CHAPTER 1

Clinical Pharmacology of Antidiabetic Drugs

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KEY POINTS

- Clinical pharmacology studies the relationship between drugs and the body and has a crucial role in the development of new therapies.
- Pharmacodynamics describes how a drug exerts its actions and pharmacokinetics is the processes a drug undergoes (absorption, distribution, metabolism and excretion).
- The drug development and regulatory process is lengthy and new medicines need to demonstrate safety, efficacy and quality. In addition, drugs intended to be used in diabetes require demonstration of cardiovascular safety.
- Pharmacoeconomics allows the provision of cost-effective therapies to those who need them and is an important tool when there is an increasing demand for healthcare and limited resource.

Introduction

Clinical pharmacology describes all aspects of the relationship between drugs and humans. An understanding not only allows for the discovery and development of new drugs that influence the course of disease, but also a better understanding of how drugs work can aid the prescriber in partnership with the patient to ensure that the most appropriate drug is chosen. This is relevant for prescribing in diabetes

Diabetes Drug Notes, First Edition. Edited by Miles Fisher, Gerard A. McKay, and Andrea Llano.

given the increase in antidiabetic drugs that are now available for glucose lowering, many with additional benefits. Choosing the correct antidiabetic drug ('antihyperglycaemic' and 'oral hypoglycaemic' are other terms used) is complicated in many cases by the need for wider cardiovascular risk management and the polypharmacy that can result from managing established complications and other co-morbidities. Before getting to the individual with diabetes, antidiabetic drugs have to go through a lengthy development process underpinned by the requirement to show safety, efficacy and quality.

A serendipitous approach to drug discovery and development based on observations and careful measurement of response has been replaced by a deeper understanding of biochemical and pathophysiological processes that influence disease. This has led to the synthesis of specific agents (chemical or biological) with specific actions. Measurement of drug concentrations in plasma and correlation with effect have aided drug development. The development of genomics and proteomics has added further sophistication such that individualisation of drug choice is a much more realistic prospect.

Clinical Pharmacology

Introduction

The dose–response relationship within an individual is a measure of sensitivity to a drug. This has two components: pharmacokinetics and pharmacodynamics. Pharmacokinetics describes the dose–concentration relationship, and pharmacodynamics describes the concentration–effect relationship. Understanding pharmacodynamics and pharmacokinetics is fundamental to the process of drug development, e.g. selecting the appropriate dose to ensure that the concentration of drug at the site of action is likely to have a therapeutic effect. Understanding pharmacokinetics and pharmacodynamics is relevant to clinical practice as it allows optimisation of therapeutic interventions for the individual being treated [1].

Pharmacodynamics

The effect that a drug has on the body can often be explained through a specific mechanism of action. This can be through action on specific receptors, enzymes or membrane ionic channels or by a direct cytotoxic action.

Action on a Receptor A receptor is normally a protein situated on the cell membrane or within the cell. Drugs bind to the receptors and can act in three ways:

- An agonist stimulates the receptor to produce an effect.
- An antagonist blocks the receptor from being activated by an agonist.

- A partial agonist stimulates the receptor to a limited extent but blocks it from being stimulated by naturally occurring agonists.

For antidiabetic drugs the main type of effect seen at receptors is an agonist effect. This can be seen for sulfonylureas, which bind to SU receptors on beta cells, and PPAR gamma agonists, which act on nuclear receptors to increase transcription of insulin-sensitive genes.

Action on an Enzyme Enzymes are proteins that, through interaction with substrates, result in activation or inhibition. Although the mechanism of action of metformin is poorly understood, part of its effect in diabetes is through activated AMP kinase. Another diabetes class acting through an effect on enzymes is DPP-4 inhibitors. These drugs inhibit the action of dipeptidyl peptidase-4, allowing for the prolongation of the action of endogenous incretins GLP-1 and GIP.

Membrane Channels Some drugs exert their action through an effect on membrane channels. SGLT 2 inhibitors work by blocking the sodium glucose co-transporter 2, resulting in the loss of glucose and sodium in urine.

Cytotoxic This mechanism of action is more relevant to drugs used to treat cancer.

Dose–Response Relationship When thinking about drugs an understanding of dose response is important. Dose–response relationships can be steep or flat (Figure 1.1). In the treatment of diabetes with insulin, a flat dose–response curve is

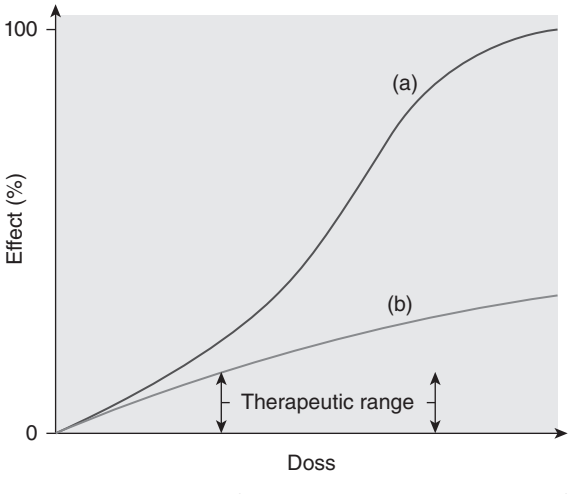

FIGURE 1.1 Dose–response relationships for drugs. Schematic examples of a drug (a) with a steep dose– (or concentration–) response relationship in the therapeutic range, and (b) a flat dose– (or concentration–) response relationship within the therapeutic range.

desirable for background insulin, but a steep dose–response curve is desirable for prandial insulin. In clinical practice the maximum therapeutic effect might not be achieved because of the emergence of undesirable effects. In drug development, if too high a dose is chosen it may be that the success of the drug is hampered by the side effects, e.g. in the case of the DPP-4 inhibitor vildagliptin, at a higher dose liver function tests need to be monitored, which is not the case for other drugs in the class. It is very important to consider this in drug development both for the desired effect and for adverse effects. This leads to the concept of therapeutic range. The difference between the concentration causing a desired effect and the concentration causing an adverse effect is termed the therapeutic index, a measure of a drug's safety.

Dose–response curves can be influenced by genetics, environment and disease, and have two components: dose–plasma concentration and plasma concentration–effect. The ability to develop assays to measure drug concentration has allowed a better understanding of the variability in response between individuals but also for some drugs with a narrow therapeutic index the ability to perform therapeutic drug monitoring.

Pharmacokinetics

Absorption After drugs have been given orally, they can be considered to have an absorption rate and bioavailability. By slowing absorption, the dose–concentration relationship can be smoothed out, giving a more sustained effect and minimising side effects, e.g. Glucophage SR® (slow-release metformin). Subcutaneous absorption of insulin can also be manipulated to provide the desired effect, both to make absorption quicker, which is desirable for prandial insulin, and to make it slower, which is desirable for basal insulin. Bioavailability is a term used to describe the fraction of drug that gets into the systemic circulation. GLP-1 receptor agonists like most peptide-based drugs generally cannot be given orally owing to them being digested, so they need to be given parenterally to get sufficient quantities into the systemic circulation. However, one oral preparation of GLP-1 receptor agonist is now available that relies on a sophisticated delivery method and at a much higher dose than the parenteral preparation to achieve sufficient systemic exposure for the desired clinical effect (see Chapter 6). Other orally administered drugs can undergo extensive first-pass metabolism in the liver, resulting in a significant reduction in systemic exposure and clinical effect.

Distribution/Plasma Protein Binding When a drug gets into the systemic circulation it is then distributed to the tissues. This process will be dependent on the properties of the drug, in particular protein binding and lipid solubility factors. In practice protein binding has little in the way of clinical relevance, but if a drug has low protein binding and is highly lipid soluble, it will have only a small amount in the circulation and thus will be considered to have a high volume of distribution. In real terms this has more of an impact on drug development.

