rely on Prozac capsules as its reference product, as these had fulfilled the ten year criterion. This meant that APS would also have to supply additional data under the hybrid abridged procedure in order to demonstrate the bioequivalence of the liquid and capsule forms. This would mean repeating the work that Eli Lilly had done to support its application for Prozac liquid in 1992.

APS applied for judicial review of the MHRA's decision in the English High Court, claiming that it should have been allowed to rely on Eli Lilly's data demonstrating bioequivalence of the liquid and capsules. The High Court referred the question to the European Court of Justice (ECJ).

The ECJ's answer to the High Court's question accorded with APS's arguments. The ECJ applied the same logic as it had applied in the Novartis case, which was on similar facts and had been decided during proceedings in the APS case. This means that applicants seeking approval for generic versions of products that are essentially similar to what are known as 'line extension' products (Prozac liquid is a line extension of Prozac capsules) that have not been authorised for ten years will be able to use the abridged procedure. The generic applicants will able to rely on the extra data submitted by the original authorisation holder when applying for the line extension product provided, of course, that the original product has authorised in the Community for the requisite six or ten year period.

This relieves generic company applicants from the burden of producing their own extra data and going through the hybrid abridged procedure. However, the MHRA is at pains to point out that these judgments do not exclude the possibility that, in specific cases, it may be necessary for the MHRA to require additional data from the generic applicant.

Freedom of information and the MHRA

On 1st January, 2005, the rights of access to information under the Freedom of Information Act 2000 came into force. The intention is to promote a culture of

openness and accountability among public authorities by providing access to information that they hold. The Act does not merely require public authorities to respond to requests for information, but places an obligation on them to be proactive and publish information.

Unlike requests for information under the Data Protection Act 1998, the rights of access apply to companies as well as individuals and there is no need for a link between the information requested and the person requesting it. Unless a relevant exemption applies, public authorities, including the MHRA, must respond to requests for information, generally within 20 days, by stating whether or not they hold such information and, if they do, supplying a copy of it. The MHRA website[1] contains an electronic request form that applicants may use. Various exemptions exist to protect from disclosure information that it would not be in the public interest to disclose, for example, relating to national security, law enforcement, health and safety, confidential information and trade secrets. The Information Commissioner has published guidance on its website on the operation of the exemptions.[2]

In compliance with the Act, the MHRA has also adopted a publication scheme which sets out details of the information it routinely publishes, much of which is available on its website. For example, outlines of the MHRA's role and organisation, monthly updates of granted marketing authorisations and parallel import licences, information about adverse drug reaction reporting as well as guidance notes and application forms for regulatory authorisations (such as marketing authorisations and clinical trial certificates) are available.

€66.34m of fines for animal feed vitamin cartel

The first example of the new Commissioner's determination to fight cartels was illustrated by the fines imposed on the members of the animal feed vitamin cartel. European companies including Akzo Nobel of the Netherlands, BASF of Germany and UCB of Belgium, as well as US companies such as DuCoa and Bioproducts, secretly met to increase prices artificially, allocate markets and control competitors and further decided that the US companies would withdraw from the European market and the Europeans would withdraw from the US market. Until 1998, the three European producers continued their anti-competitive practices on the European Economic Area (EEA) market. In 1997, the value of the animal feed vitamin market amounted to €180m worldwide, including €50m for the EEA market. The vitamins are mixed with the feed for poultry and pigs to increase growth and improve the meat quality.

In light of the nature and geographical scope of the cartel, the Commission considered this constituted a serious infringement of Article 81(1). It established the amount of fines taking into account the value of the market, the duration of the infringement, the respective weight of the companies, the fact that BASF has already been fined for similar infringements and the cooperation of the companies during the investigation. The resulting fines amounted respectively to almost €35m for BASF, €21m for Akzo Nobel and €11m for UCB.

The US companies benefited from the five year limitation period for the imposition of fines but received decisions warning them of the consequences of such behaviour.

Better access to data on medicines

Patients and researchers will be able to look at data on the safety of medicines. This change to current practice is part of a series of measures designed to improve the drug adverse effect reporting system known as the Yellow Card Scheme, which is used by the MHRA to monitor the safety of medicines in the UK. The new measures are key recommendations made by experts who reviewed the

Yellow Card Scheme last year and as a result of a public consultation.

The MHRA will publish anonymous data on suspected adverse drug reactions on its website. Researchers will also be able to access more detailed data and measures will be put in place to prevent potential abuse of the information. Every request for information will be reviewed to make sure it is ethically and scientifically sound and protects patient confidentiality.

