Part 1: The legal and regulatory background

It is impossible to give a comprehensive guide to the issue of drug licensing in the EU in a short podcast. What follows is an inadequate summary of the relevant issues in order to assist with an explanation of the background to the Avastin litigation.

When a company develops a new medicinal product in the EU - which we will refer to as a "drug" - it registers the intellectual property rights in that drug in order to ensure that no one else can copy drug and compete in the market. Drugs are given a period of exclusivity when the IP rights holder is the only company that can manufacture and market the drug in the territories covered by the EU. The term of a patent is generally 20 years from the date on which the application for the patent is filed.

However, registering a patent for a medicinal product does not make it lawful for a pharmaceutical company to market their product within the EU. In order lawfully to market a medicinal product in the EU, a pharmaceutical company needs to obtain a "Marketing Authorisation" from the European Medicines Agency - known as the "EMA" – under Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use. We will refer to this as the "Medicines Directive". The Medicines Directive has been amended a number of occasions since the original text was published in 2001, but it is not necessary to refer to the details of the amendments for present purposes. The Medicines Directive has 61 recitals and sets out a complex legislative scheme to govern the manufacture and marketing of medicinal products within the European Union.

Article 6 of the Medicines Directive provides that no medicinal product may be "*placed on the market*" of a member state unless a marketing authorisation has been issued. There is a separate system of manufacturing authorisations which give permission to holders of the authorisation to manufacture medicinal products. There is no definition in the Medicines Directive of the meaning of the term "*placed on the market*". It clearly covers the initial actions of the pharmaceutical company of making a drug available for wholesale

distribution. However, the supply chain for drugs often involves them passing through multiple hands before they end up with a doctor who prescribes a drug for a patient. One of the issues in this case was the extent to which each separate step in the supply chain was a separate placing on the market for the purposes of the Directive.

The Directive also covers the requirement for anyone who is involved in the manufacture of medicinal products to have a "Manufacturing Authorisation". Article 40.2 provides that a Manufacturing Authorisation shall be required for both total and partial manufacture and for the various processes of dividing up, packaging or presenting medicinal drugs. It goes on to contain an important exemption for pharmacies. A Manufacturing Authorisation is not required for the preparation dividing up or changes in packaging or presentation of a drug where these activities are carried out solely for retail supply by pharmacists in dispensing pharmacies or by persons legally authorised to member states to carry out such processes.

Thus pharmacists are entitled to carry out processes which, in all other circumstances, would require an EU Manufacturing Authorisation but only provided there activities are "*solely for retail supply*". That term is also not defined within the Directive and the meaning of the expression "*solely for retail supply*" became important in the case.

The EU has also adopted regulation 726/2004 which lays down the procedures which have to be followed in order to obtain either a Marketing Authorisation or a Manufacturing Authorisation for a medicinal product.

The UK government has implemented the terms of the Medicines Directive by passing the Human Medicines Regulations 2012. The wording used in the 2012 Regulations is not entirely consistent with the wording of the Medicines Directive and, in some cases, the scope of activities defined in the 2012 Regulations could be argued to be wider than those activities covered by the Medicines Directive. One of the issues in the case was the extent to which the scope of activities covered by the words in the 2012 Regulations was limited by the scope of the Medicines Directive or whether activities which were not within the scope of the Medicines Directive could nonetheless come within and thus be caught by the terms

of the 2012 Regulations. Without getting ahead of ourselves, the approach of the Court of Appeal was to interpret the meaning of the 2012 Regulations in accordance with the Medicines Directive, and therefore to provide that UK domestic law concerning medicines regulation goes no wider than the law imposed by the Medicines Directive.

The 2012 Regulations define the consequences of any breach of the terms of those Regulations. Many of the breaches constitute criminal offences. Thus it is important for anyone involved in the manufacture or handling of distribution of medicines to understand what is and is not permitted by the 2012 Regulations, because a breach could lead to an individual being brought before a criminal court. It is thus important to know whether the scope of activities governed by the 2012 Regulations is limited to matters within the scope of the Medicines Directive or whether the net has been cast in a wider way, criminalising matters undertaken in the UK even though these are not breaches the terms of the Medicines Directive.

Medicinal drugs are often referred to as having "licences". However, EU law does not govern the way in which doctors and other health professionals are entitled to use medicinal products to treat patients. That is entirely a matter for the professional judgment of clinicians, guided by the law of each member state. The terms of the licence for a drug will define the types of diseases or patient groups for whom the drug is permitted to be marketed by the licence holder. However, doctors are not limited by the terms of a drug licence.

