Australian Government
Department of Health
Therapeutic Goods Administration

The regulation of medicines in Australia

Overview

- Who's checking your medicines?
  - Regulated medicine categories
- Registered medicines
  - Over-the-counter medicine regulation
  - Generic medicines - bioavailability
  - Quality, safety and efficacy data
  - Australian Public Assessment Reports
  - Assessing and managing risk
  - Medicines scheduling
- Lower risk medicines
  - Conditions for supply
- Access to unauthorised medicines
- Advertising medicines
- Changing medicine technologies
- Other education modules

Who's checking your medicines?

The organisation that has responsibility for the import, supply, or export of medicines in Australia is the Therapeutic Goods Administration

The *Therapeutic Goods Act 1989* requires that products must be entered on the Australian Register of Therapeutic Goods (ARTG)

To make this happen a sponsor (usually the company that will supply or manufacture the product) must submit an application and pay fees to the TGA

This presentation will take you through some of the critical things the TGA does

Regulated medicines include:

- Prescription medicines (including original and generic brands)
- Over-the-counter medicines (including pharmacy, pharmacist only and unscheduled medicines)
- Complementary medicines
- Vaccines
- Blood, blood components and plasma derivatives

Two broad categories of medicines

Approach is based on risk and, in the simplest terms, has two tiers:

Registered medicines:

- higher risk medicines that are registered on the ARTG
- evaluated for quality, safety and efficacy
- Product Information is approved by the TGA

Listed medicines:

- lower risk medicines that are listed on the ARTG
- contain pre-approved, low risk ingredients
- can only make limited claims and cannot imply that they will be useful in the treatment or prevention of serious illnesses

Registered medicines

- **Higher level of risk**
  - **All** prescription medicines are registered
  - **Most** over-the-counter medicines are registered
  - **Some** complementary medicines are registered
- **R**egistered medicines have an 'AUST **R**' number on the label and/or packaging

Prescription
(any medicine that requires a prescription from a practitioner)

Over-the-counter
(lubricating eye drops from behind the counter without a prescription)

Complementary
(high dose calcium tablets from behind the counter without a prescription)

