Module 3 requirements for biologics (natural peptide/protein medicines)

Biological medicines - what are they and how are they different

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Topics for today

• Background - what are biological medicines?
  – Definition of a biological medicine and regulatory frameworks
  – What makes biological medicines different
  – examples
• Registration information and evaluation process
  – Type of data required to support registration
  – Common misconceptions
  – Variations to registrations
• Future directions
  – Where is industry going
  – How are regulators responding
What are biological medicines

A TGA definition

• Are therapeutic goods that are derived from biological sources and are regulated as registered medicines. They include proteins and polysaccharides such as:
  – vaccines
  – **products of the fermentation of recombinant cell-lines**
  – medicines derived from the fluids and tissue of humans (where specified in the Therapeutic Goods [Things that are not Biologicals] Determination No. 1 of 2011) and animals
  – bacterially-derived proteins
  – animal-derived polysaccharides like heparin
  – biological medicines do not include antibiotics and small peptides or molecules <2500 Da
  – biological medicines are distinct from 'biologicals' which are human cell and tissue products
Biological medicines – not biologicals?

• Biologicals are defined in Part 3-2A of the *Therapeutic Goods Act 1989* (the Act) as a thing *made from*, or that contains, human cells or human tissues ...

• This covers some human derived ‘medicine’ products

• Goods declared not to be biologicals - in the *Therapeutic Goods (Things that are not Biologicals) Determination No.1 of 2011* - include:
  – biological prescription medicines (vaccines, plasma derivatives, recombinant products)
  – labile *blood and blood components*
  – haematopoietic progenitor cells used for haematopoietic reconstitution (non-fresh transplants)
Why are they different

• Size – difficult or impossible to construct using chemical methods
• Complexity – rely on shape for function that comes from interactions in 3-D
• Manufactured using living cells – bacteria, yeast, mammalian cells
• Product quality and process – can’t test for quality, is a function of control of manufacturing and final testing
• Labile – complexity of structure results in lack of stability unless conditions are controlled
• Immunogenicity – proteins can stimulate a response against the product
Biological medicines – what are they and how are they different?

Source: https://www.youtube.com/watch?v=DrJnbGe8kdE
Benefits of biological medicines

• Ability to replicate naturally occurring targets
  – harness normal physiological processes
  – supplement clotting factors, enzyme replacement, growth factors
• Target molecular pathways
  – monoclonal antibodies precisely targeted, few off target effects
  – antibodies have binding and effector functions
  – platform technology: leverage information from previous products, shorter development cycle
  – direct cargo to targets
• Engineer desired properties
  – alter effector functions
  – alter biopharmaceutic properties
  – develop mimics
Common biological medicines

- Recombinant proteins
  - Monoclonal antibodies such as anti-TNF in inflammatory disease
  - Growth factors such as epoetin
  - Clotting factors such as factor VIII
- Naturally derived/extracted proteins and polysaccharides
  - Plasma derived proteins such as immunoglobulins and factor VIII
  - Heparin and its derivatives – enoxaparin, dalteparin
  - But not antibiotics or extracted small peptides
- Vaccines, toxins and anti-venoms
What’s with the names

**Golimumab or pertuzumab**

### Complete List of Stems for Monoclonal Antibody Nomenclature

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*under discussion as of February 2010*

### Components

**Substem for origin/source**

- Source subterms: mouse (top left), chimeric (top right), humanized (bottom left), chimeric/humanized (bottom middle), and human (bottom right) monoclonal antibodies. Human parts are shown in red, non-human parts in blue.

