Australian Government
Department of Health
Therapeutic Goods Administration

Drug Discovery

A Regulatory Toxicologist's Perspective

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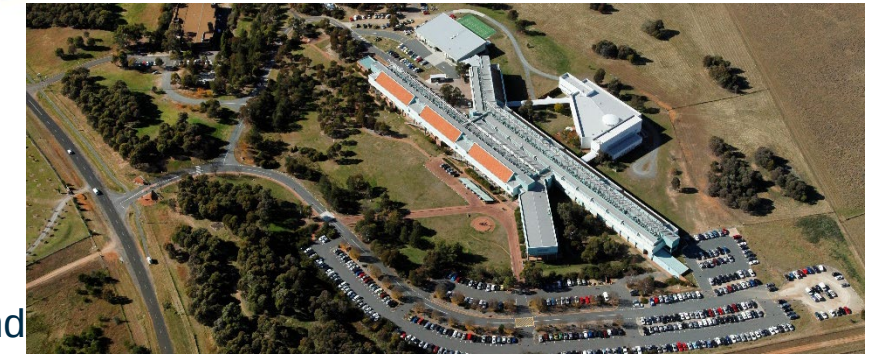

Australian Cardiovascular Alliance Drug Discovery & Translation Flagship Workshop and Symposium

01 February 2020

TGA Health Safety Regulation

Australian Government
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Outline

- Drug Approval – the Regulator's Role
- Nonclinical study requirements - overview
- Clinical Trial Regulation in Australia
- Nonclinical studies supporting First-in Human Clinical Trials

Drug Discovery and Development Timeline

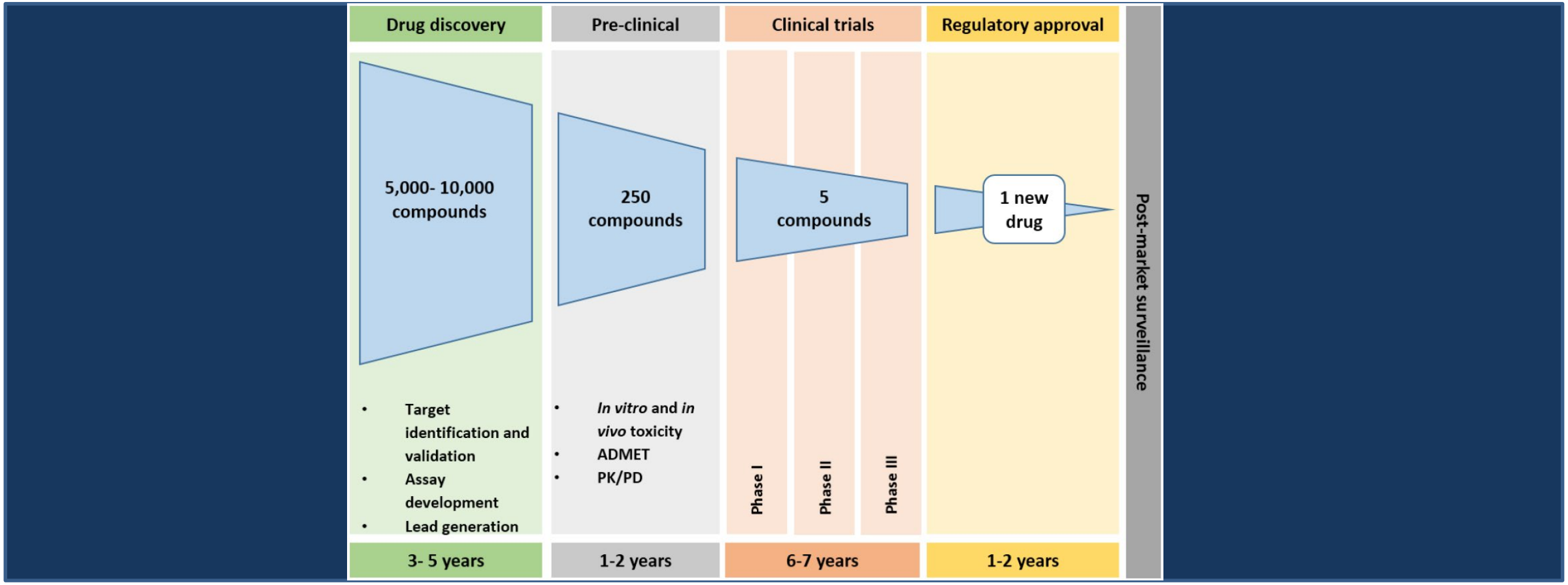


Figure reproduced from Matthews *et al* (2016) 'Omics'-Informed Drug and Biomarker discovery: Opportunities, challenges and future perspectives. DOI: 10.3390/proteomes4030028