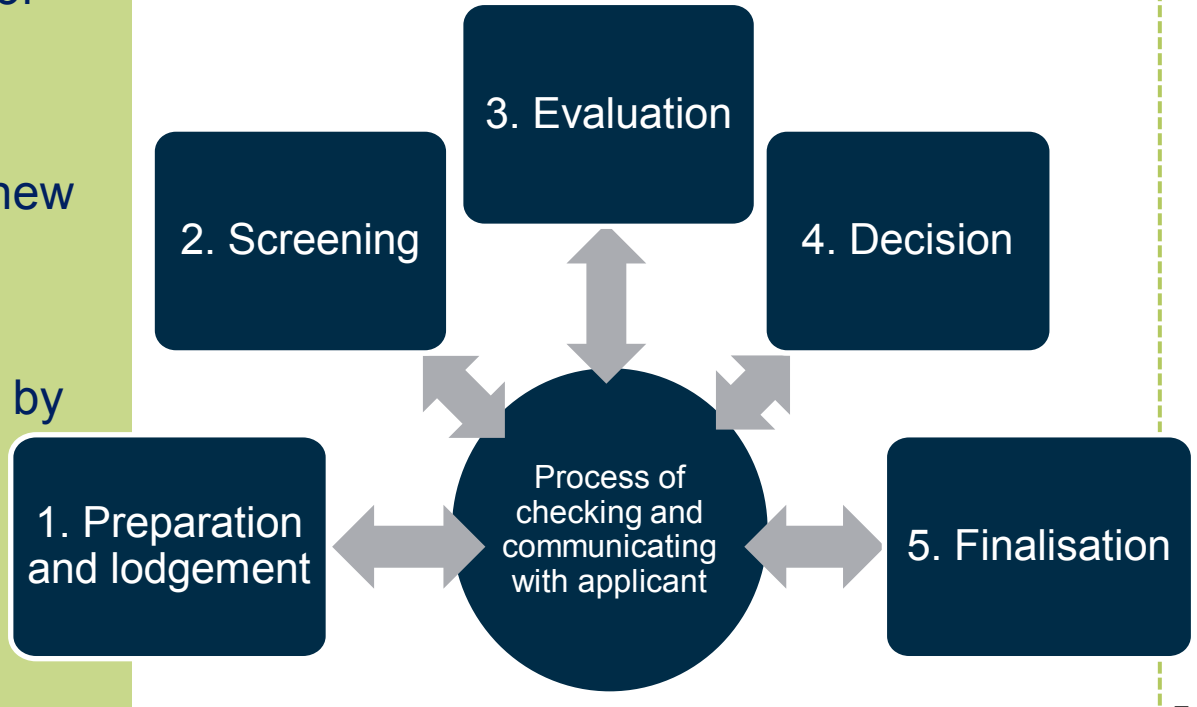
Registering a new medicine

There is a large amount of information to consider

It takes approximately 11 months to evaluate one new higher risk prescription medicine

Evaluation is undertaken by scientists and clinicians who look at data on:

- Quality*
- Safety and efficacy*

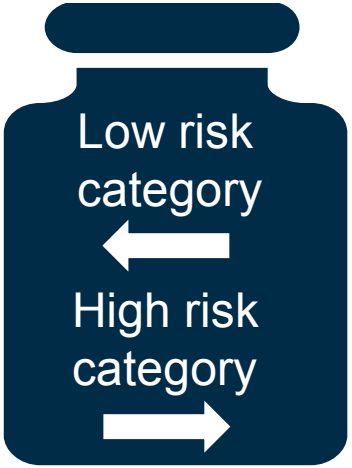


*More information about what this means is provided later in the presentation

Over-the-counter medicine regulation

Applications can be submitted in five application categories, each of which relates to different evaluation processes that corresponds to the level of risk.

- Clones (identical product to existing approved)
- Name variations
- Flavour, fragrance or colour variations

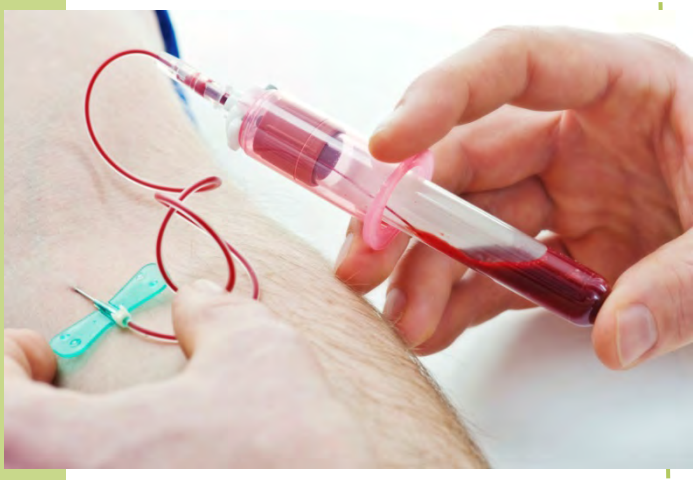


- New patient population
- New indication
- New active ingredient

Bioavailability studies – data from applicant

Generic prescription medicines must be bioequivalent

- Bioequivalence refers to whether the generic medicine releases the active ingredient into the bloodstream at the same rate and to the same extent as the original medicine
- Bioequivalence is demonstrated by conducting a bioavailability study in which volunteers (usually healthy) are given the original Australian medicine and, on a separate day, the generic medicine
- Blood samples are taken at different times and the rate and extent of absorption of the active ingredient into the blood is compared for the generic and original medicines



Decisions are based on evidence

Quality data - supplied by the applicant

Evaluated by chemists, biochemists, microbiologists and others working for the TGA

- the composition of the substance and the product
- batch consistency
- stability data
- sterility data (if applicable)
- the impurity content

Quality considerations

Batches of medicine should be ‘the same’