Clearance Clearance is the sum of all of the drug eliminated from the body and mostly depends on hepatic metabolism and renal excretion. If a drug is given by intravenous infusion or repeated doses orally, there will come a point at which a balance is reached between the drug entering and the drug leaving the body. This results in a steady-state concentration in the plasma or serum (C_{ss}). A constant-rate intravenous infusion will yield a constant C_{ss}, while a drug administered orally at regular intervals will result in fluctuation between peak and trough concentrations (Figure 1.2). Clearance depends on the liver and/or kidneys eliminating a drug and will be affected by diseases that affect these organs either directly or via blood flow to these organs. In stable clinical conditions when clearance remains constant it is directly proportional to dose rate, so-called first-order or linear kinetics. Few drugs show zero-order kinetics, e.g. alcohol when eliminating enzymes become saturated. Following a single intravenous bolus dose, it is possible to work out the time that it takes for elimination to result in half the original concentration of the drug being present (the half-life or $t_{1/2}$) and through a number of complex equations, the time at which steady state will be achieved after starting a regular treatment schedule or after any change in dose can be predicted. Generally this takes four to five half-lives.

Drug Metabolism and Elimination Drugs that are already water soluble are generally excreted unchanged by the kidney. Lipid-soluble drugs are not easily excreted by the kidney because, following glomerular filtration, they are largely reabsorbed from the proximal tubule. The first step in the elimination of such lipid-soluble drugs is metabolism to more polar (water-soluble) compounds. This is achieved mainly in the liver.

Metabolism generally occurs in two phases:

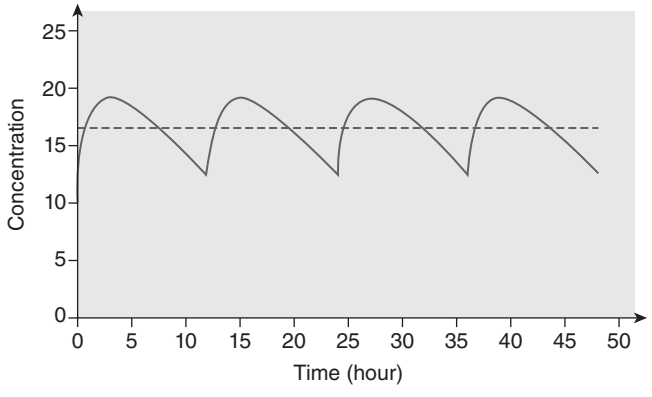

FIGURE 1.2 Steady-state concentration–time profile for an oral dose (—) and a constant rate intravenous infusion (- - - - -).

Phase 1. Mainly oxidation, but also reduction or hydrolysis to a more polar compound. Oxidation can occur in various ways at carbon, nitrogen or sulfur atoms and *N*- and *O*-dealkylation. These reactions are catalysed by the cytochrome P450-dependent system of the endoplasmic reticulum. Knowledge of P450, which exists as a superfamily of similar enzymes (isoforms), has increased greatly recently, and it is divided into a number of families and subfamilies. Although numerous P450 isoforms are present in human tissue, only a few of these have a major role in the metabolism of drugs. These enzymes, which display distinct but overlapping substrate specificity, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Phase 2. Conjugation usually by glucuronidation or sulfation to make the compound more polar. This involves the addition of small endogenous molecules to the parent drug, or to its phase 1 metabolite, and almost always leads to abolition of pharmacological activity. Multiple forms of conjugating enzymes are also known to exist, although these have not been investigated to the same extent as the P450 system.

Enzyme Induction and Inhibition Enzyme induction or inhibition can result in a pharmacokinetic drug interaction diminishing clinical efficacy or resulting in side effects, respectively. Induction is the result of a drug prolonging the action and activity of drug-metabolising enzymes. In clinical practice rifampicin, carbamazepine and phenytoin are potent enzyme inducers, as is 'over the counter' St John's Wort. These agents increase the activity of drug metabolising enzymes and increase the metabolism of medicines metabolised by the same route. Inhibition reduces metabolism and prolongs the action of a drug. In clinical practice macrolide antibiotics (e.g. clarithromycin) can inhibit cytochrome P450, prolonging the action of some drugs that are commonly used in diabetes patients, e.g. simvastatin, which should be stopped whilst on macrolide treatment.

Renal Excretion Glomerular filtration is the most common route of renal elimination. Free drug is cleared by filtration and the protein-bound drug remains in the circulation. Active secretion in the proximal tubule, which can affect both weak acids and weak bases, has specific secretory sites in proximal tubular cells and can also be a mechanism for elimination and also passive reabsorption in the distal tubule. If renal function is impaired, for example by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased. The effect of reduced renal excretion on dose for antidiabetic drugs is summarised in Chapter 16, Table 16.3.

Drug Development and Clinical Trials

Introduction

The development of drugs for therapeutic use is complex and lengthy and necessarily subject to extensive regulatory requirements. The three pillars of drug development are safety, efficacy and quality. Safety and efficacy of an investigational product are

required to be shown in well-designed and robust clinical trial programmes before regulatory approval is granted so that a drug can be marketed. This is governed by Good Clinical Practice. Quality needs to be shown in manufacturing processes and is governed by Good Manufacturing Practice. Drugs intended for use in patients with type 2 diabetes are also required to demonstrate their cardiovascular safety using outcomes such as cardiovascular mortality, myocardial infarction and stroke. There have been many changes in the development process and its regulation over the last century. The process of drug development and approval is summarised in Figure 1.3. It can take more than 12 years to take a drug into the market, at a considerable cost (>£1 billion).

Preclinical Development

Historically, remedies and treatments were derived from plants and herbs, and many drugs were discovered serendipitously. The use of *Galega officianalis* (biguanide) to treat symptoms of hyperglycaemia has been documented as far back as medieval times. Sulfonylureas were initially investigated for use in the treatment of typhoid and incidentally found to cause hypoglycaemia. SGLT2 inhibitors were derived from phlorizin,

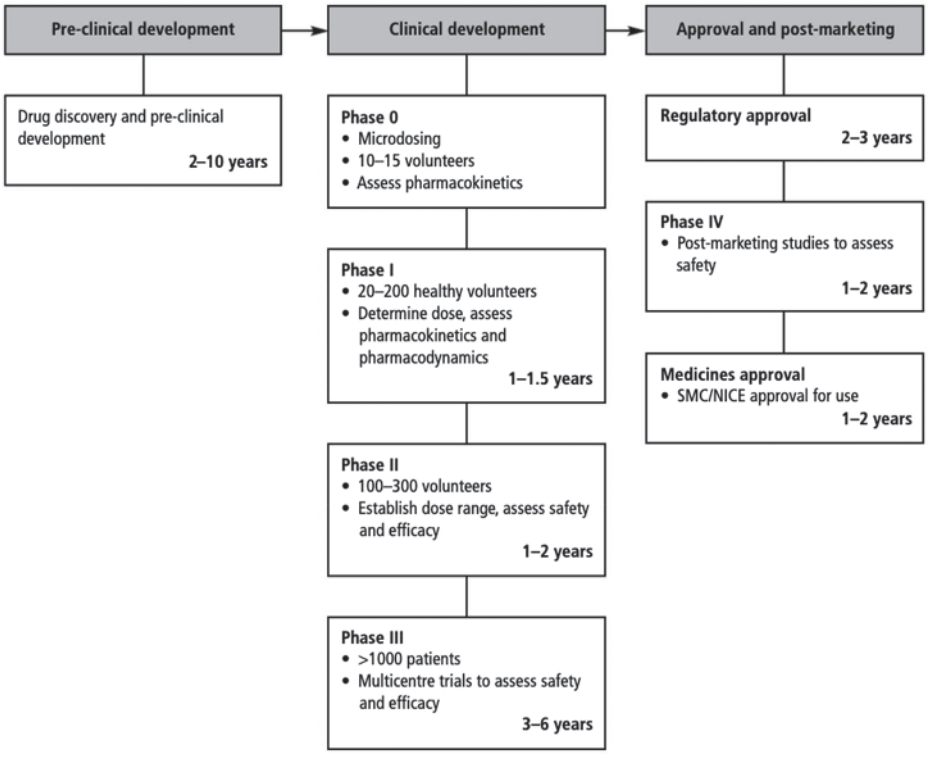

FIGURE 1.3 Drug development and approval. Clinical development consists of Phase 0, Phase I (or 1), Phase II (or 2) and Phase III (or 3). Phase IV (or 4) is part of post-marketing.

a compound derived from apple tree bark that was initially used in fever but was found to also cause glycosuria.