TGA's responsibilities

- The TGA is responsible for ensuring that therapeutic goods available for supply in Australia are **safe** and fit for their intended purpose.
- The TGA regulates therapeutic goods, including prescription, over-the-counter and complementary medicines, medical devices, biologicals, blood and blood products.
- We achieve this through regulation of therapeutic goods and certain controlled drugs and drug substances. This applies to all such goods exported, imported, supplied and manufactured in Australia.
  - Therapeutic Goods Act 1989
  - Therapeutic Goods Regulations 1990

General considerations of the nonclinical data

- **Design and scope of studies**
  - **Guidelines**
    - EU/ICH-adopted
    - Other: OECD, FDA, WHO
    - https://www.tga.gov.au/ws-sg-index
- **Validity of the findings**
  - Data quality (Good Laboratory Practice)
  - Validity of positive and negative results

Nonclinical data package based on ICH M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals Step 5 EMA/CPMP/ICH/286/1995

- Primary and Secondary Pharmacology
- **Safety Pharmacology**
- **Pharmacokinetics (ADME)**
- **Toxicity - acute, repeat-dose, toxicokinetics (TK)**
- **Genotoxicity** (***in vitro*** & *in vivo*)
- Carcinogenicity
- **Reproductive toxicity**
- **Local tolerance**
- Immunotoxicity, phototoxicity, neurotoxicity, etc

Standard Non-Clinical Safety Studies Prior to 'First in Human' trials

Examples of Guidelines for Specific Classes of Products

- Guideline on human cell-based medicinal products EMEA/CHMP/410869/2006 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-human-cell-based-medicinal-products_en.pdf

- Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-production-characterisation-specification-monoclonal-antibodies-related_en.pdf

- Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products CPMP/BWP/3088/99 https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-quality-preclinical-clinical-aspects-gene-transfer-medicinal-products_en.pdf

- ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals EMA/CHMP/ICH/731268/1998 https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals-step-5_en.pdf

Assessing the relevance of toxicological findings to human safety

- What is the **mechanism** of toxicity?
- **Commonality** of toxicity across species?
- **Exposure** associated with toxicity *cf* human exposure?
- Severity and **reversibility** of toxic effects?
- Existing nonclinical and clinical knowledge of related drugs

Clinical Trials

Clinical Trial regulation in Australia

CLINICAL TRIAL NOTIFICATION (CTN)

- Investigators' Brochure and Trial Protocol reviewed by Human Research Ethics Committee (HREC)
- No routine TGA review
- >95% of applications

CLINICAL TRIAL EXEMPTION (CTX)

- TGA review of Investigators' Brochure and Trial Protocol
- Advice provided to HREC
- HREC review & approval
- < 5% of applications