- European Union guidelines – some with TGA annotations – provide guidance on how to judge the quality of medicines
- The official standards in Australia are:
  - British Pharmacopoeia
  - European Pharmacopoeia
  - United States Pharmacopoeia-National Formulary
- Some (not all) EU guidelines are adopted by the TGA and may also refer to one or more of the standards above
- Drug substance: each batch should contain acceptable impurity levels
- Drug product: each tablet should contain ‘the same’ amount of active ingredient
- Stability studies must be conducted under conditions that represent tropical regions, because Australia contains significant populations in the tropics

Example of a container affecting quality

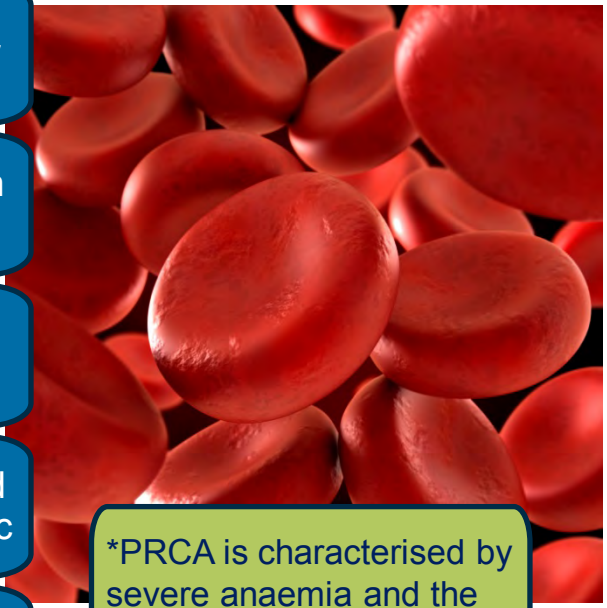
Epoetin alfa (erythropoietin) contained human serum albumin for stability

Proteins of human origin create a risk of human diseases, so the albumin was replaced with a detergent, polysorbate, with TGA approval

Within months of the formulation change, there were reports of pure red cell aplasia* (PRCA; erythroblastopenia) in Australia (TGA), the EU, Canada and Singapore

Determined that PRCA was associated with the new formulation, prefilled syringes (not vials) and subcutaneous injection, but was not batch specific

Sponsor changed to using teflon-coated plungers in syringes (with TGA approval) and PRCA dropped to previous low rate within the year.



*PRCA is characterised by severe anaemia and the absence of erythroblasts in the bone marrow.

Decisions are based on evidence

Safety and efficacy data - supplied by the applicant

Nonclinical data

Evaluated by toxicologists and pharmaceutical chemists

- Pharmacology data – laboratory data investigating efficacy
- Pharmacokinetic data
- Toxicology data – laboratory data investigating safety

Clinical data

Usually evaluated by a medical doctor

- Mostly results of clinical trials conducted by pharmaceutical companies and/or hospitals or research organisations, using volunteers

Safety information helps determine risk

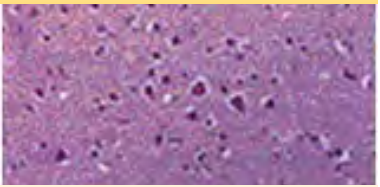
Taking medicines involves risk

- European Union guidelines describe how studies should be designed to obtain statistically valid safety information
- Considers how valid the results of nonclinical studies in animals and increasing in vitro (e.g genomic assays) are by investigating:
  - genotoxicity
  - organ toxicity
  - carcinogenicity
  - reproductive toxicity
- Any safety concerns from clinical trials?

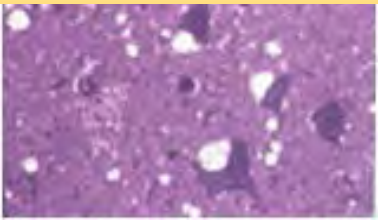
Minimising infectious diseases

Bovine spongiform encephalitis – mad cow disease transmissible to humans

Normal brain section



Affected brain section



The TGA took regulatory action when this infectious disease first emerged

Transmissible spongiform encephalitis (TSE) is a degenerative neurological disorder known in humans as variant Creutzfeldt-Jakob disease (vCJD)

The brain tissue develops holes and takes on a sponge like texture.
Clinical features include psychiatric symptoms and neurological signs.