Advances in the understanding of the pathological processes involved in disease at the cellular and molecular levels have led to more sophisticated methods of drug discovery and a more methodical approach to drug development. Biological targets are first selected and compounds which are active at this site are identified. These compounds can be designed according to the target's chemical structure or selected from a pharmaceutical research organisation's extensive compound library. Several thousand molecules are usually identified at the beginning of this process. Candidate drug molecules then enter a process known as lead optimisation where they undergo further selection and/or modification to achieve the desired pharmacological activity. Preclinical testing involves extensive *in vivo* studies undertaken to determine a compound's affinity and selectivity in cell disease models. This period takes 2–10 years and approximately 50% of lead compounds do not progress beyond this point. Various animal models are used to establish the compound's pharmacokinetic characteristics (absorption, distribution, metabolism and excretion). *In vivo* toxicology studies are used to determine the maximum nontoxic dose of the drug and establish reproductive toxicity (adverse effects on fertility, foetal development and lactation).

This is a crucial stage in drug development as the costs increase exponentially once a drug gets into clinical development in humans. If a drug shows potential toxicity in animal studies, it is important to understand that this is generally at higher concentrations than would be used clinically and does not necessarily result in it not getting tested in humans. An example of this is the GLP-1 receptor agonist liraglutide, which was shown to increase the risk of thyroid cancer in mice and rat models, but at doses 8 times higher than what humans would receive. In subsequent clinical trials the risk of developing medullary thyroid cancer, which is very rare, has not been shown. However, the animal results have meant that this potential side effect has been highlighted as something to look out for in subsequent clinical trials in the development programme.

Chemical properties such as stability and formulation are also established, and manufacturing processes developed to ensure that the lead compound can be produced in sufficient quantity and quality for clinical studies. Towards the end of this period, applications to regulatory bodies are prepared to proceed to investigation in humans [2].

Regulatory Approval

Prior to the 1960s there was no formal process of drug approval or regulation, and it was not a legal requirement to demonstrate the efficacy or safety of a drug. Thalidomide was first marketed in 1956 as a sedative and hypnotic and was used as a treatment for nausea and vomiting associated with pregnancy. No formal clinical trials or reproductive toxicology studies had been carried out prior to its marketing. It was soon noted to cause an increase in birth defects and was banned in 1961.

These findings prompted regulatory reformations necessitating that a drug's safety and efficacy be vigorously demonstrated. 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. These amendments ensure that manufacturers demonstrate a drug's safety and efficacy using controlled clinical studies in appropriate study participants and that post-marketing surveillance is carried out.

Prior to testing in humans, regulatory approval must be obtained from the relevant regulatory authority, including the European Medicines Agency (EMA) in Europe and the FDA in the US (Table 1.1). Along with the third large regulatory authority in Japan, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established and continues to meet to bring together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

On 31 January 2020, the UK formally left the European Union and entered a transition period that ended on 1 January 2021. Following Brexit, the regulation of all medicines and devices has transferred from the EMA to the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) [3]. This is likely to prove challenging as previously many of the submissions to the EMA were contracted out to the MHRA. Therefore, more work will be required as a consequence of its new status as a stand-alone regulatory body, but without the external resources coming in from the EMA. The other complicating factor is that its regulatory role only relates to approval in England, Scotland and Wales, not Northern Ireland. However, there are mechanisms in place to ensure mutual recognition, particularly given the harmonisation of regulatory approach, which may allow a more responsive process with the potential advantage of marketing authorisations being fast tracked, particularly for drugs with clear potential benefits. This process has been clearly illustrated through the granting of marketing authorisations for COVID-19 vaccines.

All clinical trials must be registered in a clinical trials database and have ethics approval. Trials must be conducted in line with Good Clinical Practice, a set of international standards covering the design, conduct, recording and reporting of clinical trials, and manufactured in line with Good Manufacturing Practice, a set of international standards ensuring the quality of the investigational product.

TABLE 1.1 The main regulatory authorities and their functions

Regulatory authority	Function
Medicines and Healthcare Regulatory products Agency (MHRA)	Formed in 2003. Functions include: regulation of clinical trials, assessment and authorisation of medicinal products in the UK; operates post-marketing drug surveillance. It will have a new role post Brexit operating separately from the EMA
European Medicines Agency (EMA)	Established in 1995. Coordinates the evaluation and supervision of the new medicinal products, grants opinion on licensing and oversees pharmacovigilance across member states
Food and Drug Administration (FDA)	Established in 1927. Responsible for regulation and supervision of drug safety: drug assessment and authorisation, post-marketing surveillance

Clinical Trials

Once the efficacy and safety of a drug have been determined in preclinical studies, it can move into investigation in the human population. Drugs progress through different stages of clinical trials prior to gaining regulatory approval and entering clinical use. Although these stages are described separately, in practice they often overlap [2].

Microdosing Microdosing was introduced in 2003 to improve the efficiency of drug development. It aims to improve the selection of preclinical candidate drugs by assessing *in vivo* human pharmacokinetic and pharmacokinetic data. It takes place after preclinical development but prior to phase 1 clinical trials and is often referred to as phase 0. Microdosing assumes that the pharmacological parameters of a drug can be determined in humans using minute doses (one hundredth of the planned dose), thereby avoiding significant side effects and eliminating candidate drugs with undesirable profiles early on in the process.

Phase 1 Trials Phase 1 trials are nontherapeutic, exploratory studies and prior to the introduction of microdosing they traditionally bridged the gap between animal and human studies. They are typically carried out in small numbers of healthy volunteers. They test pharmacodynamics, including a detailed safety screen and pharmacokinetics. In order for drugs to be tested in humans, safety data needs to be shown in two different species. Even if this is the case, sometimes unexpected toxicity has been seen, e.g. the clinical trial of TGN1412 in Northwick Park Hospital that resulted in multi-organ failure for the six healthy volunteers. So-called 'First in Human' studies generally start with low doses to establish safety, then move on to dose-ranging studies. At this stage sometimes signals of efficacy can be seen, e.g. evidence of effect on an enzyme system, but with safety established then the therapeutic potential of a drug can be tested in phase 2 and 3 clinical studies. Phase 1 studies will also continue in parallel, including studies testing for drug interactions or to answer a specific safety question, e.g. does the drug cause QTc prolongation?

Phase 2 Trials Phase 2 trials are often referred to as 'proof of concept' studies. They are undertaken in 100–300 patients who have the target condition and are generally conducted by specialists in treating the condition. They are designed to assess efficacy or markers of efficacy. For antidiabetic drugs this could be using HbA1c, capillary blood glucose monitoring or continuous glucose monitoring. The primary aim is to decide whether it is likely that the signal of efficacy is good enough and the side effect profile acceptable to justify progression into larger, more expensive phase 3 clinical trials. Phase 2 studies are usually randomised controlled trials of the drug compared with placebo or active comparator.

Phase 3 Trials Phase 3 trials are large-scale randomised controlled trials often involving several thousand patients across multiple sites. The candidate drug is usually assessed against placebo and/or existing therapies. The aim is to quantify the

extent to which the drug is effective and in which particular patients. Given that the studies are larger with more patient exposure, less common side effects may emerge. These studies are often referred to as 'pivotal' studies as it is these that are used to inform regulatory approval, labelling and patient information once the drug is marketed. Usually, two separate pivotal trials are required for each new medicine, although there are exceptions to this rule. Traditional phase 3 studies tend to be double-blind, randomised and controlled in matched groups, but are sometimes adapted for practical reasons. Ideally the primary endpoint should be clinically relevant and measurable. The trials should aim to have as much complete data as possible and to be analysed on an intention-to-treat basis. The trials also need to be large enough to be powered to detect differences between treatment groups. Further phase 3 trials often take place after a drug gets regulatory approval, e.g. to widen the licensed indication or to test on different patient populations.

