Overview of Drug Regulation in Europe

1 General

- Remember that in Europe you have a mix of national and EU law to contend with. Even the "EU law" aspects may be implemented in each country in slightly different ways e.g. The Clinical Trial Directive (2001/20/EC), so true harmonisation is not always achieved.

- Need a marketing authorisation to sell a drug (with limited exceptions e.g. named patient supply). Drug must be sold in accordance with that authorisation and the summary of product characteristics (SmPC).

- Fact that you have an approval in e.g. USA does not allow you to get an approval in Europe. Separate process and assessment.

- Everything needs to be authorised including carrying out clinical trials.

- Seek advice and seek it early to ensure that your clinical trial design will produce the data the regulators want to see.

- Effectively two systems of drug regulation in Europe:

    - National/country by country.

    - Central - European Medicines Agency (EMA).

    - Plus there are codes of practice in each country governing the promotion of medicines - generally voluntary.

- National route e.g. MHRA in UK - Medicines Act 1968

    - Mutual Recognition (if the drug has already been licensed in one EU country) and Decentralised procedures (if the drug has never been licensed in the EU) - allow authorisation granted in one country e.g. UK to be used as basis for approval in another EU country e.g. France. In both cases one country leads the procedure.

- Centralised route for all 27 EU countries - EMA - Directive 2001/83 and Regulation 726/2004

  Some products have to use this centralised route e.g.

    - All antibodies (including Biosimilars)

    - All new cancer treatments

    - All gene therapy treatments etc.

- Note - separate hurdle of pricing and reimbursement and recommendation by bodies like NICE (National Institute of Clinical Excellence in the UK) which is a national issue. NICE effectively carries out a cost/benefit analysis to determine whether a drug should be paid for by the NHS.

2 Generic/Biosimilars/Brand Names

- No patent linkage (or Orange Book equivalent) - up to generics to "clear the way" or launch at risk. Remember that the EU has the supplementary protection certificate (SPC) regime which can extend patent protection for a product by up to 5 years.

- We do have a "Bolar like" exemption for carrying necessary research (including trials) to secure a generic approval. In some countries this exemption is very broad indeed and is not limited to generics.

- Generic small molecule drugs require separate approval but for small molecules this is relatively straight forward as long as you can show bio equivalence and assuming data exclusivity (or market exclusivity for orphan drugs) has expired - so called abridged applications. Generally new clinical data not required (Articles 10(1) and 10(2) of 2001/83).

- Data exclusivity - 8 + 2 + 1 rule in the EU. Effectively 10 years of protection for the data submitted by the originator with the potential for an extra year if you develop a new indication.

- By 2014 the 6 top selling drugs are forecast to be biologics. Biosimilar therefore becoming increasingly important. Biosimilars have to be compared to and match the reference product in terms of quality, safety and efficacy. Includes comparability data which can include new clinical data (both Phase 1 and Phase 3 data). Each type of biosimilar is separately assessed and level of additional data required will vary from product to product. (Article 10(4) of 2001/83).

- If biosimilar is an antibody then clinical data will generally be required in order to show they are the same. EU at the forefront of law and guidance in biosimilars. Original guidance issued in 2006 (EMEA/CHMP/BMWP/42832/2005) - now being revised. Plus there are product specific guidelines.

- First biosimilar was introduced in EU in 2006 - Omnitrope (growth hormone). 14 in total have now been approved.

3 Off Label Promotion in EU

- Strictly prohibited in the EU (Article 87 of Directive 2001/83/EC).

- However mere "provision of information" about a drug to e.g. a medic is not - thin line between the two (Article 86(2)).

- In the end it's up to the doctors. No EU general guidelines on the topic. Generally should be in patient's best interests and based on a sound scientific basis. NHS in the UK announced on 5 October 2011 that they would be engaging experts to provide better information to doctors with regard to off label uses of drugs.

4 OTCs

- Switch to OTC is regulated at a national and central level. You can apply to the EMA for a centralised switch for all 27 EU member states but

- Centralised procedure is relatively new and not all products qualify for the procedure. So most OTC switching still happens at a national level.

5 Foreign Clinical Trial Data

- Can it be used? Yes, provided can show that trials carried out in accordance with EU equivalent laws.
- But additional data may be required depending on data submitted e.g. to deal with ethnic differences depending on where data generated.
- See also ICH guideline E5.

6 Post Marketing Obligations

- General obligations to report adverse events through pharmacovigilance.
- May be required to carry out specific post marketing studies as a condition to approval, particularly for biosimilars.
- Pharmacovigilance rules currently being revised to improve adverse event reporting and data collection e.g. with regard to off label use.

7 Corporate/Individual Responsibility

- Generally corporate - personal liability of e.g. a director is very rare.
- But possible for executives to have personal responsibility for corporate manslaughter e.g. recent Servier - Mediator scandal in France.

Patrick Duxbury
Wragge & Co LLP
6 October 2011

implementation of that switch approval by the EMA occurs at a national level.