The terms of a drug licence thus limit the way in which pharmaceutical companies can market a drug but they do not, of themselves, limit the way in which doctors can use drugs. For example, drugs which have only been licensed for adults are frequently and entirely lawfully prescribed for children. This can be because there are significant ethical problems in undertaking randomised controlled trials of paediatric drugs, and accordingly it is often very difficult to get drugs licensed by the EMA for paediatric use. This means that pharmaceutical companies are not entitled to market an adult drug for use for children.

However, once the drug arrives at the hospital, paediatricians are fully entitled to use their clinical judgment to decide what drugs should be used for which patients.

In making these decisions doctors and pharmacists are subject to a series of different regulatory constraints. Firstly, all doctors operating in the UK have to be registered with the General Medical Council – the GMC. The GMC publishes a code of practice - Good Medical Practice - which guides how doctors exercise their professional duties. A doctor who acts contrary to the guidance contained within the code may be referred to the GMC for professional disciplinary action. It is not unlawful - in the sense that the doctor breaks a legal obligation to which the doctor is subject - for a doctor to act contrary to the Guidance in Good Medical Practice. The potential sanction doing so is not a fine imposed by a criminal court or a finding of liability in a civil court. The potential sanction is disciplinary action in a case brought by the GMC before the specialist medical tribunal. Doctors can be suspended from practice or be struck off the register if their fitness to practice is impaired - and acting in breach of the GMC Code of Practice can be evidence of impaired fitness to practice. However departing from the GMC Code of Practice does not necessarily indicate that the doctor has fitness to practice. That all depends on the individual circumstances of the case.

Pharmacists are subject to regulation by the General Pharmaceutical Council - the GPC - in a similar manner.

Hospital doctors are employed by NHS Trusts. They will have terms and conditions of their employment, and could face disciplinary sanctions from their employers if they act in breach of the terms of the contract of employment.

Lastly, by way of background, is important to say something about the way the NHS is structured. The NHS systems, as set up by the National Health Service Act 2006 - as amended by the Health and Social Care Act 2012 and a series of other domestic statutes - involve a large number of different public bodies. The Secretary of State for Health and Social Care sits at the apex of the NHS pyramid, discharging his role under the NHS Acts.

However, the Secretary of State has a largely political and strategic role. The structures deliberately ensure that, save in the case of an emergency, precise decisions about which medical treatment should be provided to which patient and in what way are made by medical professionals and not by politicians.

The Secretary of State for Health and Social Care has wider legal obligations than as the Cabinet member responsible for the NHS. One such role is in connection with medicines regulation. The Medicines and Healthcare Products Regulatory Agency - known as the MHRA - is an executive agency responsible for ensuring the safety and efficacy of medicines in the UK. It has no separate legal personality from the Secretary of State and is, in effect, the national organisation which gives effect to the EU obligations set out in the Medicines Directive. It issues licences to carry out certain functions in the UK with respect to medicines, to the extent that this is permitted under the Medicines Directive.

There is no single legal organisation called "the NHS" as there is, for example, in the case of the local authority. The NHS is made up of a very large number of different legal organisations who work together as a result of a complex series of contractual and statutory arrangements.

NHS bodies can be divided into regulators, commissioners and providers. There are two types of commissioners - NHS England which is a national commissioner and locally based clinical commissioning groups. Clinical commissioning groups - known as CCGs - are membership organisations made up of the NHS GP practices in a geographical area.

The role of CCGs is to enter into a series of contracts with a range of provider organisations that deliver care to NHS patients so that the NHS is able to deliver as comprehensive a service as possible. NHS England is both a regulator and a commissioner of specialised services. CCGs do not directly provide any services to NHS patients. They are strategic bodies who seek to organise the services and area, making sure that each provider organisation is working effectively to deliver the services that NHS patients need - and is delivering on the terms of the contracts put in place to give effect to those obligations.

NHS Trusts and NHS Foundation Trusts are provider organisations. They are public bodies that run hospitals, community services and mental health services. They contract with both CCGs and NHS England to provide services to NHS patients.

GP practices contract with NHS England, although many CCGs now handle GP contracting for their local areas acting on behalf of NHS England.

CCGs set the broad strategic framework for the delivery of NHS services and area and adopt policies about how NHS services should be delivered. However, decisions about precisely how NHS care is to be delivered in a hospital are taken by hospital trusts, and the doctors employed by the hospital trust, and not by the CCG. CCG policies can influence the way that hospitals deliver care to NHS patients but the trust, not the CCG, is the final decision-maker about what care should be delivered and to whom. Trust will only get paid by the CCG the care which is delivered in accordance with the contracts put in place between the CCG and the Trusts but those contracts given element of clinical freedom to the hospital Trusts to decide how care is to be delivered.

The important distinctions in decision-making between CCGs and Trusts were very significant in the outcome in the Avastin litigation. It is perhaps important to say at the outset that the distinctions were always clearly understood by those operating within the NHS and those advising the NHS but the significance of these distinctions may not have been fully appreciated by all the other parties.