Phase 4 Trials Phase 4 trials are studies that are conducted after marketing authorisation. These may be carefully designed marketing studies, but more often are considered as post-marketing surveillance or pharmacovigilance with particular emphasis on safety (see later in this chapter). Observational studies have been used to assess both safety and efficacy in clinical practice, and are sometimes referred to as real-world studies. As observational studies they sit below meta-analysis and randomised control trials in the evidence-based hierarchy. They should not be considered a substitute for a well-designed randomised controlled trial against placebo or an appropriate comparator, but rather as a reassurance that the results seen in the pivotal trials used to underpin regulatory approval are realised in clinical practice.

Drug Licensing of Antidiabetic Drugs

Each regulatory body has guidance on the clinical development of drugs to be used to lower blood glucose in patients with diabetes. These stipulate that clinical trial participants must be representative of the target population in terms of age, ethnicity, presence of comorbidities and metabolic control. Long-term glucose control is measured using HbA1c and reduction in HbA1c is associated with reduced risk in the development of microvascular complications. HbA1c is therefore a primary endpoint for treatments to be used in diabetes and should measure the difference in baseline HbA1c between the investigational drug and comparators.

Cardiovascular Outcome Trials

Cardiovascular disease is the leading cause of death in people with diabetes. Prior to 2008, there were no specific requirements for new therapies for people with type 2 diabetes to demonstrate cardiovascular safety and it was only necessary to demonstrate glycaemic efficacy and safety. This change in legislation was a consequence of a

meta-analysis of individual patient data which suggested that rosiglitazone was associated with a greater incidence of myocardial infarction, and possibly an increase in cardiovascular death (see Chapter 12).

In the rosiglitazone meta-analysis there were significant weaknesses; across the studies there was no standard method for identifying or validating outcomes and events in eligible or ineligible trials may have been missed or misclassified. Also, the total number of events was relatively small. The meta-analysis was controversial at the time, and even today it is uncertain whether rosiglitazone is associated with an increase in atherosclerotic cardiovascular events or not. Regardless, the response of the FDA was to make significant changes to regulations for the licensing of new antidiabetic drugs and this was closely followed by the EMA for licensing in Europe.

The major changes were:

- The phase 3 study population should include subjects at high risk of cardiovascular events, including patients with long-standing diabetes, existing cardiovascular disease or chronic kidney disease and the elderly.
- All cardiovascular events in the development programme should be blindly adjudicated and analysed.
- Long-term safety data (greater than two years) was required, and this was generally collected as part of a dedicated cardiovascular outcome trial (CVOT).
- As the concerns around rosiglitazone were for atherosclerotic events, the particular focus of the FDA was on either three-point MACE (major adverse cardiovascular events, a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) or four-point MACE (MACE plus hospitalisation for unstable angina), and hospitalisation for heart failure was a secondary concern.
- If it was deemed by the regulator that there was sufficient cardiovascular data from the development programme to indicate cardiovascular safety then the CVOT could be completed after licensing, which was the situation for most new antidiabetic drugs.
- If completed post-licensing, the first safety analysis of the new drug with the comparator was for noninferiority, and if noninferiority was demonstrated, the data could then be analysed for possible superiority.
- If the data from the phase 3 programme was deemed insufficient to demonstrate cardiovascular safety, then the CVOT would need to be completed and show noninferiority before licencing, as happened for alogliptin and lixisenatide in the US.
- As an alternative to demonstrate safety before licensing, a smaller CVOT could be performed and analysed for noninferiority, as happened for oral semaglutide.

Cardiovascular outcome trials have been completed and published for most of the newer antidiabetic drugs, and many drugs not only demonstrate cardiovascular safety but also show cardiovascular benefit compared with placebo, for example empagliflozin, canagliflozin, dapagliflozin, liraglutide, dulaglutide and semaglutide (see Chapters 4–6, and summary in Chapter 16). On review in 2020 the FDA noted that none of the CVOTs had identified an increase in the risk of ischaemic cardiovascular

events, so they removed the requirement for a bespoke CVOT. The importance of cardiovascular safety data was not removed, but the dedicated CVOT was replaced with a wider safety database with data from controlled clinical trials and clinical trial extensions, including:

- at least 4000 patient years of exposure to the new drug in phase 3 clinical trials;
- at least 1500 patients exposed to the new drug for at least one year;
- at least 500 patients exposed to the new drug for at least two years;
- at least 500 patients with stage 3/4 chronic kidney disease exposed to the new drug;
- at least 600 patients with established cardiovascular disease exposed to the new drug;
- at least 600 patients older than 65 years of age exposed to the new drug.

This new guidance was issued for feedback in draft form in 2020 during the COVID-19 pandemic and has now replaced the 2008 guidance on the FDA website [4].

Marketing Authorisation

Following completion of phase 3 trials, a Marketing Authorisation Application is submitted to the relevant licensing authority. Product registration is in important aspect of the regulatory process and is required prior to marketing a drug. The Marketing Authorisation Application contains a product's quality, safety and efficacy data. Each licensing authority has a panel of specialists comprising clinicians, statisticians and scientists, who review the application before recommending whether a marketing authorisation should be granted. The timeline of events leading to the marketing authorisation of dapagliflozin, as an example of antidiabetic drug development, is described in Table 1.2.

Development and Licensing of Insulin

Insulin Regulatory Approval

The regulatory approval for new insulins, like with any drug, requires safety and efficacy to be established through a clinical trial programme. The EMA published guidelines to sponsors of clinical trials for all drugs being developed for use in diabetes and insulin is considered separately. Studies need to be done in both type 1 and type 2 diabetes. Pharmacokinetic studies are required to be done in all types of patients for whom treatment is intended, including the young and the elderly, the former an important group given that their glycaemic variability and susceptibility to hypoglycaemia are higher compared with adults. Pharmacokinetic (PK) data need to include peak insulin concentration, time to peak concentration, area under the insulin–time curve and half-life. It is also necessary to show that the PK characteristics remain the same if the insulin is used in mixtures. Although insulin analogues are usually developed for

TABLE 1.2 **Dapagliflozin timeline as an example of antidiabetic drug development [5]**

Date	Event
1835	Phlorizin isolated from apple tree bark
1886	Phlorizin noted to cause glycosuria in animals
1930s	Phlorizin given i.v. in human subjects and noted to cause glycosuria Used to investigated renal blood flow and glomerular filtration
1950s	Phlorizin used to characterise SGLT receptors
1960s	Phlorizin derivatives developed (e.g T095) with better bioavailability and less gastrointestinal upset
1990s	Phlorizin and derivatives blunt glucose rises in animal models, used to investigate glucose metabolism
2008	Pre-clinical studies with dapagliflozin published
2009–2015	Phase 1–3 studies published
2012	EMA approval for use in type 2 diabetes
2014	FDA approves dapagliflozin for use in type 2 diabetes
2019	Approval of dapagliflozin as an adjunct in patients with type 1 diabetes
2020	Approval of dapagliflozin for treatment of heart failure
2021	Approval of dapagliflozin for treatment of chronic kidney disease

novel PK properties, differences in parameters of PK/PD (pharmacodynamics) alone cannot be used on their own to claim superiority. Pharmacodynamic data in insulin-sensitive type 1 diabetes are important to compare insulins with the glucose-clamp technique, the preferred method to assess time–action profiles.

In short-term exploratory studies, the efficacy outcome is usually 24 h glucose profiles, and in confirmatory studies of longer duration (6–12 months) using an appropriate insulin as a comparator. Outcomes should include achieving glycaemic targets (HbA1c and variability in glycaemic control). In trials in type 1 diabetes a run-in period is required to define the variability in glycaemic control and frequency of hypoglycaemia in each group before active comparison begins. Hypoglycaemia is the major obstacle to achieving good glycaemic control. Continuous glucose monitoring can be used to identify hypoglycaemia. The incidence and rate of both overall hypoglycaemia overall and severe hypoglycaemia should be determined in all clinical trials. Definitions of hypoglycaemia need to be harmonised across studies and the EMA guidelines cite the International Hypoglycaemic Study Group recommendations (Table 1.3) [6]. There has been some debate as to what the glucose alert value adds, but with increased use of continuous glucose monitoring, asymptomatic hypoglycaemia may be helpful in comparing different insulins in clinical trials whilst perhaps being less useful as a definition in the clinical setting.

