Drug development and licensing in diabetes

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Abstract
The drug development process is long and expensive. Regulatory approval is granted following assessment of efficacy and safety, and drugs intended for use in the treatment of type 2 diabetes are also required to demonstrate cardiovascular safety. Once marketing approval has been granted in the UK, an additional step is required prior to a drug’s use: cost-benefit assessment by the Scottish Medicines Consortium and by the National Institute for Health and Care Excellence. Empagliflozin, an SGLT-2 inhibitor, has recently been granted marketing authorisation and approval for use in the UK. It will be used to illustrate the processes of drug development and licensing. Copyright © 2016 John Wiley & Sons.

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Key words
drug development; clinical trials; drug licensing; diabetes; empagliflozin

Introduction
The process by which a new drug becomes available to clinicians and their patients is a complex and expensive one, necessarily subject to extensive regulatory requirements. Prior to the 1960s, there was no formal process in drug licensing and regulation. Clinical trials did not require regulatory authority approval or monitoring, and post trial follow up was uncommon. The birth defects associated with thalidomide prompted changes to regulations, necessitating vigorous demonstration of a drug’s safety and efficacy. The Food and Drug Administration (FDA) produced the Drug Amendments Act of 1962 in the US, and the Medicines Act 1968 in the UK set down the legal framework by which medicines are licensed and controlled.

There have since been several changes to drug regulation as unacceptable side effects from several high-profile drugs came to light, prompting further assessment of drug safety. In particular, the events surrounding rosiglitazone resulted in the need for demonstration of cardiovascular safety in drugs intended for use in type 2 diabetes.

Pre-clinical development
Historically, drugs were often derived from natural plant extracts or discovered by serendipity. Sulfonylureas were initially investigated for use against typhoid and were noted to cause hypoglycaemia in 1942. They were subsequently found to stimulate insulin release from beta cells and tolnbutamide became the first commercially available sulfonylurea in 1956.1 Biguanides have an even longer history. Their use has been documented in mediaeval times when Galega officinalis, a herb containing guanidine, was used to treat symptoms of hyperglycaemia.2

Nowadays, the development of new drugs commonly begins with the selection of a particular biological target and identification of molecules active at this site. This can be achieved in several ways: through the synthesis of chemical analogues of existing drugs or compounds with the desired pharmacology, or by selecting novel agents from the extensive compound libraries which show activity against the required target.3

There follows a process of lead optimisation where compounds are further selected and/or modified to obtain the desired pharmacological activity. During lead optimisation there is extensive in vitro and animal testing in order to establish pharmacodynamic (PD) and pharmacokinetic (PK) parameters. A compound’s stability and formulation will also be established at this stage.3

Clinical development
Traditionally, the assessment of a new drug in humans can be split into four phases, described in Figure 1. In practice, these phases commonly overlap. Furthermore, the rising cost and lengthy timescales of drug development have prompted the need for alternative approaches.4

Introduction

Pre-clinical development

Clinical development


3. The Lancet. The Lancet. 2015

One such approach has been microdosing studies or phase 0 trials. Microdosing assumes that the pharmacokinetic parameters of a drug can be measured using small doses (1/100th of the expected pharmacological dose) in man, thereby avoiding significant side effects. Current guidelines allow a microdose to be administered in man based on a single dose toxicity study in animals. Drugs with an undesirable PK profile are therefore eliminated early on in the drug development process.

Phase I studies are non-therapeutic, exploratory trials, which traditionally form the bridge between animal and human studies if phase 0 trials have not been undertaken. They are small scale (20–200 patients) and are generally performed in healthy volunteers. The maximal tolerated dose is established by assessing escalating doses of the new drug and this information is used to set doses in subsequent studies.

Phases II and III assess a drug’s therapeutic potential. Phase II studies are larger in size (100–300 patients) and establish efficacy and optimal dosages in the target disease population. Side effects and safety are also assessed. Once a drug has demonstrated efficacy without significant toxicity, phase III studies can begin. These trials are large-scale (>1000 patients), multi-centre, randomised controlled trials. The investigational drug is assessed against placebo and/or current therapies and safety is examined.

Prior to testing in humans, approval must be given from the
appropriate regulatory authority (Medicines and Healthcare products Regulatory Agency (MHRA)/European Medicines Agency (EMA)/FDA; see Table 1) in the form of a Clinical Trial Authorisation (CTA, European Union [EU]) or Investigational New Drug (IND, US).Ethics approval and registration within a clinical trials database, i.e. EudraCT, is also necessary. All trials must be conducted in line with the principles of Good Clinical Practice, which offers guidance on how clinical trials should be designed, run and reported.

Cardiovascular safety in diabetes
Cardiovascular disease is a major cause of mortality and morbidity in diabetes. Prior to 2008, there were no specific requirements for new therapies in patients with type 2 diabetes to show cardiovascular safety. However, in 2007 the use of rosiglitazone was restricted following the publication of a meta-analysis suggesting a greater incidence of myocardial infarction (MI) and stroke in patients treated with rosiglitazone versus controls. The drug was subsequently withdrawn from sale in the UK and severe restrictions were placed on its use in the US.