Nonclinical data to support first-in-human and early clinical trials

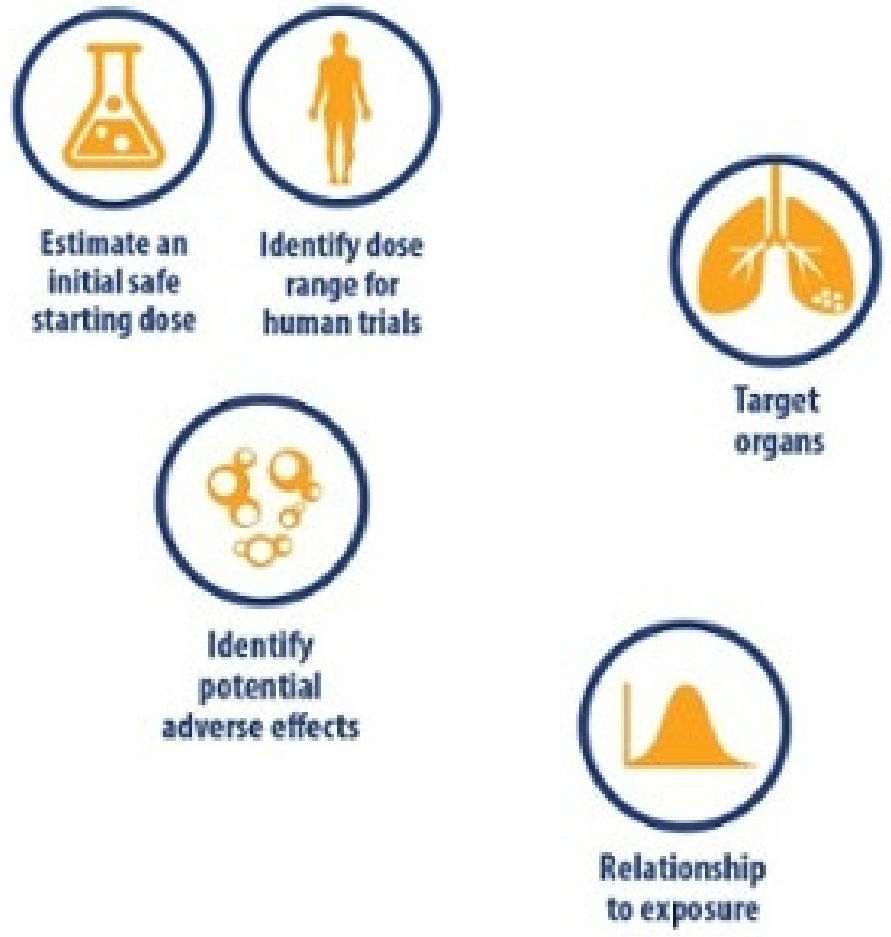
Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

EMEA/CHMP/SWP/28367/07 Rev. 1

Establishing the adequacy of nonclinical data supporting clinical trials

The ethical conduct of a clinical trial, particularly a First-In-Human (FIH) trial of a new medicine, requires nonclinical data that are adequate. Such data should:

- Consider current internationally accepted guidelines
- Be obtained using scientifically credible study designs
- Be derived from experiments in relevant species
- Use the 3Rs principles on animal use (Reduce/Refine/Replace)

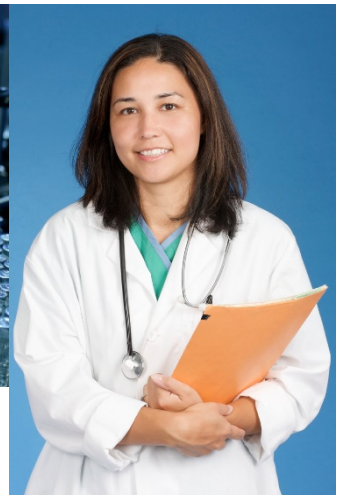


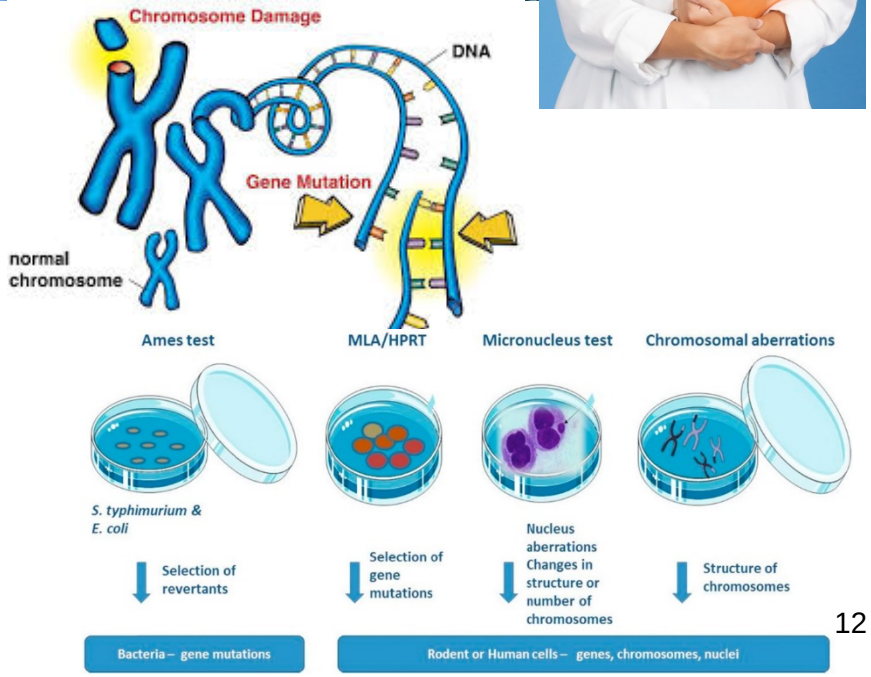
Good Laboratory Practice (GLP) for pivotal safety and TK studies