Additional adverse effects seen that are specific for insulin are local reactions, toxicity and immunogenicity. Specifically for insulin analogues, affinity for the IGF-1

TABLE 1.3 **Proposed glucose levels when reporting hypoglycaemia in clinical trials**

Level	Definition
Level 1 (glucose alert value)	Glucose level 3.9mmol/l (70 mg/dl) or less
Level 2 (serious, clinically important hypoglycaemia)	Glucose level of <3.0 mmol/l (<54 mg/dl)
Level 3 (severe hypoglycaemia)	Severe cognitive impairment requiring external assistance for recovery

Source: Based on [6].

and insulin receptors is required and if increased it is recommended that longer-term studies should include fundal photographs to look for any retinal changes. The FDA guidance that resulted in the need for CVOTs in all new treatments in development for treating type 2 diabetes specifically excluded insulin because it was considered a life-saving treatment in type 1 diabetes and that such studies would be impractical.

Development and Approval of Biosimilar Insulin

Introduction Biosimilars are manufactured copies of previously approved biological drugs. Owing to variation in their manufacture and final protein molecule, they cannot be considered identical versions of their reference drug, hence the term biosimilar [7]. The biopharmaceutical market is rapidly growing with many such products, for example biosimilars of infliximab, filgrastim and erythropoietin. Three biosimilar insulins are available at present: Abasaglar® (insulin glargine), Semglee® (insulin glargine) and Admelog® (insulin lispro). Another insulin glargine, Lusduna®, was approved by the FDA and EMA but withdrawn in 2018.

Insulin Production The manufacture of insulin has evolved significantly since it was first isolated in 1922. Initially, insulin was derived from bovine or porcine pancreatic extracts. Nowadays, insulin is manufactured using recombinant DNA technology which makes use of *Escherichia coli* or *Saccharomyces cerevisae* expression systems. DNA is isolated from human cells and inserted into an appropriate vector before transfer into the host cell. The recombined host cell then produces its product, which is recovered and refolded to a pro-insulin like-molecule. After C-peptide is removed, the insulin product undergoes purification and storage. Extensive testing is undertaken to assure the purity and stability of the product. As living cells are used, the manufacturing process can be affected by changes to physical conditions which introduce subtle changes to the end product. This is of importance as the biological activity may also be affected.

This manufacturing process is complex and the exact details closely guarded. Even once a patent expires, pharmaceutical companies are not obliged to make manufacturing details available. Once a patent expires, other companies will be unable to identically replicate the production process.

Biosimilar vs. Generic Drugs The nature of chemical drug molecules allows them to be readily reproduced and generic drugs have identical chemical structures and pharmacological profiles. Biologics in contrast, are larger and more complex, with several layers of structure. Unlike drugs that are synthesised chemically, biological molecules require expression systems. Reproduction of a biologic produces a biosimilar, and the complexities of production (which are not shared after patent expiry) and the final protein molecule mean that the end product is not identical and cannot be considered generic (Table 1.4). While generic drugs offer bigger savings (up to 80%), biosimilars offer less expensive alternatives, costing up to 20–30% less than their originator drug, thereby providing significant cost savings. This is important in expanding competition in a market dominated by a few pharmaceutical companies and in increasing access to treatment.

Regulatory Considerations for Biosimilars Marketing Authorisation Applications for both generic and biosimilars can only be submitted on patent expiry of the reference drug. Regulatory submissions must provide evidence that the generic product is identical in structure, strength and formulation (pharmaceutical equivalence) and approval requires demonstration of bioequivalence. This term refers to the absence of a significant difference in the bioavailability between a generic and its reference drug. If both drugs have equivalent biosimilarity they can be considered to have the same clinical effects. The maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) are used to determine bioequivalence and there should be no more than a 20% difference in these pharmacokinetic parameters [8].

TABLE 1.4 **Comparison of biosimilar and generic drugs**

	Generic	Biosimilar
Size	Small	Large, complex
Structure	Structurally identical to reference product	Similar to reference product but not identical owing to natural variability in protein molecule and manufacturing process
Manufacture	Chemical synthesis	Recombinant DNA technology in cell lines
Equivalence	Bioequivalence and therapeutic equivalence must be demonstrated	No clinical significant differences in terms of purity, safety and potency
Interchangeability	Interchangeable with reference product	Not interchangeable
Name	Generic name is used	Should be prescribed by brand name
Cost savings	Up to 80%	20–30%
Development time	2–3 years	8–10 years
Development costs	$1–5 million	$100–200 million

The regulatory requirements for biosimilars were first published in 2005 by the EMA and include specific guidance relating to insulin biosimilars [9]. Post-Brexit, biosimilars are regulated by the MHRA under the Human Medicine Regulation 2012. Comparability with its reference product in terms of safety, purity and potency must be established. Manufacturers are required to provide details of the structural and functional characteristics of the product, its manufacturing process and quality control. Comparability studies are carried out to demonstrate that the pharmacokinetic and pharmacodynamic profiles are not significantly different between a biosimilar and its originator drug.

Safety of Biosimilars Immunogenicity is an important safety aspect in the use of biological medicines. Antibody formation can be stimulated following the use of any biological drug, which can result in adverse reactions such as allergy and anaphylaxis in addition to altering the biologic's therapeutic action. Pharmaceutical companies are therefore required carry out safety studies detailing antibody testing strategies and the incidence of antibody formation to the biosimilar.

Post-marketing surveillance is important with biological drugs as unexpected adverse effects are more likely. A risk-management plan must be submitted with information on pharmacovigilance monitoring.

Interchangeability and Substitution A biosimilar is considered interchangeable if biosimilarity has been established and the same therapeutic effect is achieved in each patient. There should be no impact on safety or efficacy if the reference drug is switched with the biosimilar. This an important safety aspect as it may result in the substitution of a prescribed biological medicine with a biosimilar without the prescriber's knowledge, an action termed automatic substitution. Guidance regarding substitution varies throughout the world. In the UK, the MHRA advises against automatic substitution of a biological drug and states that, unlike chemical drugs normally prescribed by generic name, biosimilars must be prescribed by brand name [10].

Prescribing Considerations for Biosimilars A diverse and large armoury of insulins is available and the introduction of biosimilars could add confusion to an already complex prescribing situation. Position statements on the prescribing of insulin biosimilars have been published by Diabetes UK [11] and the Association of British Clinical Diabetologists [12] that recommend consideration of the factors outlined in Box 1.1.

Box 1.1 Prescribing considerations for biosimilar insulin

- Biosimilar insulin should be considered when initiating insulin.
- Ensure biosimilar is prescribed using brand name and delivery device is stated.
- Changing to a biosimilar should be done with the mutual consent of the prescriber and the patient.
- Adverse reactions should be reported using the Yellow Card scheme.
- It is not recommended that patients who are established on insulin and stable are changed to biosimilar insulin.

Source: Adapted from [12].

Pharmacovigilance

When a new medicine enters clinical use following marketing authorisation, it will have shown a positive risk: benefit assessment in clinical trials, usually of relatively short duration (6–24 months) and involving commonly 5000–10 000 subjects chosen to match the entry criteria of the clinical trials. Efficacy will have been shown and common adverse effects will have been identified and deemed acceptable or manageable. There are still important unknowns for a new medicine:

- Are there rare (but serious) adverse effects which were not seen in the clinical trials?
- Are there significant adverse effects apparent in subjects who would have been excluded from the clinical trials?
- Are there significant adverse effects which are only apparent in long-term use?