The first pilots of patients directly reporting unexpected effects of drugs to the regulator were also launched. Forms to report unexpected drug reactions will available in 4,000 surgeries across the UK and are also available directly from the MHRA. Patients will also be able to file reports online through the Yellow Card website.[3]

NOTES FROM THE USA

Proposition 71: Californians pledge three billion dollars to support stem cell research

Background on Proposition 71

On 2nd November, 2004, California voters issued a historic mandate for stem cell research by passing Proposition 71, the California Stem Cell Research and Cures Initiative. Supported by 59 per cent of California voters, Proposition 71 will infuse approximately US$300m dollars annually into stem cell research at Californian universities and research institutions over the next ten years, for a total of US$3bn. This money represents more than ten times the annual funding currently available for stem cell studies from the Federal government. Proposition 71 has generated widespread interest among academics, scientists and commercial biotechnology companies from throughout the world. The myriad of questions include the opportunities for research partnerships, and the impact on new commercial ventures, intellectual property ownership and public policy. Many observers predict that the passage of Proposition 71 will make Californian research institutions the global leaders in embryonic stem cell research, with a strong positive impact on the biotechnology industry in this state.

The passage of Proposition 71 triggered several immediate changes. First, it created a state constitutional right to conduct stem cell research in California. Secondly, Proposition 71 established a state agency, the California Institute for Regenerative Medicine, to direct and oversee California's stem cell research programme, the largest effort of its kind in the world. Thirdly, it expressly prohibited the funding of human reproductive cloning; instead, priority funding will be given to pluripotent stem cell and progenitor cell research that is unlikely to receive Federal funding under current policies.

Since the November election, numerous entities, including academic institutions and private stem cell research groups, have publicly announced their intention to apply for Proposition 71 funds. Bolstered by the promise of funds, California universities and research institutes are forming partnerships to apply for grants. Other states, including New Jersey, Wisconsin and Illinois, have started budgeting taxpayer dollars or proposing similar initiatives to support their research institutions and biotechnology companies.

Allocation of funds

Beginning in 2005, up to US$3bn in general obligation bonds may be issued and sold over a ten year period, subject to an annual limit of US$350m. If less than US$350m in bonds is issued in any year, the remaining permitted amount can be carried over to one or more subsequent years. Proceeds from the bond sales, after repayment of start-up costs associated with Proposition 71, will be deposited into the California Stem Cell Research and Cures Fund and allocated according to specific guidelines.

Administrative hierarchy of Proposition 71

The California Institute for Regenerative Medicine is the agency primarily responsible for carrying out the purposes

of Proposition 71. The Institute is charged with making grants for stem cell research and facilities and establishing regulatory standards and oversight bodies for research and facilities development. The Independent Citizen's Oversight Committee (ICOC), the Institute's governing body, has begun the search for management talent for the Institute. The ICOC has also authorised its Chairperson to hire interim staff and other technicians and professionals to carry out the Institute's functions.

The ICOC members were appointed by various university and state officials and include representatives from California universities, non-profit research institutes, California commercial life science entities and various disease advocacy groups. The ICOC's primary responsibilities include oversight of the Institute's operations and development of long-term strategic plans. It will decide research standards and make all final grant awards. All ICOC actions require a majority vote of a quorum, and it must award all grants, loans and contracts in public meetings.

Three working groups, each with specific responsibilities, will assist the ICOC in making its final decisions. The Scientific and Medical Accountability Standards Working Group is primarily responsible for recommending scientific, medical and ethical standards to the ICOC. This Working Group is composed of 19 members: 5 ICOC members, 9 scientists, 4 medical ethicists and the ICOC Chairperson.

The Scientific and Medical Research Funding Working Group is responsible for recommending criteria for funding research applications and for awarding research grants and loans. This Group is composed of 23 members: 7 ICOC members, 15 scientists and the ICOC Chairperson. Proposition 71 provides some general criteria for evaluating grant applications; including: (1) the applicant's record of achievement in pluripotent stem cell and progenitor cell biology; (2) the quality of the research proposal; (3) the potential for achieving significant research or clinical results; (4) the timeliness of results; (5) the importance of the research objectives; and (6) the innovativeness of the proposed research. The ICOC may adopt additional criteria for evaluating grant applications. Once such criteria are adopted, the 15 scientist members of the Group will score grant and loan applications for scientific merit and recommend prospective grantees to the ICOC.