Biological medicines – what are they and how are they different?
Regulation framework – medicines

• Application through the prescription medicines registration process
• Submissions in CTD format
  – require supporting quality, toxicology and clinical data
  – quality requirements are different to small molecules
  – hopefully now in eCTD
• Same guidelines as other medicines
  – Australian Regulatory Guidelines for Prescription Medicines (ARGPM)
  – adopted European Medicines Agency (EMA) and International Conference on Harmonisation (ICH) scientific guidelines
  – specific scientific guidelines for biological medicines
Evaluation for registration

- Regulated as any other medicine
  - Prescription medicines registration process (Cat1) for new products and biosimilars
  - 9D applications (Cat3) for variations
- Clinical and tox handled the same as for other medicines
- Quality assessed in specialist areas
  - Biological Science Section
  - Vaccines in Laboratories Branch
  - Secondary assessments for viral safety, endotoxin, sterility, containers

Perjeta (pertuzumab) and Herceptin (trastuzumab) binding to its target HER2

Biological medicines – what are they and how are they different?
Quality evaluation – biological medicines

• Drug substance is the most critical part of manufacture
• Involves multi-step process:
  – produce the target molecules
  – separate it from the cellular production system
  – refine it to the final spectrum of product characteristics
  – formulate it for storage prior to filing
• Drug product usually minimal manipulation
  – dilution with few excipients added
  – sterile filtration
  – filling and storage at final temp
Quality evaluations – process control

• Starting materials
  – choice of cell lines
  – molecular engineering of DNA
  – development of cell lines, genetic stability, viral safety

• Fermentation process
  – controlled process - array of in process controls to deliver consistent process
  – closed process

• Purification process
  – multiple steps of chromatography
  – remove process related impurities
  – reduce product related impurities

Multi-step manufacturing process for drug substance
Quality evaluations – key aspects

• Know your product
  – extensive product characterisation
  – extensive cell line characterisation
  – stability studies are important

• Consistency of manufacturing
  – critical quality attributes
  – control strategy
  – validation and verification

• Process development
  – demonstrate process knowledge
  – link to product knowledge
  – demonstrate link through non-clinical to clinical and commercial processes
Balance of controls

Registered biological medicine

- Control strategy
- CQAs
  - Product variables which are linked to clinical outcomes
- CPP
  - Process controls which affect CQAs
- QTPP
- GMP sites
- Conditions of registration

Biological medicines – what are they and how are they different?
Common misinterpretations

• Critical materials
  – cell lines: full history and characterisation
  – animal and human ingredients
• Process development and variations
  – justification based only on manufacturing parameters
  – changes need to be brought back to the patient context i.e. clinical implication
• Stability
  – most biological medicines are effected by temperature – shipping conditions, deviations, variations
  – extrapolation not accepted. More in ARGPM guidance 14.4 Specific requirements on stability of biological medicines
  – stability impact following variations
• GMP
  – clearances required for critical steps in manufacture especially at drug substance including cell banks

Take home: look at the specific guidelines on the TGA website
Common questions

Do I need to put in a variation?

• Look at the minor variations guidance on the TGA website
  – lists self assessable changes (different to chemical entities)
  – guides on data requirements for other changes
  – key scientific guideline is ICH Q5

• Evaluation approach
  – what is the risk to the product control i.e. does it increase likelihood
  – does the data control this risk
  – the Secretary is satisfied that the variation requested does not indicate any reduction in the quality, safety or efficacy of the goods for the purposes for which they are to be used

• Ask
  – Biological.Medicines@tga.gov.au
Post market assessment

• Complexity of manufacture and products attributes make them a high risk product
• New biological medicines are covered by a Risk Management Plan (RMP)
• TGA Laboratories Branch:
  – undertakes batch release testing of all new biological medicines
  – a survey program is in place to periodically check that quality is as expected
• GMP clearance
  – Biological medicines require GMP clearances for more steps involved in manufacturing than small molecule. Additional GMP requirement for biotech manufacturers
Future directions – industry and regulatory approach

Industry
• Platform technology
• Disposable technology
• In-line real time testing
• Increased product knowledge
• Biosimilars

Regulators
• ICH quality guidelines 8,9,10 and 11 (and 12?)
  – Improved product understanding leads to more flexible regulatory controls?
  – QbD
  – Expanding risk based approach
• Evolving biosimilars approach
  – FDA registration of 1st US biosimilar
  – TGA review of biosimilars guideline
  – World Health Organization (WHO) naming