Australian cattle were unaffected, so Australia was in a position to take tough regulatory action in relation to medicines containing ingredients that came from cattle in order to protect human health

First known protein adventitious agent

Scientific dogma: all infectious diseases must involve nucleic acid (RNA or DNA) - multiplication occurs by replication

For TSE no nucleic acid is involved: prions are misfolded PrP protein that can induce host PrP protein to undergo conformational change

PrP^{c} (α-helical conformation) changes to PrP^{sc} (misfolded protein – β sheet structure, resistant to proteinase digestion)

Normal sterilisation techniques including gamma and UV radiation have no effect on the protein

Regulatory control focused on restricting the source of bovine material in medicines to countries known to be free from BSE

PrP^{c} normal

PrP^{sc} diseased

Efficacy information helps determine benefit

There must be evidence of clinical benefit

- European Union guidelines provide guidance on how to judge the efficacy of medicines
- Could it work? – nonclinical studies and animal studies
  - in vitro, such as receptor-binding
  - in vivo
- Does it work? – clinical trials
  - "end points" to judge clinical benefits need to be agreed
  - needs to be both clinically and statistically significant
  - placebo effect needs to be accounted for
- Mechanism of action
  - sometimes informs safety information
  - sometimes informs drug interaction information

History of paliperidone

Using medicines in a new patient population

1. An application was made to the TGA to allow the use of the medicine paliperidone in adolescents aged 12-17 years old with schizophrenia—this use was authorised in approximately 10 countries, including the USA
2. Paliperidone and the related medicine risperidone are both used to treat schizophrenia. The Australian Product Information states that paliperidone ‘should not be used in patients younger than 18 years’ and risperidone ‘is lacking evidence in children with schizophrenia aged less than 15 years’
3. The TGA was concerned about the design of the main clinical trial to support use of paliperidone in Australian adolescents and asked the Advisory Committee on Prescription Medicines for advice

Outcome for paliperidone

Using medicines in a new patient population

4. The Advisory Committee on Prescription Medicines considered the study inadequate to support the proposed use in adolescents. The committee expressed significant concern about the design, duration, patient selection, screening and analysis of the main clinical study

5. The TGA was also advised that different adverse events are associated with each of the two medicines. Risks include abnormal movement disorders and metabolic syndrome, causing weight gain and diabetes

6. After receiving the TGA evaluation reports, overview and advice from the Advisory Committee on Prescription Medicines, the application was withdrawn and the Product Information for paliperidone still states that it should not be used in patients younger than 18 years

Find out more by reading an AusPAR!

An Australian Public Assessment Report provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve an application to register a prescription medicine

Recent updates

Active ingredient	Product name
29 October 2013	
Amino acids, Lipids and Glucose, with and without Electrolytes	PeriOlimel N4-600E, Olimel N5-860E, Olimel N7-960, Olimel N7-960E, Olimel N9-840,Olimel N9-840E
Cetuximab	Erbitux
Fidaxomicin	Dificid
Filgrastim (rbe)	Zarzio
Rivaroxaban	Xarelto

Includes summaries of pharmacodynamics, pharmacokinetics, efficacy and safety, as well as the first and second round benefit-risk assessments

Assessing and managing risk

What do we do?