Monitoring the new medicine to look for such adverse events is known as 'pharmacovigilance'. Structured pharmacovigilance surveillance of new medicines is a condition of regulatory approval and is the responsibility of the manufacturer of the medicine. Relatively rare side effects are often not identified in clinical trials as too few events occur to be detected and linked to the medicine. As Table 1.5 shows, an event with a frequency of 1 in 1000 needs 3000 subjects to be exposed to the medicine to be 95% sure of seeing just one case, and larger numbers to see the two or three cases that would be needed to trigger a potential signal that the event was drug related. Rarer events need even larger numbers. Pharmacovigilance procedures fall into one of two broad categories, passive and active.

Passive Pharmacovigilance

Passive pharmacovigilance rests on prescribers (or patients) reporting suspected adverse drug reactions to the regulatory authority and/or the manufacturer of the medicine. The manufacturer will forward all such reports to the regulator so that they have a full picture of events reported and can assess whether any safety 'signals' can be identified. Signals are then further evaluated to decide whether they were related to the drug or a coincidence. In the UK, newly licensed medicines have a 'black triangle' (▼) as part of their documentation and packaging, inviting the reporting of *all* suspected events related to the medicine, not only events seen as serious or significant. This ensures intensive monitoring for newly authorised medicinal products. Prescribers, pharmacists and patients are encouraged to report events in what is known as the 'Yellow Card Scheme', founded in 1964 after the thalidomide incident. Many reports now are submitted online, but the process retains its old name.

Passive reporting (also known as a spontaneous reporting scheme) is useful in identifying rare, and sometimes unusual, events but is limited by requiring the individual reporting the event to have made the link (or at least suspected the link) between the medicine and the event. Signal detection of possible adverse drug reactions is the main objective of a spontaneous reporting scheme.

TABLE 1.5 **The numbers of patients needed to observe to have a 95% chance of detecting one, two, or three cases of an adverse reaction at a given incidence of the reaction**

Expected incidence	Number of patients to be observed to detect one event	Number of patients to be observed to detect two events	Number of patients to be observed to detect three events
1 in 100	300	480	650
1 in 200	600	960	1 300
1 in 1 000	3 000	4 800	6 500
1 in 2 000	6 000	9 600	1 300
1 in 10 000	30 000	48 000	6 500

Spontaneous reporting of suspected adverse drug reactions is poor at assessing the true frequency of events as it is often estimated that only around 10% of events are actually reported. It is also poor at providing reassurance that events are not occurring, given the low reporting rates.

Active Pharmacovigilance

Active pharmacovigilance involves undertaking active surveillance of recipients of the new medicine, often identified from primary care prescription data or secondary care disease registries and other sources. Identified recipients of the medicine in question are 'followed' over months or even years and all health-related events recorded. The overall dataset can then be reviewed and any events that appear to be in excess of predicted numbers can be investigated. This methodology records all events, and so does not require any link to the medicine to have been made.

Often, data on a comparator group are collected simultaneously, the subjects having the same underlying diagnosis but not receiving the new medicine. This allows the background event rate to be known with reasonable certainty, and thus allows any excess events in the subjects receiving the new medicine to be reasonably confidently attributed to the medicine and the magnitude of the excess event rate established. A key principle in pharmacovigilance is to compare the frequency of events observed in users of a new medicine with what would be expected if these patients received the standard existing treatment or no treatment (observed vs. expected).

Active pharmacovigilance can not only detect rare or unusual events but can also detect an increased frequency of common events related to a new medicine. It is, for example, unlikely that an individual prescriber would attribute an acute vascular event (e.g. acute coronary syndrome) in a subject with type 2 diabetes to a new medicine

(but rather to the diabetes), but active pharmacovigilance could pick up an increased incidence of such events across a larger population.

As all events are recorded, data from active pharmacovigilance can also provide evidence of the absence of any increased risk related to a new medicine. This was important when cases of acute pancreatitis were reported in subjects treated with GLP-1 receptor agonists at rates above the population rate. Pharmacovigilance data showed an increased rate of acute pancreatitis in subjects with type 2 diabetes (compared with the nondiabetic population), but no increased risk specifically in those taking GLP-1 receptor agonists, reassuring prescribers and patients alike.

Active pharmacovigilance clearly has many advantages over passive surveillance, but it is expensive, often difficult to undertake and has to be time delimited, so eventually only passive surveillance can continue. The two approaches are complementary.

Pharmacoeconomics

Introduction

Scarcity of resource is a feature of all healthcare systems. If the system cannot do everything, then it must make choices amongst interventions, usually aiming to choose interventions that provide the maximum health benefits for the resources expended. Using economic evaluation, pharmacoeconomics aims to provide a structured approach to making such choices, looking at the full clinical benefits of a new intervention such as a new medicine, but also looking at all the costs associated with its use, comparing these with the benefits and costs of existing therapies. It also is mindful that resources can only be used once, so any use of a new medicine will come at the expense of another intervention somewhere in the healthcare system which will not be undertaken, the opportunity cost of adopting the new medicine. Pharmacoeconomics is a relatively inexact science, but it does offer a structured approach to assessing the clinical value and cost-effectiveness of new medicines [13]. As in diabetes there is a wide range of proven interventions of good efficacy available at reasonable cost, it is vital that new medicines are fully assessed and only adopted if their benefits justify their cost and the opportunity cost of their introduction.

Different countries use different approaches to their analysis of costs and benefits and overall assessment of cost-effectiveness. In the UK, the approach favoured by NICE (the National Institute for Health and Care Excellence) and the SMC (Scottish Medicines Consortium) is a cost–utility analysis. This captures the benefits of a medicine for both duration of life (= survival) and for quality of life and combines these into a single metric, the Quality Adjusted Life Year (or QALY). Figure 1.4 shows the health benefits of a new medicine over current therapy, the gain in A being in quality of life, while the gain in B shows a survival benefit. The overall benefit of the new medicine is thus A + B.

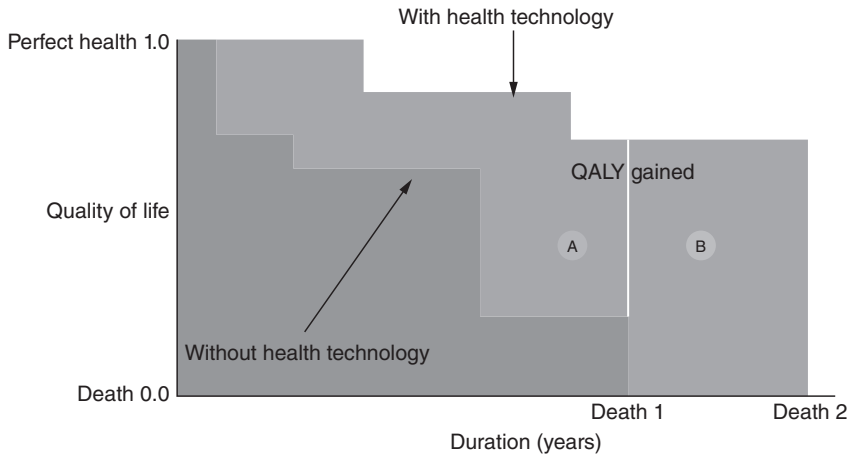

FIGURE 1.4 Health benefits of a new medicine over current therapy, the gain in A being in quality of life, while the gain in B shows a survival benefit. The overall benefit of the new medicine is A + B. *Source:* From [1].

Cost–utility analysis has the advantage of being able to evaluate health benefits independently of the disease involved, and thus allow comparison of interventions amongst diseases, for example a new diabetes medicine compared with new medicines for dementia and/or lung cancer. With the QALY as the outcome measure, it is even possible to compare the cost-effectiveness of new medicines with that of nonmedical interventions (e.g. surgery).