The FDA responded to concerns regarding post-authorisation drug safety by changing guidance relating to therapies for type 2 diabetes to ensure new drugs are not associated with an additional cardiovascular risk. These regulations stated that: an upper bound 95% confidence interval for relative risk should be <1.8; study participants should be reflective of patients with diabetes, i.e. include those with long-standing diabetes, renal impairment and advanced age; a minimum of two-year safety data should be included; major adverse cardiovascular events (MACEs) should include cardiovascular mortality, MI and stroke. Additionally, following phase III trials, meta-analysis of data from phase II and III trials should be performed to evaluate whether there is unacceptable cardiovascular risk to patients.

The EMA has less stringent recommendations but follows similar principles. Like the FDA, the EMA recommends that trial patients are representative of the target population and that a safety analysis of MACEs are included; their view is that further safety trials are only mandatory if there are suspicions of adverse cardiovascular outcomes. In contrast, the Japanese regulatory authorities have no such requirement to demonstrate cardiovascular safety so that drugs can receive authorisation in Japan based on shorter-term studies with relatively small numbers of subjects.

In view of the fact that drugs under development are normally intended for use in both the US and EU, sponsors follow FDA guidelines. The overall result of these recommendations has been the need to have larger and longer trials and requirement to enrol patients with existing cardiovascular disease. The lengthy process can delay time to market and is associated with greater expense.

Marketing authorisation
Once phase III trials have been completed, a regulatory dossier, the Marketing Authorisation Application (MAA), is produced and submitted to the relevant licensing authority. This contains a full review of all the quality, safety and efficacy data.

Licensing in the UK can occur via two routes:

- The national authorisation procedure of the MHRA.
- The ‘centralised procedure’ of the EMA.

The centralised procedure allows a drug to be used throughout the EU and is compulsory for several types of drugs, including:

- Medicines derived from biotechnology processes, for example genetic engineering.
- Orphan medicines.

Evaluation is carried out by a committee of clinicians, statisticians and scientific assessors and also takes in independent advice from the main advisory body of the MHRA, the Commission on Human Medicines. The assessment can take up to 210 days after which the committee recommends whether a marketing authorisation should be granted. The final decision on marketing authorisation is made by the European Commission.

Phase IV
Information gathering continues once marketing approval has been granted, with ongoing assessment of safety where data are gathered from clinical practice in the form of phase IV studies.

This process is known as pharmacovigilance and involves continuous surveillance of unexpected adverse effects and long-term effects of a new drug, as well as post-marketing studies of efficacy. In the UK, the Yellow Card System whereby clinicians report suspected serious adverse reactions to the MHRA also forms a method of pharmacovigilance. A drug may be withdrawn following market authorisation if evidence suggests significant adverse effects, as occurred with rosiglitazone.

Table 1. Regulatory authorities in the US and EU and their roles

<table>
<thead>
<tr>
<th>Regulatory authority</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines and Healthcare Regulatory products Agency (MHRA)</td>
<td>Formed in 2003. Functions include: regulation of clinical trials, assessment and authorisation of medicinal products in the UK; operates post-marketing drug surveillance</td>
</tr>
<tr>
<td>European Medicines Agency (EMA)</td>
<td>Established in 1993. Coordinates the evaluation and supervision of the new medicinal products, grants opinion on licensing and oversees pharmacovigilance</td>
</tr>
<tr>
<td>Food and Drug Administration (FDA)</td>
<td>Established in 1927. Responsible for regulation and supervision of drug safety; drug assessment and authorisation, post-marketing surveillance</td>
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</table>
Example of drug development to licensing: empagliflozin

Although SGLT-2 (sodium glucose co-transporter 2) inhibitors are among the newest therapies for type 2 diabetes, their history dates back to 1835 when phlorizin was initially isolated from the bark of apple trees. The bitter taste of phlorizin was noted to be similar to extracts of willow bark and Cinchona and it was subsequently used in the treatment of fevers and infectious diseases. Shortly after, it was noted that high doses of phlorizin produced glycosuria, a finding that led to its later use investigating glucose handling by the kidneys. By the 1950s, its action as a non-specific SGLT inhibitor was established and its potential use in the treatment of type 2 diabetes was suggested by its ability to normalise plasma glucose levels and improve insulin sensitivity in diabetic rat models in the late 1990s.

Its poor bioavailability and propensity to cause significant gastrointestinal upset made phlorizin unsuitable for further clinical development. Several derivatives were subsequently developed and, although many were discontinued, three SGLT-2 inhibitors are now available and several others are undergoing clinical trials.