- GMP: chemistry/manufacturing control
- GCP: clinical aspects
- GLP: nonclinical

Pivotal

safety pharm, tox (not dose-range), TK





Use of relevant species and animal models

Pharmacologically relevant (comparative pharmacodynamics)

- Target expression: structure, sequence homology, expression of receptor or epitope
- Target receptor binding affinity, receptor occupancy, on/off rate – compared to human
- *In vitro* bioactivity / potency – compared to human
- Functional consequences of receptor occupation (including cell signalling)
- Pharmacologic activity (*in vivo*)

Pharmacokinetically relevant (comparative pharmacokinetics)

- Major metabolites found in humans are also formed in the test species
- Cross-reactivity studies using human and animal tissues (mainly Monoclonal Antibodies)

If NO Relevant Species exist:

- *Consider the use of transgenic animals expressing the human target*
- *Consider the use of homologous proteins*

Pharmacodynamics (PD)

- Mode of action related to intended therapeutic use and target interactions
- Primary and secondary PD characterisation: *in vitro* and *in vivo* using animal models, as relevant

Consider the following:

- Irreversible or long lasting binding to the primary target
- Long lasting effects due to the PK profile of the compound
- Data in humans with compounds that have the same, similar or related modes of action
- PD data following repeated administration
- Evidence from animal models (e.g. knock-out, transgenic or humanised animals) indicative of potential serious pharmacologically-mediated toxicity

ADME and Exposure

Toxicokinetic and pharmacokinetic data should be available in all species used for safety studies before going into humans

- Predict pharmacokinetics in humans
- Absorption (drug exposure in animals)
- Tissue distribution (target organ of toxicity)
- Metabolism and excretion
- PK data may be obtained from toxicity studies

Biotech products

- no metabolism/mass-balance
- measure neutralising Abs to aid interpretation

Safety Pharmacology

The effects of the investigational drug on vital functions, such as cardiovascular, central nervous and respiratory systems should be evaluated prior to first human exposure. These evaluations may be conducted as additions to toxicity studies or as separate studies

- For new chemical entities and biologicals
- Core: CNS, Cardiovascular, Respiratory
- Supplementary: Renal, Gastrointestinal and others as required
- QT interval (*in vitro* hERG channel assay and in vivo QT assay)
- Relevant animal species and sufficient number of animals
- Toxicokinetic sampling

Scientific Justification for Starting Dose

- MRSD based on NOAEL
  - The highest ‘safe’ starting dose
  - Safety window based on toxicological threshold
- MRSD based on MABEL
  - The lowest ‘active’ dose
  - Safety window based on pharmacological threshold

MRSD = Maximum Recommended Starting Dose
NOAEL = No Observed Adverse Effect Level
MABEL = Minimum Anticipated Biological Effect Level

NOAEL vs MABEL: TGN1412

Toxicology

- **NOAEL** monkey **50.0 mg/kg**
- **Human Equivalent Dose 16.0 mg/kg**
- Apply >10-fold safety factor

  = 1.6 mg/kg
- increased to 160-fold for uncertainties

  = **<u>0.1 mg/kg</u>**

MABEL

- *in-vitro* human T-cell proliferation **(0.1 µg/mL)** using murine parent to TGN1412 (5.11A1)
- adjust for anticipated **exposure** in man
  = ~0.003 mg/kg in man
- Consider receptor occupancy:
  initial 10% receptor occupancy **<u>~0.001 mg/kg</u>** in man