The costs of using a new medicine are not limited to its acquisition costs, but also to costs (or savings) associated with the administration, monitoring and the management of any adverse effects. Economic evaluation should also take into account any downstream changes in the resources used in disease management, e.g. reductions in hospitalisations or physician visits owing to better symptom control with the new treatment. Once all costs have been identified, it is possible to create an incremental cost-effectiveness ratio (ICER), in which the costs are divided by the benefits to create a 'Cost per QALY'.

$$\text{ICER} = \frac{\text{incremental cost of new treatment } (£)}{\text{incremental benefit of new treatment } (\text{QALY})}$$

New treatments across disease areas can be compared, the one with the lowest ICER representing the best 'value for money'. To aid decision-making and ensure consistency over time, NICE and SMC use informal ICER thresholds such that a medicine with an ICER <£20 000 will usually be accepted for NHS use while a medicine with ICER >£30 000 will not usually be accepted. Medicines with ICERs in the range £20 000–30 000 may or may not be accepted depending on factors such as the extent of unmet clinical need, the tolerability of existing therapies and the quality of the evidence supporting the ICER estimation. Medicines with an ICER >£30 000 may also be accepted for use if, for example, there is a high level of unmet clinical need or other special circumstances.

Utility Values

Utility values are a measure of quality of life and can range from 1, meaning perfect health, to 0, equivalent to death. They describe in numerical form the quality of life experienced by patients in different health states and are a crucial part of the calculation of QALYs, especially for medicines that improve symptoms but may not affect overall survival. Ideally utility values are derived from actual patients in individual health states, although in some circumstances healthy people may be asked to imagine disease states and respond to whichever technique is being used to elicit utility values. There is no perfect way to elicit utilities, but most involve balancing the benefits of improved health against reduced survival (Box 1.2).

An alternative approach to utility derivation is frequently used by NICE and is based on a five-item questionnaire (EuroQol 5 Dimensions or EQ-5D), a frequently used Patient Reported Outcome measure in clinical trials. EQ-5D asks patients to grade themselves across five domains (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression). An algorithm has been developed that allows responses to the questionnaire to be converted into a utility value. This method has been criticised as possibly not capturing all aspects of quality of life but has nevertheless found widespread use. Obviously utility values may differ according to the methodology used to derive them. The effects of this can be tested by varying utility values in sensitivity analysis (see below).

Health Economic Modelling

Clinical trials of new medicines in a chronic disease such as diabetes are usually of relatively short duration (6–24 months). Pharmacoeconomics ideally seeks to see the costs and benefits of a new medicine over a much longer time horizon,

Box 1.2 Examples of eliciting utility values

Time Trade-off
With time trade-off the subject is asked to assume that they will live for (say) 10 years in their present state of health and is then asked how much of that 10 years they would forego to return to full health. The more survival they are willing to give up, the worse their current quality of life is assumed to be. If they give up 2 years, their utility value will be 0.8, if they give up 5 years, it will be 0.5.

Standard Gamble
With standard gamble the subject is told that a treatment exists that could return them to full health, but which also has a chance of causing instant death. They are asked what risk of death they are willing to take to be 'cured'. Once again, the greater the risk they are willing to accept, the lower their current quality of life, and hence utility value, is assumed to be.

10–20 years or even a lifetime. In addition, clinical trials usually collect data on surrogate outcomes (e.g. HbA1c, blood pressure) and not on the endpoints that really matter to patients such as survival, incidence of vascular events, incidence of visual loss, etc. Health economic modelling is the mechanism that is used to bridge these gaps. The aim of such modelling is to extrapolate the trial data to a longer time horizon and to translate the surrogate outcomes into meaningful clinical outcomes for patients [13].

Modelling uses data from epidemiological and interventional studies to predict differences in outcome with different treatments and thus evaluate the overall health gain from a new treatment to populate the 'incremental benefit' part of the ICER calculation. Diabetes has extensive datasets from both disease registries and interventional studies which allow the modelling to be reasonably robust and credible in a pharmacoeconomic evaluation.

For example, if a new medicine leads to, on average, a reduction in HbA1c of 8 mmol/mol compared with the current therapy, it is possible to derive from existing datasets the impact that this will have on long-term survival and the incidence of myocardial infarction, visual loss, end-stage renal disease, etc., which then forms part of the estimation of the QALY associated with the new treatment. There are a variety of modelling techniques, but one that is commonly used would see the creation of an 'imaginary' cohort of perhaps 1000 patients with diabetes reflecting the demographics of the relevant UK diabetes population. This cohort would then be 'treated' with existing therapy (and all outcomes recorded) and then with the new therapy, again recording all outcomes, all simulated using computer programs. Survival gain can be estimated, as can reductions in diabetes-associated co-morbidities. By applying a reduction in quality of life to each of the co-morbidities, the differences in both survival and quality of life, the essential components of the QALY, can be estimated.

Sensitivity Analysis

It will be obvious from the above that health economic assessment relies heavily on extrapolation of clinical trial data, estimates of utility values and assumptions about other parameters that have not been formally measured in clinical trials. This extrapolation and assumption introduce considerable uncertainty into assessment of the ICER, uncertainty that is tested in sensitivity analysis. In one-way sensitivity analysis, individual parameters are varied across a plausible range of possibilities to see which have the biggest impact on the ICER and which are less important. It may then be possible to try to find data from other sources that can inform the estimate of the most important parameters and reduce the uncertainty in the ICER assessment.

In probabilistic sensitivity analyses, multiple parameters are varied simultaneously within plausible ranges and according to defined data distributions for each parameter (e.g. normal distribution). This creates both an 'average' ICER but also a range of possible ICERs which may be useful in decision-making. Finally, several parameters may be varied at the same time within, or to the extremes of, their ranges in scenario analyses, aiming to establish the likeliest true value of the ICER and best and worst case scenarios.

Ultimately, while health economists can undertake modelling, extrapolation and sensitivity analyses, it is for decision-makers at NICE or SMC (for example) to decide, based on their clinical knowledge and the available data, which estimate(s) of the ICER

they find most plausible and then make their decisions based on this while fully aware of the extent of the prevailing uncertainty.

For example, the NICE Technology Appraisal for dapagliflozin with insulin for treating type 1 diabetes (TA597) was presented with a base case ICER by the manufacturer of £6,618 per QALY [14]. NICE was not persuaded by some of the assumptions in the base case, and when these were removed the ICER rose to £19,122, a significant increase, taking the ICER much closer to NICE's usual threshold for acceptance, although still allowing the medicine to be accepted for NHS use in this indication.

A number of health economic models of diabetes (type 1, type 2 or both) have been developed and refined over many years and are used frequently to estimate the cost-effectiveness of interventions [15]. Each model uses slightly different data inputs and modelling assumptions and thus the outputs vary somewhat. Commonly used models include the UKPDS Outcomes Model, the CORE Model, the Sheffield Model and the Cardiff Model. No model is perfect, but the Mount Hood Diabetes Challenge Network brings model developers together every two years to encourage further model development and refinement.

Discounting

Discounting is the way in which economic evaluations are adjusted for the fact that individuals (and societies) are not ambivalent about when they receive a benefit or incur a cost, the so-called time preference. The convention in the UK is to regard current benefits of interventions (not just in healthcare) as more 'valuable' than future benefits, discounting the value of future benefits by 3.5% per year. Costs are similarly discounted, but this situation may be problematic in a chronic disease such as diabetes, where costs may be incurred in the present and short-term future to avoid long-term complications many years later. A health gain of 1 QALY is, for example, valued at only 0.55 QALY if it occurs in 20 years' time, almost doubling the ICER. This has been identified as a significant problem in chronic diseases and there are currently suggestions that the discount rate be reduced to 1.5% (which would increase the QALY in the above example to 0.82 QALY).

Indirect Comparison and Network Meta-analysis

It is often the case that the clinical trials with a new medicine have not been undertaken with an active comparator, but against a placebo. Alternatively, the trials may have been undertaken with an active comparator therapy but not the appropriate comparator in current clinical practice. In these circumstances some form of indirect comparison against current practice is necessary. This, at its simplest, involves finding data on the new medicine and the appropriate comparator each compared with a common intervention (either placebo or another medicine). The common intervention helps to correct for differences in the study populations and thus the true effects of the new medicine and its comparator can be seen. An example is shown in Box 1.3.