Empagliflozin was selected from several SGLT-2 inhibitors as it had the highest selectivity for SGLT-2. Animal studies demonstrated dose-dependent increases in urinary glucose excretion, reduction in HbA1c and improved glucose tolerance. Published phase 1 studies found that doses of 1–800mg were well tolerated in 72 German and 48 Japanese healthy volunteers. Subsequent crossover studies performed in healthy subjects found no significant interactions with commonly used drugs, including ramipril, simvastatin and warfarin.

These promising preliminary results led to several phase II trials. Two of these were published and demonstrated significant reductions in HbA1c and body weight with empagliflozin monotherapy or in combination with metformin and sitagliptin using doses of 5, 10, 25 or 50mg. The phase III trials formed part of a large-scale multinational programme involving over 10 studies and 145 000 patients which further assessed the efficacy and safety of empagliflozin (10 and 25mg) as both monotherapy and combination therapy with metformin, sulfonylurea, pioglitazone and insulin.

Renal impairment is a known complication of diabetes and empagliflozin’s mechanism of action necessitated additional studies in patients with chronic kidney disease. As would be expected, deteriorating renal function was associated with reduced efficacy of empagliflozin. Pooled analyses from existing trials have found no adverse cardiovascular events to date and results from EMPA-REG OUTCOME were recently reported. This showed a significantly lower risk of death from cardiovascular events and from any cause (38% and 32% relative risk reduction, respectively) in patients receiving empagliflozin.

Submissions for marketing authorisation began in 2013 and marketing approval was granted by the EMA in May 2014 and by the FDA in August 2014. Shortly after, the SMC approved empagliflozin for restricted use and it was recommended for use by NICE in March 2015.

Box 1. From plant extract to licensed SGLT-2 inhibitor: empagliflozin

### Approving a medicine for use in the NHS – NICE/SMC

For medicines in the UK, once a marketing authorisation has been granted there is one final hurdle: SMC or NICE approval. Guidance from these bodies reflects the clinical and cost effectiveness of a drug, rather than its efficacy and safety.

### Scottish Medicines Consortium

The SMC advises NHS boards and their Area Drug & Therapeutics Committees (ADTCs) on the use of all drugs that have been granted a marketing authorisation. The SMC was set up in 2001 in order to reduce ‘postcode prescribing’. Prior to this, decisions regarding use of a drug were made locally and could vary quite markedly between health boards. Members of the SMC include clinicians, pharmacists, health economists and representatives of the pharmaceutical industry and government. A decision from the SMC may be: medicine accepted for use in NHS Scotland; accepted for use with restrictions; not recommended for use. ADTCs are not obliged to accept SMC decisions: approximately 85% of drugs accepted for use by the SMC are added to local formularies.

### National Institute for Health and Care Excellence

In contrast to the SMC, NICE only considers drugs that have been

### Table 2. The history of phlorizin and SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>Years</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1835</td>
<td>Phlorizin isolated from willow tree bark</td>
</tr>
<tr>
<td>1886</td>
<td>High doses of phlorizin noted to produce glycosuria</td>
</tr>
<tr>
<td>1930s</td>
<td>Investigation of renal glucose excretion using phlorizin</td>
</tr>
<tr>
<td>1950s</td>
<td>Mechanism of action established</td>
</tr>
<tr>
<td>1990s</td>
<td>Phlorizin noted to improve hyperglycaemia and insulin sensitivity</td>
</tr>
<tr>
<td>2000s</td>
<td>Development of phlorizin derivatives, SGLT-2 inhibitors, for the treatment of type 2 diabetes</td>
</tr>
<tr>
<td>2012</td>
<td>Dapagliflozin licensed for use by EMA</td>
</tr>
<tr>
<td>2013</td>
<td>Canagliflozin licensed for use by EMA and FDA</td>
</tr>
<tr>
<td>2014</td>
<td>Dapagliflozin and empagliflozin licensed for use by FDA and EMA</td>
</tr>
</tbody>
</table>

### Review

Drug development and licensing in diabetes

were referred by the Department of Health and produces a Health Technology Assessment (HTA) via a process of single or multiple technology appraisal. The former is a rapid process for assessing new drugs similar to that of the SMC while the latter is more in-depth and a longer process. Unlike drugs accepted by the SMC, NHS England & Wales are obliged to adhere to NICE guidance on new drugs.

### Example of drug development to licensing

Empagliflozin is described as an example of drug development to licensing in Box 1 and Table 2.

### Conclusions

As the prevalence of type 2 diabetes increases, there is increasing pressure to find therapies that improve glycaemic control without further increasing the cardiovascular risk. The process by which a drug moves from laboratory to clinical practice is lengthy and expensive...
intended for diabetes to have to fulfill rigorous criteria in order to demonstrate cardiovascular safety, making diabetes drug development more complex and expensive.

Declaration of interests
Professor Fisher has received honoraria for talks and advisory boards from Boehringer Ingelheim. Professor McKay has received honoraria for talks, advisory boards and support for attendance at conferences from Boehringer Ingelheim.

References