The Scientific and Medical Facilities Working Group is responsible for recommending criteria for funding facilities and equipment applications and for awarding such grants and loans. This working group is composed of 11 members: 6 members from the Research Funding Working Group, 4 real estate specialists and the ICOC Chairperson. To guide the decisions of this group, Proposition 71 establishes some baseline criteria for evaluating facilities grant applications. First, applicants must be not-for-profit entities. Second, all funded facilities and equipment must be located solely within California. Third, grantees must secure matching funds from outside sources in an amount equal to at least 20 per cent of the grant award. Priority is given to facilities that will be available for research within two years of the grant award. The ICOC may adopt additional criteria for evaluating facilities grant applications.

Research projects that will receive priority funding under Proposition 71

Currently, federal policy prohibits the federal funding of research on human embryonic stem cell lines that are not listed on the National Institutes of Health (NIH) Human Embryonic Stem Cell Registry. According to the NIH, there are currently 22 human embryonic stem cell lines that federally supported researchers may purchase. Because Proposition 71 is designed to close this funding gap, priority will be given to research that is unlikely to receive federal funding under current policies, with an

emphasis on pluripotent stem cell and progenitor cell research. Research categories that are currently funded by the NIH will not be funded under Proposition 71. In some cases, funding can also be provided for other types of research that may lead to new types of cures or treatments of diseases and injuries. Notwithstanding the foregoing, Proposition 71 included an explicit prohibition on the funding of research on human reproductive cloning.

Legal issues affecting grantees

There are a number of intellectual property issues for prospective and future grantees to consider. Under Proposition 71, the ICOC must establish standards that require all grant and loan awards to be subject to intellectual property (IP) agreements in which the State of California will share in patents, royalties and licences resulting from funded projects. While Proposition 71 requires the ICOC to adopt such standards, it offers little guidance as to what standards the ICOC should adopt. Instead, Proposition 71 broadly calls upon the ICOC to balance the

> opportunity of the State of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements.[4]

In addition to this vague language, the ICOC has come under political pressure to guarantee that the State recoups its investment, at least in part, through IP revenues. For example, already a California state senator has introduced legislation that would explicitly require the State to receive a share of royalties commensurate with its role of providing funding for the research.[5]

Prospective grantees must also navigate the thicket of patent rights that currently exist in the stem cell field. For example, the University of Wisconsin and its licensee, Geron Corporation, a company based in Menlo Park, California, have taken strong positions with respect to their stem cell patents and claim broad patent rights to any commercial products developed using certain techniques with stem cells. Given the emergence of such claims, grantees will need to carefully consider their positions and if necessary, enter into the appropriate IP arrangements.

In addition to IP issues, grantees should be aware of Proposition 71's indemnity provisions. Under Proposition 71, the ICOC may sue and be sued. Proposition 71 calls upon the ICOC to establish standards that require grantees to indemnify and hold the Institute harmless against any and all losses and liabilities, arising from research conducted by the grantee pursuant to the grant. Alternatively, grantees may be required to name the Institute as an additional insured and submit proof of such insurance.

Attention should also be given to the public and financial accountability standards under which the Institute and ICOC must operate. For example, Proposition 71 requires the Institute to issue a public annual report that discloses a variety of information, including the grantees for the prior year, the number and dollar amounts of research and facilities grants and a summary of research findings, including promising research areas. The ICOC is also required to make all grants, loans and contracts in public meetings and adopt all governance, scientific, medical and regulatory standards in public meetings. Additionally, the ICOC's records must comply with the California Public Records Act. While the public meeting and public record requirements of Proposition 71 carve out exceptions for sensitive matters, including confidential intellectual property, work product and prepublication research data, grantees need to be aware of these requirements.

References and notes

1. URL: http://www.mhra.gov.uk
2. URL: http://www.informationcommissioner.gov.uk
3. URL: www.yellowcard.gov.uk
4. Cal. Health and Safety Code §125290.30(h).
5. The Proposition 71 Public Accountability Act proposes additional requirements. For example, the Act would require grantees to make treatments available and affordable for state programmes and low-income residents. It also calls for the State to recoup its legal and administrative costs associated with patent and licensing associated with grants. With respect to the ICOC, the Act requires members to disclose economic and other interests in the same manner as other public officials. The Act also requires the ICOC to ensure that its working groups abide by open meeting laws. The validity of this legislation is likely to be challenged by the ICOC, since Proposition 71 includes a provision prohibiting amendments during the first three calendar years of the proposition's implementation.