- Consider risks – what are they?
- Balance benefits with risks
- Consider whether a medicine should be used in the proposed population for the proposed indication
- Use Product Information document as a risk management tool
- Consider other risk management tools

Product Information document

A risk management tool

- The document is approved by the TGA
- The product is only authorised for specified patient population for specified indications
- All other use is ‘off-label’ and the benefit-risk profile has not been considered by the TGA
- The precautions section gives details of some of the risks involved

Example of PI as a risk management tool

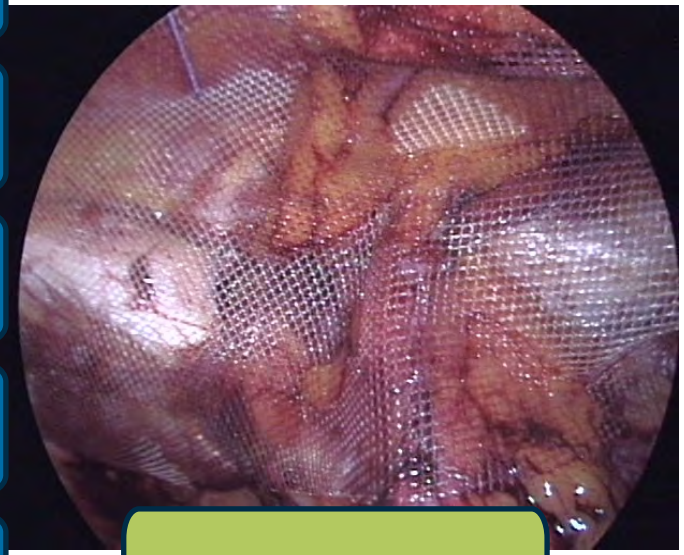
A fibrin sealant was already authorised for a number of indications

The application was to extend the indications to include fixing meshes used in hernia repair operations

This submission consisted mostly of studies published in the literature

When the fibrin sealant was used in nonclinical studies to fix a mesh to the **peritoneum**, the mesh often did not stay in place

This information is now in the precautions section of the Product Information



Mesh graft

Picture source: Anpol42

Planning for safety

A risk management plan states how safety concerns will be identified and mitigated. It is a required component in the premarket authorisation process and is also updated to cover the entire life of the product

It consists of:

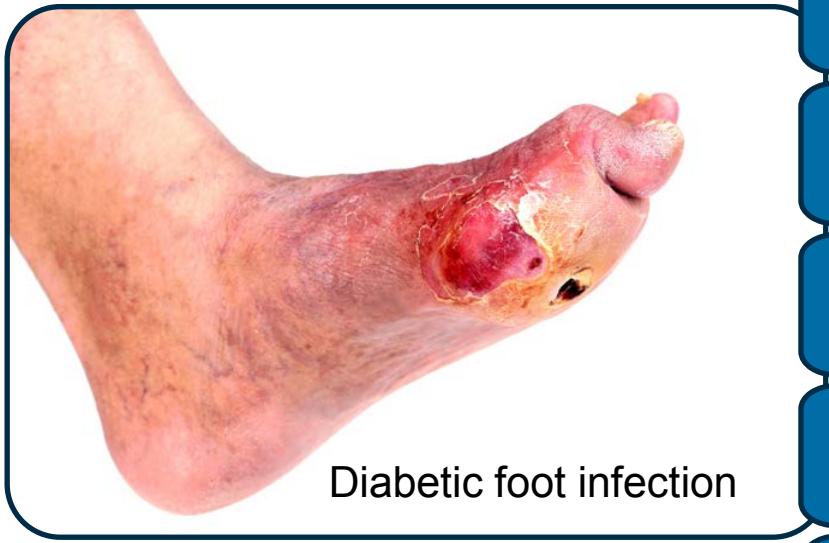
- an overview of the safety profile
- a pharmacovigilance plan
- a risk minimisation plan

How can we control use?