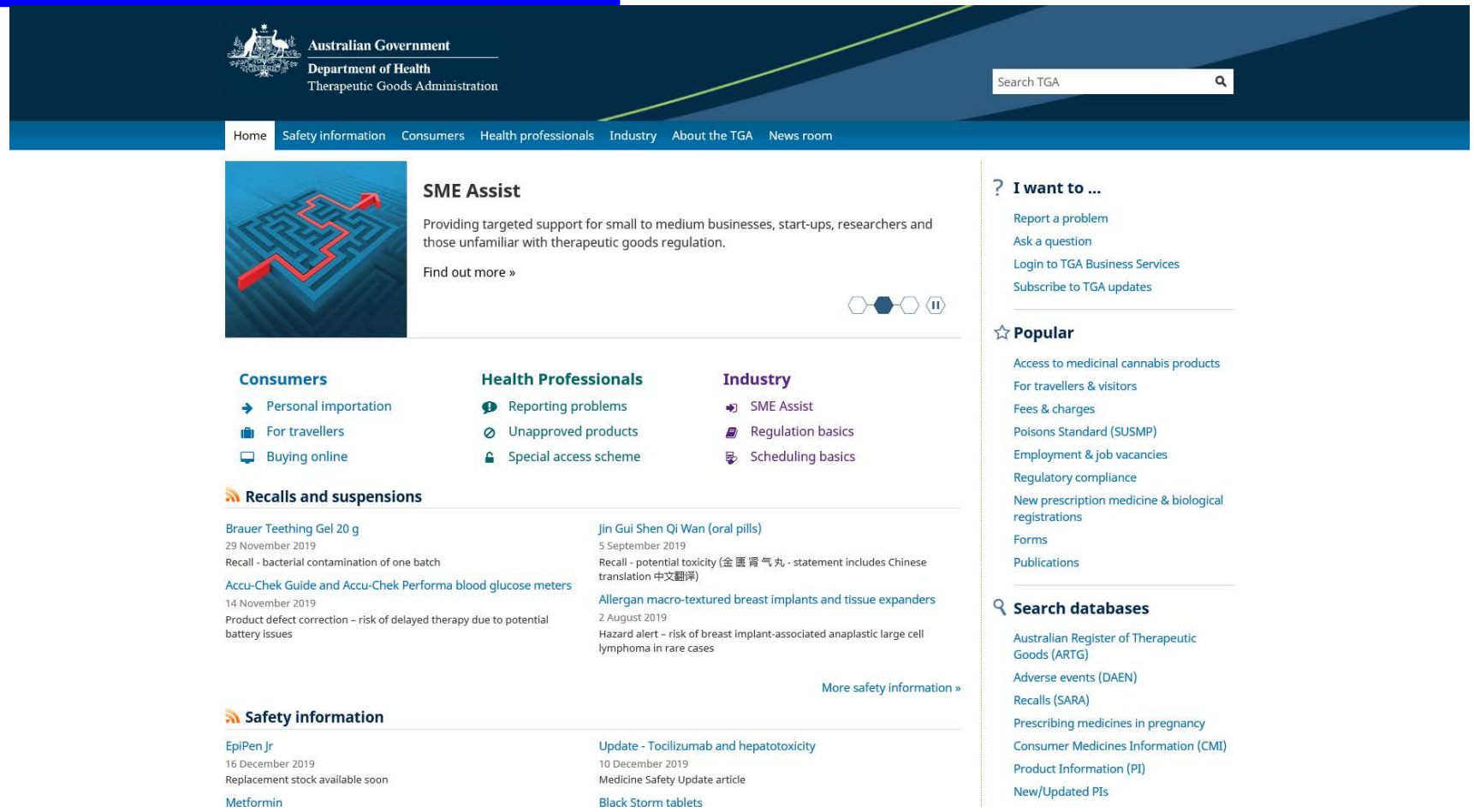
MRSD = 0.001 mg/kg

TGN1412 recommendations

Factors that increased the risk:

- Species specificity of an agent making nonclinical risk assessment difficult
- Novel agents and novel mechanisms of action
- Agonistic or stimulatory actions
- The potency of an agent eg compared with a natural ligand
- Multifunctional agents, eg bivalent antibodies, FcR binding domains
- Cell associated targets
- Targets that bypass normal control mechanisms
- Immune system targets
- Targets in systems with potential for large biological amplification *in vivo*

Visit www.tga.gov.au for more information



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