In diabetes there are many clinical trials and other sources of efficacy information on a wide range of medicines, some compared with placebo and others with two medicines compared 'head-to-head'. All of these data can be combined into a network of

Box 1.3 Example of an indirect comparison

Current therapy: HbA1c reduced by 10 mmol/mol (placebo 4 mmol/mol)
New therapy: HbA1c reduced by 14 mmol/mol (placebo 7 mmol/mol)

At first sight the new medicine appears considerably more effective than current therapy, but once the difference in placebo response is factored in, the advantage of the new medicine is quite small (7 mmol/mol more than placebo vs. 6 mmol/mol more than placebo). A simple indirect comparison such as this cannot completely adjust for differences in the patient populations studied but is significantly better than just comparing the unadjusted efficacy numbers.

comparative efficacies, into which data on a new medicine can be incorporated. Such a network meta-analysis is, given the multiple comparisons made, more robust than the simple indirect comparison described above. Network meta-analysis can allow comparisons between medicines in different classes (e.g. GLP-1 receptor agonists vs. DDP-4 inhibitors) or assessment of the relative efficacy of medicines within a class (NICE Technology Appraisal TA390 compared three different SGLT2 inhibitors, for instance) [14]. As with economic modelling, indirect comparison is a relatively inexact science and is dependent on the data used – NICE TA390 assessed four different indirect comparisons, one from each of the manufacturers of the three medicines considered and a fourth developed by NICE itself. Indirect comparison is thus better than naive unadjusted comparison, but nothing is as good a reflection of relative efficacy as an actual head-to-head trial against the appropriate comparator.

Network meta-analyses are frequently described as showing that (for example) Medicine A is 'better' than Medicine B. No such 'value judgment' can be drawn as the analysis will simply show that, at the doses used in clinical studies, Medicine A showed greater efficacy than Medicine B, the latter possibly showing other features (such as ease of administration or better tolerability) that might make it 'better' overall.

Future Developments in Diabetes Clinical Pharmacology

Drug Development

Advances in the genetics and molecular biology are changing the traditional process of drug discovery and development. Proteomics, the study of proteins and their role in biological functions, has had an important role in the identification of biomarkers and drug targets. A better understanding of the molecules involved in the pathophysiology of type 2 diabetes has led to the development of several new classes of drugs with many other classes in the pipeline (see Chapter 14). Proteins such as interleukin

6, adiponectin and leptin and their role in type 2 diabetes are being characterised and could lead to novel drug therapies.

Inter-individual drug variability has been explained in part by pharmacogenomics, the study of the genomics of the drug response. Individuals with reduced function CYP2CP alleles metabolise sulfonylureas more slowly and have a better glycaemic response than those with normal function copies [16]. Information from genome-wide association studies has been used to determine the association between nucleotide variations and an individual's response to drugs. These studies have been used to show that the response to metformin is in part due to nucleotide variations in genes such as ATM and SLC22A1. A greater understanding of the factors underlying variability in drug response can help personalise medicine and ensure that patients receive the maximal therapeutic benefit with minimal side effects.

Pharmacovigilance

The increasing use of electronic medical records and the ability to link different databases offer the possibility to incorporate active pharmacovigilance into routine practice within healthcare systems. This leads to the concept of 'big data', where large amounts of anonymised data are collected and analysed, looking for patterns that might suggest drug safety signals. Of course, with such large patient numbers and large quantities of data, apparent associations between events and drug use will inevitably arise by chance. Considerable care is needed to avoid over-reacting to chance findings of associations if unnecessary 'drug scares' are to be avoided. A variety of techniques are available. One relatively straightforward technique is to divide the dataset into two and look for associations in one half of the data. Any associations found can then be looked for in the other half of the dataset; only if the association is found again is it possibly of significance. Possible benefits from the application of artificial intelligence and machine learning to analyse big datasets are being explored. Assessment of any medicine is based on balancing risks and benefits, the latter hopefully outweighing the former. Pharmacovigilance has focussed on identifying and quantifying risks but has rarely looked at confirming and quantifying benefits in the 'real-world' use of medicines. The availability of larger linked datasets opens up the possibility of pharmacovigilance being about ongoing risk–benefit assessment, which is more valuable to patients, prescribers and regulators than looking at risks in isolation.

Pharmacoeconomics

Traditionally, pharmacoeconomic assessment of new medicines has been undertaken after regulatory approval, but this has been criticised as delaying access to potentially valuable new medicines. In some countries, including the UK, pharmacoeconomic assessment is set to occur alongside regulatory assessment, such that both will reach their conclusions virtually simultaneously.

While this streamlined approach may speed the availability of new medicines, it does mean that the pharmacoeconomic assessment will be made using less mature data than might have been available previously, introducing more uncertainty into the assessment. Indeed, the final details of the indication for therapy may not be clear when the pharmacoeconomic assessment is begun, requiring close coordination of the regulatory and pharmacoeconomic assessment processes to ensure that they remain aligned.

References

1. McKay, G., Walters, M., and Ritchie, N. (2021). *Lecture Notes: Clinical Pharmacology and Therapeutics*, 10th edn. Wiley Blackwell.
2. Blass, B. (2021). *Basic Principles of Drug Discovery and Development*, 2nd edn. London: Academic Press.
3. Medicines and Healthcare Products Regulatory Agency (2020). New guidance and information for industry from the MHRA. https://www.gov.uk/government/collections/new-guidance-and-information-for-industry-from-the-mhra (accessed 27 September 2021).
4. Chong, W.H., Yanoff, L.B., Andracac-Carrere, E., and Hai, M.T. (2020). Asessing the safety of glucose-lowering drugs – a new focus for the FDA. N Engl J Med 383: 1199–1202.
5. National Institute for Health and Care Excellence (NICE) (2016). Technology appraisal guidance [TA390]: canaglilfozin, dapagliflzoin and empagliflozin as monotherapies for treating type 2 diabetes. https://www.nice.org.uk/guidance/ta390 (accessed 27 March 2021).
6. International Hypoglycaemia Study Group (2017). Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 40: 155–157.
7. Llano, A., Fisher, M., and McKay, G. (2017). Biosimilar insulin: the current landscape. Practical Diabetes 34 (2): 51–54.
8. Committee for Medicinal Products for Human Use (CHMP) (2014). Guideline on similar biological medicinal products. https://www.ema.europa.eu/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf (accessed 27 September 2021).
9. Committee for Medicinal products for Human Use (CHMP) (2015). Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. https://www.ema.europa.eu/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-0.pdf (accessed 27 September 2021).
10. Medicines and Healthcare Products Regulatory Agency (MHRA) (2021). Guidance on the licensing of biosimilar products. https://www.gov.uk/government/publications/guidance-on-the-licensing-of-biosimilar-products/guidance-on-the-licensing-of-biosimilar-products (accessed 27 September 2021).
11. Diabetes UK (2019). Position statement: biosimilar insulins. https://www.diabetes.org.uk/resources-s3/2019-09/Biosimilars%20PS%20Final.pdf (accessed 27 September 2021).
12. Jayagobal, J., Drummond, R., and Nagi, D. (2018). Association of British Clinical Diabetologists (ABCD) position statement on the use of biosimilar insulin. Br J Diabetes 18: 171–174.

13. Walley, T. and Haycox, A. (1997). Pharmacoeconomics: basic concepts and terminology. Br J Clin Pharmacol 43: 343–348.
14. National Institute for Health & Care Excellence (NICE) (2019). Technology Appraisal Guidance [TA592]: dapagliflozin with insulin for treating type 1 diabetes. https://www.nice.org.uk/guidance/ta597 (accessed 27 September 2021).
15. Henriksson, M., Jindal, R., Sternhuvud, C. et al. (2016). A systematic review of cost-effectiveness models in type 1 diabetes mellitus. Pharmacoeconomics 34: 569–585.
16. Pearson, E. (2019). Diabetes: is there a future for pharmacogenomics guided treatment? Clin Pharmacol Ther 106: 329–337.