A risk management plan might require the sponsor to:

- Report on adverse events
- Develop educational program
- Limit supply to authorised prescribers
- Keep a registry of patients
- Automatically recruit on registry when product is prescribed

First medicine in class – dapagliflozin



Diabetic foot infection

Selective and reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the major transporter for glucose reabsorption in the kidney

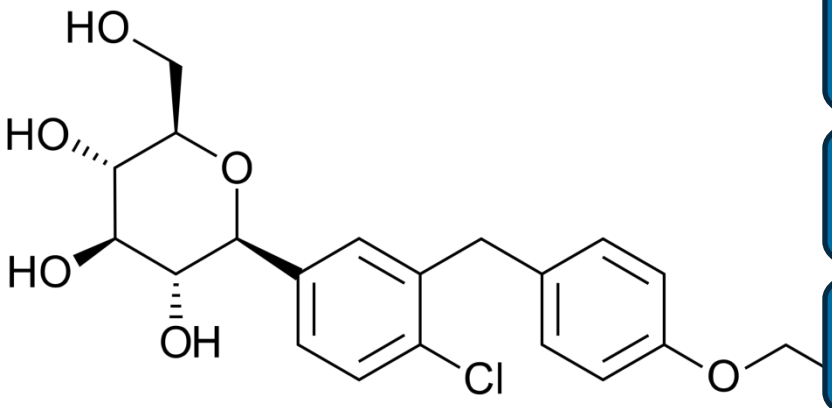
Used for the treatment of type 2 diabetes as an adjunct to diet and exercise

Long term benefits are likely to follow from reducing blood glucose levels in type 2 diabetes

Safety concerns: renal impairment, urinary tract infections, genital infections, dehydration, osteoporosis

Nonclinical studies did not indicate any carcinogenic concerns. Bladder and breast cancer in clinical trials was considered by the TGA as unlikely to be treatment-related, but this could not be ruled out

Dapagliflozin – conditions of registration



New class means limited relevant clinical knowledge in real world – the TGA did not authorise first line monotherapy because of safety record of metformin

Authorised only for type 2 diabetes.
Not authorised in the moderately renally impaired (defined as: eGFR <60 mL/min)

A specific condition of registration was that a **postmarket study strategy** be agreed by the TGA prior to marketing

The sponsor was required to conduct an **education program for health professionals** to minimise the possibility of dapagliflozin being used for weight loss

An **Australian-specific** Annex to the risk management plan was required, to outline pharmacovigilance measures if there were delays in authorisation by the EU and/or US

Medicines scheduling–the Poisons Standard

- Potentially dangerous drugs and chemicals are restricted to enable their safe and effective use
- Scheduling is the legal process used to achieve this
- Scheduling decisions are made by a senior TGA medical officer taking into account the advice of the Advisory Committee on Medicines Scheduling
- The higher the number of the schedules, the more access is restricted
- Scheduling is in legal terms a State matter, but all States now adhere closely, or entirely, to the Poisons Standard, which is administered by the Department of Health
- Scheduling decisions are published on the TGA website

Remember: only registered medicines are scheduled

Examples of scheduled medicines

Schedule classification	Type of medicine	Example
Schedule 2	pharmacy only medicine	large packet sizes of paracetamol
Schedule 3	pharmacist only medicine	topical thrush treatments
Schedule 4	prescription only medicine	blood pressure medications
Schedule 8	controlled drug – S8 has additional restrictions on the storage and supply of medicines	strong upload painkillers

Rescheduling alprazolam

Alprazolam belongs to a group of medicines called benzodiazepines which are used to treat anxiety and panic disorders.

Submissions to the TGA suggested that Alprazolam should be rescheduled from Schedule 4 to Schedule 8 due to:

- Increased morbidity and mortality in overdose with possible increased toxicity
- Rapid increase in use and evidence of widespread misuse
- Concerns that the current pack size is inappropriate for indications
- Evidence of misuse with opioids

As of 1 February 2014, alprazolam will be a Schedule 8 controlled substance. More information: <http://www.tga.gov.au/industry/scheduling-decisions-final.htm> June 2013

Listed medicines

- **Lower level of risk**
  - **Some** over-the-counter medicines are listed
  - **Most** complementary medicines are listed
- **L**isted medicines have an 'AUST **L**' number on the label
- Must **NOT** contain substances that are scheduled in the Poisons Standard
- Must contain pre-approved ingredients

Regulating listed medicines premarket

Only pre-approved low risk ingredients may be used in listed medicines

Listed medicines, including most complementary medicines, receive a lesser degree of checking than higher risk products

Regulation centres on the safety of the ingredients and the consistency of the manufacturing process; sponsors must hold evidence to support the claims

Independent expert advice may be sought on new ingredients proposed for use in listed medicines

Listing on the ARTG is the final stage of the process and usually occurs once the sponsor has paid their fees and signed a statutory declaration

Conditions for supplying low risk medicines

Contains pre-approved low-risk ingredients

Does not claim or imply it will be useful in the treatment or prevention of serious illnesses

The TGA inspects and licenses manufacturing sites in Australia and assesses sites overseas. This allows us to enforce standards in relation to sterility and quality of the ingredients used and the process followed.

Patients sometimes need special access

We help health professionals gain access to products that their patients need, but which have not been approved for use in Australia.

Clinical Trial Exemption (CTX) and Clinical Trial Notification (CTN) schemes

Access unapproved medicines through participation in a clinical trial

Special Access Scheme (SAS)

Import and/or supply an unapproved therapeutic good for a single patient on a case-by-case basis

Authorised Prescribers

Authorised prescribers can prescribe a specified therapeutic good (more than once) to a patient with a particular medical condition

Advertising medicines
It's important

- The labelling, packaging and description of what the medicine should be used for are all regulated by the TGA
- Advertising of prescription medicines to consumers is illegal in Australia

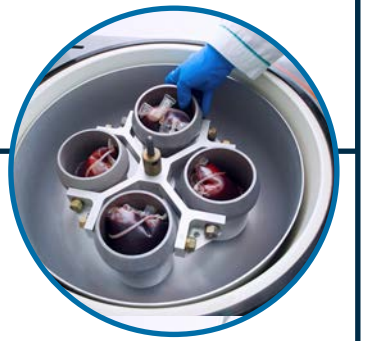
Changing medicine technologies

1960s

- Medicines were relatively small molecules
- Manufactured from chemicals, such as aspirin, or were a product of fermentation, such as penicillin and cortisone

1970s

- Human plasma started to be used to provide products such as Factor VIII for haemophilia



1980s

- Human proteins produced in bacteria using recombinant DNA technology
- Human insulin produced - avoided problems of allergic reactions to animal insulin
- Human proteins available: insulin, growth hormone and interferon

1990s

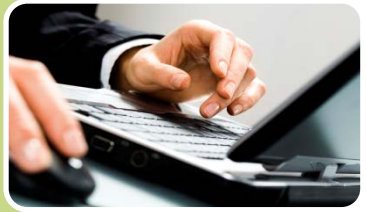
- More than a hundred protein medicines were produced using recombinant DNA technology
- Virus proteins could be produced without the actual virus and used as vaccines

Protein/peptide medicines registered in 2012

Medicine	Disease state
Belimumab (Benlysta)	Systemic lupus erythematosus
Peginterferon Alfa 2a (Pagasys)	Hepatitis C
C 1 esterase inhibitor (Cinryze)	Hereditary angioedema attacks
Velaglucerase alfa (Vpirv)	Glucocerebrosidase deficiency (Gaucher disease)
Afibercept (Eylea)	Age related macular degeneration
Human fibrinogen and thrombin (Tachosil)	Cardiovascular surgery
Adalimimab (new presentation - Humira)	Arthritis, Crohn's Disease
Insulin aspart (multidose – Novorapid Fextouch)	Diabetes
Eptacog alfa (NovoSeven RT)	rFactor VIIa – uncontrolled bleeding

Regulation after product is on the market

- We have created a separate educational module on postmarket regulation, which details what we do once products are in the supply chain. This is an integral part of the regulatory system.
- The module covers:
  - tools used in postmarket monitoring
  - signal investigation
  - recall actions



There are five other modules in this suite of educational material. These can be accessed by the links on the next slide.

Other education modules include:

- Introduction to the TGA
- Biologicals
- Medical devices
- Postmarket monitoring
- Good Manufacturing Practice